Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: Genetic Testing - Human Leukocyte Antigen Testing for Celiac Disease

Description/Background

Celiac disease (CD) is currently diagnosed by serology, medical history, and response to a gluten-free diet, with confirmation by small intestinal biopsy. Human leukocyte antigen (HLA) testing may be useful for ruling out disease in symptomatic individuals when findings of other tests are inconclusive.

Diagnosis

Celiac disease, also referred to as celiac sprue or gluten-sensitive enteropathy, is a relatively common disorder with variable clinical expression. Population-based screening surveys suggest a worldwide prevalence of 1% with approximately 2 million people affected in the U.S.(1) However, this prevalence may vary widely depending on how the disease is defined, and whether only clinically apparent cases are considered, as opposed to including all people with any serologic or histologic evidence of disease.

Celiac disease 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 symptoms of CD (e.g., diarrhea, abdominal pain, weight loss) are nonspecific and are often discounted. 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.

Celiac disease 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 1 of these 2 alleles will develop CD. It is believed that approximately 25% to 40% of the general population of the U.S. 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.(2,3)

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 the 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 a consistent history and serologic results, followed by clinical response to a gluten-free diet.(4)

Testing

While a positive biopsy result is considered the criterion standard for diagnosis, the serologic evaluation of individuals 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 individuals 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 test.(5-8) Guidelines have indicated that the IgA antibody to anti-endomysium antibody test has similar sensitivity and specificity as the tissue transglutaminase IgA test, but national organizations have indicated that the anti-endomysium antibody test is more prone to interpretation error. For subjects with known selective IgA deficiency, testing with tissue transglutaminase IgG and/or anti-endomysium antibody IgG 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 (CLIA).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 CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Medical Policy Statement

The effectiveness and clinical utility of human leukocyte antigen *(HLA)-DQ2* and *HLA-DQ8* testing to rule out a diagnosis of celiac disease has been established. It may be considered a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:
Human leukocyte antigen *(HLA)-DQ2* and *HLA-DQ8* testing to rule out celiac disease may be considered medically necessary when one of the following are met:

- Individuals with persistent symptoms despite negative serology (IgA tissue contaminants) and histology (biopsy)
- Symptomatic individuals with discordant serologic and histologic (biopsy) findings
- Symptomatic individuals with positive serology who are unable to undergo biopsy evaluation

Exclusions:

- Familial testing of asymptomatic family members of individuals with proven disease
- All other situations

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81376 81377 81382 81383

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Genetic Testing for Symptoms Suggestive of Celiac Disease

Clinical Context and Test Purpose

The purpose of genetic testing for the human leukocyte antigen (HLA) genes *HLA-DQ2* and *HLA-DQ8* of individuals with symptoms suggestive of celiac disease (CD) are to rule out CD in:

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

The following PICO was used to select literature to inform this review.

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

Interventions
The test being considered is genetic testing for the HLA genes *HLA-DQ2* and *HLA-DQ8.* 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. Commercial testing is available from numerous companies.

Comparators
The following practice is currently being used to diagnose CD: clinical management without genetic testing.

Outcomes
The general outcomes of interest are test validity, other test performance measures, and change in disease status.

The potential beneficial outcomes of primary interest would be the avoidance of all downstream consequences that occur with a lack of correct diagnoses such as the use of ineffective disease management options or the 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 delays in appropriate treatment and lifestyle changes and subsequent avoidance of morbidity associated with the disease. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

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

Study Selection Criteria
For the evaluation of the clinical validity of this test, studies that meet the following eligibility criteria were considered:

Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)

Included a suitable reference standard (describe the reference standard)

Patient/sample clinical characteristics were described.

Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews
A report conducted by Maglione et al (2016) for the Agency of Healthcare Research and Quality indicated that HLA testing could be used to rule out CD with close to 100% sensitivity.(10) The report cited the 2013 American College of Gastroenterology estimates (8) of negative predictive value (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 study found that HLA testing had a sensitivity of 100% and specificity of 18.2%. A 1999 cohort study also reported a sensitivity of100% and a specificity of 33.3%.

Prospective and Retrospective Studies
Several studies have established that HLA typing has high sensitivity and a high NPV for the diagnosis of CD. Werkstetter et al (2017) reported on the results of a large, international prospective study to validate a biopsy free approach for diagnosis of CD in symptomatic children with levels of immunoglobulin A against tissue-transglutaminase (TGA-IgA) 10 times or more the upper limit of normal, confirmed by positive findings for *HLA-DQ2*, *-DQ8*, and endomysium antibodies.(11) The primary aim was to determine whether the non-biopsy approach would identify children with CD with a positive predictive value (PPV) above 99% in clinical practice. Data on symptoms, total IgA, TGA, endomysium antibodies, and biopsy findings (reference standard) were collected from 803 consecutive pediatric patients (≤18 years) on a gluten-containing diet. When results were concordant, cases were classified as a proven CD. Those with low TGA-IgA levels (3 times or below the upper limit of normal) but without other features of CD were classified as 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, and16 had inconclusive results. Test results of TGA-IgA 10 times or more the upper limit of normal, detection of endomysium antibodies, and any symptom identified children with CD (n=399) with a PPV of 99.75% (95% confidence interval [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.

Oliveira et al (2022) evaluated serologic tests as markers of CD in a retrospective cohort study in 94 children with type 1 diabetes mellitus who underwent screening for CD. Type 1 diabetes mellitus confers high risk for CD and baseline propensity for HLA-DQ2 or -DQ8 positivity was assessed.(12) Data for HLA testing were missing in 42 patients. Among the 52 patients with available results, 44 (84.6%) were positive for HLA-DQ2 or -DQ8. Four (4.3%) patients screened positive for CD by IgA or IgG antibodies against TGA or endomysium, all of whom underwent biopsy and had histology consistent with CD. Of these 4 patients diagnosed with CD, 3 had undergone HLA testing, all of whom were positive for HLA-DQ2 or -DQ8, corresponding to 100% sensitivity and NPV. Specificity and PPV of HLA testing for CD were 16.6% and 9.1%, respectively.

Pallav et al (2014) retrospectively assessed HLA testing in 256 patients with known or suspected CD.(13) Taking into account all available clinical and laboratory data, 44 out of 256 patients were diagnosed with CD. Celiac disease was ruled out in 173 patients and a final diagnosis could not be obtained in 39 (15%) of 256 patients. *HLA-DQ2* or *-DQ8* alleles were absent in 40% of patients without CD and 2 patients with CD. 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 1 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.

A prospective study by Hadithi et al (2007) included a total of 463 patients who were referred for evaluation of CD.(14) Sixteen (3.5%) of the 463 patients met European Society of Paediatric Gastroenterology, Hepatology and Nutrition diagnostic criteria for CD (i.e., characteristic histologic findings) (Marsh III) on small bowel biopsy and experienced 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 447 patients who did not meet diagnostic criteria for CD were positive for 1 or both of these alleles. 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%).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Randomized controlled trials assessing the use of *HLA* testing were not identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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, including the implementation of a gluten-free diet. For patients in whom CD is excluded as a diagnosis, this further allows the implementation of appropriate diagnostic strategies to ascertain true etiologies of their symptoms (i.e., microscopic colitis, Crohn's disease).

Section Summary: Genetic Testing for Symptoms Suggestive of Celiac Disease
In individuals who are suspected of having CD and have negative or discordant serologic and biopsy findings, several studies have reported that the sensitivity and negative predictive value (NPV) 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. One prospective study found that testing positive for *HLA-DQ2* or *HLA-DQ8* had a NPV of 100% (95% CI, 98.6% to 100%) but a PPV of 7.7% (95% CI, 4.5% to 12%).Confirming exclusion of a diagnosis of CD in clinically ambiguous patients may lead to avoidance of improper or ineffective interventions, including the implementation of a gluten-free diet. For patients in whom CD is excluded as a diagnosis, this further allows the implementation of appropriate diagnostic strategies to ascertain true etiologies of their symptoms.

Summary of Evidence
For individuals who are suspected of having CD and have negative or discordant serologic and biopsy findings, the evidence includes a systematic review and several retrospective and prospective cohort studies. Relevant outcomes are test validity, other test performance measures, and changes in disease status. Several studies have reported that the sensitivity and NPV 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 an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology
In 2013, a guideline from the American College of Gastroenterology stated the following:

"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."(10)

The American College of Gastroenterology guideline for diagnosis and management of celiac disease was updated in 2023; the recommended diagnostic approach did not change since the 2013 guideline.(8)

National Institute for Health and Care Excellence
The 2009 NICE guidance, which was updated in 2015, on celiac disease (CD) included the following statement on human leukocyte antigen (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).”(15)

American Gastroenterological Association Institute
In 2021, the American Gastroenterological Association (AGA) Institute released a clinical practice update on the evaluation and management of patients with suspected enteropathy, but negative serologic test results for CD and included the following statement on HLA genetic testing:

> "In cases of suspected seronegative CeD [celiac disease], genetic testing should be performed to determine whether the patient carries an HLA genotype (DQ2 or DQ8) that is compatible with developing CeD...HLA genetic testing is most helpful for patients if results are negative, as this excludes the possibility of seronegative CeD as a diagnosis. However, compatible genetics infer that the patient has a risk of developing CeD, but these results cannot stand alone as a diagnostic criterion."(16)

These guidelines also recommend that a gastroenterologist or CD specialist review and evaluated all reported and tested alleles before determining that a patient is HLA-negative.

In 2019, the clinical practice update on diagnosis and management of CD from the AGA Institute stated the following on human leukocyte antigen (HLA) gene testing:

> "Determination of HLA-DQ2/DQ8 has a limited role in the diagnosis of CD. Its value is largely related to its negative predictive value to rule out CD in patients who are seronegative in the face of histologic changes, in patients who did not have serologic confirmation at the time of diagnosis, and in those patients with a historic diagnosis of celiac disease; especially as very young children prior to the introduction of celiac-specific serology."(17)

In 2006, the American Gastroenterological Association Institute issued their original position statement on the diagnosis and management of CD. Regarding serologic testing, the Institute concluded that, in the primary care setting, the transglutaminase immunoglobulin (Ig) A antibody test is the most efficient single serologic test for diagnosing CD.(6) The guidelines indicated that the antiendomysial antibodies IgA test is more time-consuming and operator dependent than the tissue transglutaminase (tTG) test. 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, patient scan proceed to biopsy without testing for HLA alleles.

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
In 2016, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, in conjunction with the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, released a clinical report on the diagnosis and treatment of gluten-related disorders. Regarding HLA tests, the authors stated that HLA testing should not be used as an initial test used for diagnosis of CD.(18) This testing should be reserved for patients where discrepancies are found between their serological and histologic findings, or when patients have commenced a gluten-free diet prior to any testing. In these patients, if neither *HLA-DQ2* nor *DQ8* is found upon testing, the diagnosis of CD is unlikely.

National Institutes of Health
In 2004, the National Institutes of Health issued a consensus statement based on a meeting and an independent literature review.(19) 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 the Institutes considered to be of equivalent accuracy. In patients with suggestive symptoms and negative tTG IgA or EMA tests, it was recommended that consideration be given to IgA deficiency and, if identified, that a tTG IgG or EMA IgG be performed. When the diagnosis of CD is uncertain because of indeterminate results, testing for certain genetic markers (HLA haplotypes) was recommended to stratify individuals into high- or low-risk for CD. Greater than 97% of individuals with CD have the *DQ2*and/or *DQ8* marker, compared with about 40% of the general population. Therefore, an individual negative for *DQ2* or*DQ8* would be extremely unlikely to have CD (high negative predictive value). Biopsy of the proximal small bowel was indicated in those with a positive CD antibody test, except those with biopsy-proven dermatitis herpetiformis. No specific approach was suggested when there was a positive serology and normal biopsy findings. Options included additional biopsies, repeat serology testing and a trial of a gluten-free diet. Testing was indicated in patients with gastrointestinal tract symptoms and other signs and symptoms suggestive of CD.

U.S. Preventive Services Task Force Recommendations
The US Preventative Service Task Force (2017) released guidelines on screening adults and children for CD.(20) These guidelines reviewed the use of tTG IgA testing followed by an intestinal biopsy to screen asymptomatic patients. Inadequate evidence was identified regarding the effectiveness of screening for CD.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in September 2021 did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations
National:
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.

Local:

There is no local coverage determination.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Ingestible Capsule for Assessment of Gastrointestinal (Motility) Disorders
- Wireless Capsule Endoscopy to Diagnose Disorders of the Small Bowel, Esophagus, and Colon

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through April 5, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/22	6/21/22		Joint policy established
9/1/23	6/13/23		• Routine maintenance (slp) • Vendor managed: Avalon • Inclusions align with vendor
9/1/24	6/11/24		• Routine maintenance (slp) • Vendor managed: Avalon

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING - HUMAN LEUKOCYTE ANTIGEN TESTING FOR CELIAC DISEASE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.