Genetic Testing for Lactase Insufficiency

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Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of targeted MCM6 -13910C>T variant analysis for the prediction of lactase insufficiency to be **investigational.***

Background/Overview

LACTASE

The predominant carbohydrate in milk is the disaccharide, lactose, comprising the simple sugars, glucose, and galactose. The brush-border enzyme, lactase (also called lactase-phlorizin hydrolase), hydrolyzes lactose into its monosaccharide components, which are absorbable by the intestinal mucosa. Except in rare instances of congenital hypolactasia, most infants can produce lactase, and enzyme levels are highest at birth. Sometime after weaning in most children, there is a decrease in lactase production through a multifactorial process that is regulated at the gene transcription level.

The decrease in lactase level varies significantly by ethnic group both in terms of the lowest level of lactase and time from weaning necessary to reach the nadir of lactase activity. By 2 to 12 years of age, 2 groups emerge: a group with insufficient levels of lactase activity (primary hypolactasia or lactase nonpersistence) and a group that retains the infant level of lactase activity through adulthood (lactase persistence). Ethnic groups with the highest prevalences of lactase insufficiency are Asian, Native Americans, and blacks, with the lowest prevalences in people of northern European origin (see Table 1).

Table 1. Prevalence of Lactase Insufficiency by Ethnicity

Populations	Percent Lactase Insufficient,[a] %
Northern Europeans	2-15
American whites	6-22
Central Europeans	9-23
Northern Indians	20-30
Southern Indians	60-70
Hispanics	50-80
Ashkenazi Jews	60-80
Blacks	60-80
American Indians	80-100
Asians	95-100

Adapted from Sahi (1994).
[a] Identified through hydrogen breath test or lactose tolerance blood test.

Several terms are used to describe lactose malabsorption: lactase insufficiency, lactose malabsorption, and lactose intolerance. We discuss each below.

Lactase Insufficiency
Lactase insufficiency (lactase nonpersistence or primary hypolactasia) indicates that lactase activity is a fraction of the original infantile level. Direct measurement of lactase activity is tested biochemically through duodenal biopsy. Lactase insufficiency is highly correlated with the C/C genotype at -13910 in the lactase promoter region. In adults homozygous for the lactase persistence genotype (T/T), lactase levels are approximately 10 times higher than in those who are homozygous lactase insufficient (C/C); heterozygous persons (C/T) have intermediate lactase activity levels. In heterozygous people, symptoms of lactose intolerance may appear if the quantity of ingested lactose exceeds the maximum digestible by the reduced level of lactase.

Lactose Malabsorption
Lactose malabsorption indicates that a large portion of lactose cannot be absorbed in the small bowel and is delivered to the colon. Malabsorption is tested by hydrogen breath test (HBT) or lactose tolerance blood test.

Lactose Intolerance
Lactose intolerance indicates that lactose malabsorption causes gastrointestinal symptoms. There is no genetic test for lactose intolerance; demonstration of lactose intolerance requires patients to self-report symptoms (see Table 2) after lactose ingestion. Diagnosis of lactose intolerance is highly susceptible to the placebo effect, and studies should conduct a blinded lactose challenge with an indistinguishable placebo. A meta-analysis by Jellema et al (2010) has indicated that no specific patient complaint could predict lactose malabsorption; for common lactose intolerance symptoms, sensitivity and specificity ranged from 0% to 90% and 18% to 96%, respectively. Similarly, patient self-reported milk intolerance was inaccurate for predicting lactose malabsorption, with sensitivity and specificity ranging from 30% to 70% and 25% to 87%, respectively.

Table 2. Symptoms of Lactose Intolerance

Symptoms	Percent of Total Patients Who Experience Symptoms, %
Gut-related symptoms	
Abdominal pain	100
Gut distention	100
Borborygmi (stomach rumbling)	100
Flatulence	100
Diarrhea	70
Nausea	78
Vomiting	78
Constipation	30
Systemic symptoms	
Headache and light headedness	86
Loss of concentration and poor short-term memory	82
Muscle pain	71

Joint pain and/or swelling	71
Long-term fatigue	63
Allergy (eczema, pruritus, rhinitis, sinusitis, asthma)	40
Mouth ulcers	30
Heart arrhythmia	24
Increased frequency of micturition	<20
Sore throat	<20

Adapted from Matthews et al (2005).

Symptoms

Lactase insufficiency is common, occurring in approximately 70% of persons after weaning. Lactase insufficiency results in lactose malabsorption, which may lead to symptoms of lactose intolerance such as abdominal pain, bloating, diarrhea, and increased flatulence, caused by bacterial fermentation of undigested lactose in the colon. However, demonstration of lactose malabsorption does not necessarily indicate that a person will be symptomatic. Factors that determine whether a person with lactose malabsorption will develop symptoms include the dose of lactose ingested; residual intestinal lactase activity; ingestion of food along with lactose; the ability of the colonic flora to ferment lactose; and individual sensitivity to the products of lactose fermentation. Because of these factors, the number of persons reporting symptoms of lactose intolerance is likely only a portion of those who are lactase insufficient. Also, lactose malabsorption may be secondary (secondary hypolactasia) to acquired conditions, such as small bowel bacterial overgrowth; infectious enteritis; mucosal damage due to celiac disease; inflammatory bowel disease; antibiotics; gastrointestinal surgery; short bowel syndrome; radiation enteritis; or other conditions that may lead to reduced lactase expression in the small intestine.

Clinical Diagnosis

Mucosal biopsy of the duodenum followed by biochemical lactase assay to directly measure lactase activity is the criterion standard for diagnosing lactase insufficiency. Although this approach also may exclude other causes of secondary lactose malabsorption, the utility is limited due to the invasiveness of the procedure and the patchy expression of lactase in the duodenum.

Two common alternatives to this direct method of measuring lactase activity are the HBT and the lactose tolerance blood test, which measure lactose malabsorption. Because lactose malabsorption is nearly always attributable to lactase insufficiency, insufficiency typically can be imputed from the assessment of lactose malabsorption.

The HBT measures by gas chromatography the amount of hydrogen exhaled for up to 3 hours after ingesting 25 to 50 g of lactose. Persons undergoing HBT are required to fast overnight and refrain from activities that may elevate breath hydrogen during testing. A rise in breath hydrogen of 0.31 to 2.5 mL/min is indicative of bacterial fermentation from malabsorbed lactose. A negative HBT can exclude lactose malabsorption as the cause of symptoms, and a positive result indicates that symptoms may be attributable to lactose ingestion. The following factors are associated with increased breath hydrogen and may cause false-positive results if present at the time of testing:

- Diabetes
- Small bowel disease (eg, celiac, giardiasis)
- Bacterial overgrowth
- Altered colon pH
- Antibiotic usage
- Probiotic usage
- Smoking
- Exercise
- Aspirin usage
- Colonic bacterial adaptation.

The lactose tolerance blood test measures blood glucose increase over time with blood drawn at 15, 30, 60, and 90 minutes after ingesting a 25- to 50-g dose of lactose. A glucose increase of less than 20 mg/dL above an 8-hour fasting level indicates an abnormal test. The following factors are associated with increased blood sugar when undergoing a lactose tolerance test and may cause false-positive results:

- Diabetes
- Small bowel disease (eg, celiac, giardiasis)
- Thyroid disorders
- Motility disorders (stomach, small bowel)
- Bacterial overgrowth.

Molecular Diagnosis

Enattah et al (2002) identified the first DNA variant to control transcription of lactase. This variant (*MCM6* -13910C>T) is located in a noncoding region of the *MCM6* gene that is upstream of the lactase gene (*LCT*). The less common T allele has been associated with lactase persistence and has demonstrated an autosomal dominant pattern of inheritance. This variant is thought to be related to the domestication of animals during the last 10,000 to12,000 years, and persons with the C/C genotype have been shown to be associated strongly with a lactase insufficiency phenotype in whites. Other variants in the same *MCM6* regulatory region are associated with other ethnic groups (eg, Africans, Arabs), but prevalence varies geographically and, to date, no commercially available testing kits have incorporated these variants.

Prometheus's *Lacto*TYPE®‡ is a commercially available polymerase chain reaction–based test that assesses the most common lactase nonpersistence variant (*MCM6* -13910C>T) in patients with suspected lactose intolerance. Fulgent Clinical Diagnostics Lab also offers *MCM6* sequencing as well as deletion and duplication analysis using next-generation sequencing. Demonstration of the C/C genotype can be used as indirect evidence of lactase insufficiency and lactose malabsorption.

Treatment

The goal of treatment should be to ensure adequate nutrition for skeletal health. For patients with lactase insufficiency, dietary adjustment to restrict the consumption of foods containing lactose is the principal form

of therapy. However, even lactose maldigesters can usually tolerate small amounts of lactose (12 g/d) with no or minimal symptoms. Lactase enzyme preparations are available for symptom relief but may not be effective in all patients.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination was identified.

Rationale/Source

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other.

SUSPECTED LACTASE INSUFFICIENCY

Clinical Context and Test Purpose

The purpose of targeted testing for the *MCM6* -13910C>T variant in adults who have suspected lactase insufficiency is to inform a decision whether to undergo the HBT, lactose tolerance blood test (LTT), or biopsy.

The question addressed in this evidence review is: Does testing for the *MCM6* -13910C>T variant in adults who have suspected lactase insufficiency improve their net health outcome?
The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with suspected lactase insufficiency.

Interventions

The test being considered is targeted testing for the *MCM6* -13910C>T variant.

Comparators
The following practice is currently being used: dietary restrictions.

Outcomes
The potential beneficial outcomes of primary interest include establishing a molecular genetic diagnosis of lactase insufficiency to inform management decisions based on test results.

Timing
The time frame for outcome measures varies from several weeks to months for the improvement of symptoms to long-term alleviation of symptoms.

Setting
Patients with suspected lactase insufficiency are managed in primary care and may be referred to gastroenterology.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

Many studies have evaluated the diagnosis of lactase insufficiency using polymerase chain reaction variant analysis of *MCM6* -13910C>T, and those that have assessed the agreement between genotyping and HBT, LTT, or biopsy are presented in Table 3. Nineteen studies have compared genotyping of the single nucleotide variant (SNV) -13910C>T with HBT and found sensitivities and specificities ranging from 71% to 100% and 64% to 100%, respectively. Five studies compared genotyping with LTT and reported sensitivities and specificities ranging from 85% to 100% and 87% to 95%, respectively. The study by Enko et al (2014) compared genotyping with a hydrogen/methane breath test, which may be more sensitive than HBT, and reported moderate agreement (Cohen's κ=0.44). Heterogeneity in study populations, a dose of lactose given during the HBT and LTT, and age of participants contributed to the wide range of observed sensitivities and specificities. Direct comparison of these tests is not possible because no identified studies compared both genotyping and HBT or LTT with the criterion standard of duodenal mucosal biopsy. The indirect comparison is also not possible because of the small number of studies comparing genotyping, HBT, or LTT with biopsy.

The incomplete agreement is expected between genotyping for lactase insufficiency and indirect tests of lactose malabsorption because these tests do not measure the same parameters. LTT and HBT are

intended to diagnosis lactose malabsorption, which can be caused by factors other than lactase insufficiency. Additionally, because lactase activity persists for years after weaning, the inclusion of children can affect the concordance between HBT or LTT and genotyping. Di Stefano et al (2009) found that the overall κ value for agreement between HBT and genotyping was 0.74, but for those younger than and older than 30 years of age, κ values were 0.56 and 1.0, respectively (p<0.005 for both comparisons).

The SNV -13910C>T is not the only *MCM6* variant implicated in regulating transcription of the lactase (*LCT*) gene. A study by Eadala et al (2011) recruited patients with inflammatory bowel disease along with healthy control patients and found that, although the C/C genotype was strongly associated with experiencing symptoms of lactose intolerance after HBT, there was a high proportion of lactose sensitivity in C/T and T/T genotype patients as well. A Colombian study by Mendoza Torres et al (2012) found low specificity (46%) when comparing HBT with genotyping. The authors attributed this to the genetic heterogeneity of the Colombian and Caribbean population studied, and recommended against using genotyping to assess lactase insufficiency in this population. Similarly, Santonocito et al (2015) found a similar proportion (≈80%) of homozygous genotypes for lactase nonpersistence among 1426 patients with gastrointestinal symptoms and 1000 healthy volunteers in south-central Italy. These results would suggest that unmeasured genetic variation may more fully explain lactase insufficiency.

Table 3. Reported Sensitivities and Specificities Between Genotyping and HBT, LTT, and Intestinal Biopsy[a]

Study, Country	N	Sensitivity (95% CI), %	Specificity (95% CI), %
Targeted variant analysis of SNV -13910C>T vs HBT			
Gugatschka et al (2005), Austria	51	90 (73 to 98)	95 (76 to 100)
Buning et al (2005), Germany	166	98 (93 to 100)	83 (71 to 91)
Hogenauer et al (2005), Austria	123	97 (86 to 100)	86 (77 to 93)
Bulhoes et al (2007), Brazil	20	90 (55 to 100)	100 (69 to 100)
Schirru et al (2007), Italy	84	84 (72 to 93)	96 (81 to 100)
Bernardes-Silva et al (2007), Brazil	147	76 (59 to 89)	100 (40 to 100)
Szilagyi et al (2007), Canada	30	93 (68 to 100)	80 (52 to 96)
Kerber et al (2007), Austria	120	97 (86 to 100)	72 (61 to 95)
Mattar et al (2008), Brazil	50	96 (82 to 100)	100 (85 to 100)
Krawczyk et al (2008), Germany	58	100 (78 to 100)	95 (84 to 99)
Mottes et al (2008), Italy	112	71 (60 to 80)	83 (61 to 95)
Waud et al (2008), Wales	200	100 (88 to 100)	64 (57 to 71)
Di Stefano et al (2009), Italy	32	88 (70 to 98)	100 (54 to 100)
Nagy et al (2009), Hungary	186	77 (68 to 85)	94 (87 to 98)
Szilagyi et al (2009), Canada	57	97 (83 to 100)	93 (76 to 99)
Babu et al (2010), India	153	87 (80 to 93)	97 (85 to 100)
Pohl et al (2010), Germany	194	90 (80 to 96)	98 (94 to 100)
Mendoza Torres et al (2012), Columbia	126	97	46
Morales et al (2011), Chile	51	96.3	87.5
Targeted variant analysis of SNV -13910C>T vs H/MBT			
Enko et al (2014), Austria	263	79	87
Targeted variant analysis of SNV -13910C>T vs LTT			
Nilsson et al (2004), Sweden	35	100	88
Gugatschka et al (2005), Austria	46	85	90

Study, Country	N	Sensitivity (95% CI), %	Specificity (95% CI), %
Ridefelt et al (2005), Canada	51	90	95
Szilagyi et al (2007), Canada	30	93	87
Babu et al (2010), India	153	97	87
Targeted variant analysis of -13910C>T vs biopsy-determined lactase activity			
Rasinpera et al (2004), Finland	329	NA	NA
	<5 y: 109	80	65.4
	6-11 y: 142	94.6	81.9
	≥12 y: 78	93.3	100
Nilsson et al (2004), Sweden	35	100	88
Kuchay et al (2011), India	176b	NA	NA
	>5 y: 108b	96	78.9
	>8 y: NR	97.2	100
Mattar et al (2013), Brazi	32	100	48
Targeted variant analysis of -22018G>A vs HBT			
Bernardes-Silva et al (2007), Brazil	147	73	82
Kerber et al (2007), Austria	166	100	71
Di Stefano et al (2009), Italy	123	89	100

CI; confidence interval; HBT: hydrogen breath test; H/MBT: hydrogen methane breath test; LTT: lactose tolerance blood test; NA: not applicable; NR: not reported; SNV: single nucleotide variant.

[a] There was heterogeneity in how the HBT and LTT were conducted (eg, using 25 g or 50 g of lactose) and in populations tested (eg, inclusion of children or racial/ethnic composition of study populations).
[b] Children.

A meta-analysis by Marton et al (2012) compared the diagnostic accuracy of HBT and LTT testing with -13910C>T genotyping for prediction of lactase insufficiency phenotype. Seventeen studies evaluated HBT, and 5 evaluated LTT. Overall sensitivity and specificity of HBT were 88% (95% confidence interval [CI], 85% to 90%) and 85% (95% CI, 82% to 87%), respectively. Both sensitivity and specificity showed substantial heterogeneity (I^2=78% and 87%, respectively), and reviewers detected potential publication bias. For LTT, overall sensitivity was 94% (95% CI, 90% to 97%) and specificity was 90% (95% CI, 84% to 95%). No significant statistical heterogeneity was observed. Three studies also assessed -22018G>A genotype, which has been described in European populations, and found less accurate overall sensitivity (87%; 95% CI, 79% to 93%) and specificity (76%; 95% CI, 67% to 83%), compared with the -13910C>T variant.

Section Summary: Clinically Valid

Evidence of clinical validity for variant analysis of -13910C>T includes genotype-phenotype correlation studies and a meta-analysis. Discordance between genotyping for lactase insufficiency and indirect tests of lactose malabsorption such as LTT and HBT have been noted given that lactose malabsorption can be caused by factors other than lactase insufficiency. Studies have demonstrated that analysis of the -13910C>T variant can detect lactase insufficiency.

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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

No studies were identified that attempted to demonstrate improved patient outcomes or changes in patient management because of genetic testing for lactase insufficiency.

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.

Lactase insufficiency is the normal phenotype for most adults, and a confirmatory diagnosis with HBT, LTT, or genotyping is unnecessary. Empirical diagnosis by dietary restriction is adequate in most circumstances because this is the primary treatment for lactase insufficient patients. Patients who achieve satisfactory symptom control after dietary modification require no further diagnostic testing. For most patients who do not achieve symptom control after dietary modification, testing is indicated for the presence of other conditions that can cause similar symptoms.

The proposed clinical utility of genotyping for lactase insufficiency is that the test offers a more comfortable assessment for patients when compared with HBT, LTT, or biopsy. Traditional testing methods may be associated with discomfort caused by the ingestion of a large volume of lactose, and there are dietary preparations and fasting before testing. Additionally, factors that may cause false-positive HBT, and LTT results will not cause false-positive genotype results. Arroyo et al (2010) suggested that genetic testing, when used with HBT, can help in the diagnosis of secondary hypolactasia when there is a positive HBT and the patient is not -13910C/C genotype.

Section Summary: Clinically Useful
Direct evidence for the clinical utility of genotyping for lactase insufficiency is lacking. Genetic testing has the potential advantage of sparing patients the discomfort of fasting and experiencing symptoms of lactose intolerance during the administration of HBT, LTT, or biopsy. However, meaningful improvements in health outcomes through the use of genotyping for lactase insufficiency have not been demonstrated.

SUMMARY OF EVIDENCE
For individuals with suspected lactase insufficiency who receive targeted testing for the *MCM6* -13910C>T variant, the evidence includes genotype-phenotype studies and a meta-analysis. Relevant outcomes are

symptoms, morbid events, functional outcomes, health status measures, and quality of life. Studies have demonstrated a high correlation between the -13910C>T single nucleotide variant upstream of the gene encoding the enzyme lactase, and lactase insufficiency in persons of European ancestry. Studies in white populations have reported a high degree of agreement for the diagnosis of lactase insufficiency between genotyping and both hydrogen breath test and lactose tolerance blood test. However, there is no current treatment for lactase insufficiency, and management involves dietary restriction and palliation of lactose intolerance symptoms. Therefore, an empirical diagnosis of lactose intolerance in the absence of confirmation by hydrogen breath test, lactose tolerance blood test, or genotyping, followed by treatment with dietary restriction of lactose, is suitable. Currently, the evidence does not support the conclusion that assessment of the genetic etiology of lactose intolerance would affect patient management or improve clinical outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 07/17/2013
Current Effective Date: 07/11/2018

06/27/2013	Medical Policy Committee review
07/17/2013	Medical Policy Implementation Committee approval. New policy.
07/10/2014	Medical Policy Committee review
07/16/2014	Medical Policy Implementation Committee approval. No change to coverage.
06/25/2015	Medical Policy Committee review
07/15/2015	Medical Policy Implementation Committee approval. No change to coverage.
06/30/2016	Medical Policy Committee review
07/20/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
07/06/2017	Medical Policy Committee review
07/19/2017	Medical Policy Implementation Committee approval. No change to coverage.
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. Coverage statement reworded.

Next Scheduled Review Date: 07/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81400
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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