CONCERT GENETIC TESTING: METABOLIC, ENDOCRINE, AND MITOCHONDRIAL DISORDERS

See Important Reminder at the end of this policy for important regulatory and legal information.

OVERVIEW

Hereditary metabolic disorders, also known as inborn errors of metabolism, are genetic disorders that interfere with the body’s metabolism. There are hundreds of inherited metabolic disorders, and many are screened for at birth through newborn screening programs, while others are identified after a child or adult shows symptoms of the disorder. Genetic testing for metabolic disorders aids in quickly identifying the specific disorder so that proper treatment can be initiated and at-risk family members can be identified.

Hereditary endocrine disorders are a group of conditions involving the endocrine system, a network of glands that produce and release hormones in order to regulate body functions. This document aims to address hereditary endocrine disorders that are non-cancerous in nature.

Mitochondrial disorders are a clinically heterogeneous group of disorders caused by dysfunction of the mitochondrial respiratory chain. The diagnosis of a primary mitochondrial disease can be difficult, as the individual symptoms are nonspecific and symptom patterns often overlap significantly. Mitochondrial disorders can be caused by mutations in the genes encoded by the mitochondrial DNA (mtDNA), which are transmitted by maternal inheritance, or by genes encoded by the nuclear DNA, which can be transmitted in an autosomal recessive or autosomal dominant manner. There are over 1000 nuclear genes coding for proteins that support mitochondrial function. These disorders can present at any age and many involve multiple organ systems, often with neurologic and myopathic features.

Genetic testing for metabolic, endocrine, and mitochondrial disorders aids in identifying the specific disorder that is present, so that proper treatment (if any) can be initiated, and at-risk family members can be identified.
Of note, a family history in which affected women transmit the disease to male and female children and affected men do not transmit the disease to their children suggests the familial variant(s) is in the mtDNA, rather than in a nuclear gene.

**POLICY REFERENCE TABLE**

Below are a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

**Coding Implications**

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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| **MTHFR Variant Analysis** | Methylenetetrahydrofolate Reductase (MTHFR) Thermolabile Variant, DNA Analysis (LabCorp) | 81291            | E03.9, E55.9, E72.12, E78.2, E78.5, E88.9, O03, N96, R53.83, Z00.00 | 1, 2 |

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### Maturity Onset Diabetes of the Young (MODY) Panel

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### OTHER RELATED POLICIES

This policy document provides coverage criteria for metabolic, endocrine, and mitochondrial disorders. Please refer to:

- **Genetic Testing: Prenatal and Preconception Carrier Screening** for coverage criteria related to prenatal or preconception **carrier** screening.
- **Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss** for coverage related to prenatal and pregnancy loss **diagnostic** genetic testing.
• **Genetic Testing: Preimplantation Genetic Testing** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.

• **Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay** for coverage criteria related to genetic disorders that affect multiple organ systems.

• **Genetic Testing: Hereditary Cancer Susceptibility Syndromes** for coverage criteria related to genetic testing for hereditary endocrine cancer predisposition syndromes.

• **Genetic Testing: General Approach to Genetic Testing** for coverage criteria related to metabolic, endocrine, and mitochondrial disorders not specifically discussed in this or another non-general policy.

**CRITERIA**

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

**KNOWN FAMILIAL VARIANT ANALYSIS FOR METABOLIC, ENDOCRINE, AND MITOCHONDRIAL DISORDERS**

I. Targeted mutation analysis for a known familial variant (81403, 81404, 81405, 81406, 81407, 81479) for a metabolic, endocrine, or mitochondrial disorder is considered **medically necessary** when:

   A. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant causing the condition.

II. Targeted mutation analysis for a known familial variant (81403, 81404, 81405, 81406, 81407, 81479) for a metabolic, endocrine, or mitochondrial disorder is considered **investigational** for all other indications.
MTHFR VARIANT ANALYSIS

I. MTHFR targeted variant analysis (examples: 677T, 1298C) (81291) is considered investigational for all indications, including:
   A. Evaluation for thrombophilia or recurrent pregnancy loss
   B. Evaluation of at-risk relatives
   C. Drug metabolism (e.g., pharmacogenetic testing)

MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

Maturity-Onset Diabetes of the Young (MODY) Panel

I. Multigene panel analysis to establish or confirm a diagnosis of maturity-onset diabetes of the young (MODY) (81403, 81405, 81406, 81407, 81479) is considered medically necessary when:

   A. The member/enrollee meets one of the following:
      1. The member/enrollee has a diagnosis of diabetes within the first 6 months of life, OR
      2. The member/enrollee has a diagnosis of diabetes before 35 years of age, AND

   B. The member/enrollee meets one of the following:
      1. The member/enrollee has features atypical for type 1 diabetes mellitus. including at least one of the following:
         a) Absence of pancreatic islet autoantibodies, OR
         b) Evidence of endogenous insulin production beyond the honeymoon period (i.e., 3 to 5 years after the onset of diabetes), OR
         c) Measurable C-peptide in the presence of hyperglycemia (C-peptide 0.60 ng/mL or greater, or 0.2 nmol/L), OR
         d) Low insulin requirement for treatment (i.e., less than 0.5 U/kg/d), OR
e) Lack of ketoacidosis when insulin is omitted from treatment, OR

2. The member/enrollee has features atypical for type 2 diabetes mellitus, including at least one the following:
   a) Onset of diabetes before age 45 years, OR
   b) Lack of significant obesity, OR
   c) Lack of acanthosis nigricans, OR
   d) Normal triglyceride levels and/or normal or elevated high-density lipoprotein cholesterol (HDL-C), AND

C. The member/enrollee has a family history of diabetes consistent with autosomal dominant inheritance AND

D. The panel includes, at a minimum, the following genes: *GCK*, *HNF1A*, and *HNF4A*.

II. Multigene panel analysis to establish or confirm a diagnosis of maturity-onset diabetes of the young (MODY) (81403, 81404, 81405, 81406, 81407, 81479) is considered investigational for all other indications.

**MITOCHONDRIAL GENOME SEQUENCING, DELETION/DUPLICATION, AND/OR NUCLEAR GENES**

I. Mitochondrial genome sequencing (81460), deletion/duplication (81465), and/or nuclear genes analysis (81440) to establish or confirm a diagnosis of a primary mitochondrial disorder is considered medically necessary when:

A. The member/enrollee has a classic phenotype of one of the maternally inherited syndromes (e.g., Leber hereditary optic neuropathy, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes [MELAS], myoclonic epilepsy with ragged red fibers [MERRF], maternally inherited deafness and diabetes [MIDD], neuropathy, ataxia, retinitis pigmentosa [NARP], Kearns-Sayre syndrome/CPEO); or of a nuclear DNA mitochondrial disorder (e.g., mitochondrial neurogastrointestinal encephalopathy [MNGIE]); OR
B. The member/enrollee has non-specific clinical features suggestive of a primary mitochondrial disorder and meets ALL of the following:

1. Clinical findings of at least two of the following:
   a) Ptosis, OR
   b) External ophthalmoplegia, OR
   c) Proximal myopathy, OR
   d) Exercise intolerance, OR
   e) Cardiomyopathy, OR
   f) Sensorineural deafness, OR
   g) Optic atrophy, OR
   h) Pigmentary retinopathy, OR
   i) Diabetes mellitus and deafness, OR
   j) Fluctuating encephalopathy, OR
   k) Seizures, OR
   l) Dementia, OR
   m) Migraine, OR
   n) Stroke-like episodes, OR
   o) Ataxia, OR
   p) Spasticity, OR
   q) Chorea, OR
   r) Multiple late term pregnancy loss, AND

2. Conventional biochemical laboratory studies have been completed and are non-diagnostic, including at least: plasma or CSF lactic acid concentration, ketone bodies, plasma acylcarnitines, and urinary organic acids, AND

3. Additional diagnostic testing indicated by the member’s/enrollee’s clinical presentation (e.g., fasting blood glucose, electrocardiography, neuroimaging, electromyography, echocardiography, audiology, thyroid testing, electroencephalography, exercise testing) have been completed and are non-diagnostic.

II. Mitochondrial genome sequencing (81460), deletion/duplication (81465), and/or nuclear genes analysis (81440) to establish or confirm a diagnosis of a primary mitochondrial disorder is considered investigational for all other indications.
OTHER COVERED METABOLIC, ENDOCRINE, AND MITOCHONDRIAL DISORDERS

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

I. Genetic testing to establish or confirm one of the following metabolic, endocrine, and mitochondrial conditions to guide management is considered **medically necessary** when the member/enrollee demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below):

   A. Congenital adrenal hyperplasia, including:
      1. 21-Hydroxylase deficiency

   B. Congenital disorders of glycosylation

   C. **Congenital hyperinsulinism**

   D. Disorders of amino acid and peptide metabolism, including:
      1. Glutaric acidemia type I (GA-1)
      2. Homocystinuria caused by cystathionine beta-synthase (CBS) deficiency
      3. Methylmalonic acidemia
      4. Propionic acidemia
      5. **Maple Syrup Urine Disease (MSUD)**

   E. Disorders of biotin metabolism, including:
      1. **Biotinidase deficiency**

   F. Disorders of carnitine transport and the carnitine cycle, including:
      1. Carnitine palmitoyltransferase II deficiency
      2. **Primary carnitine deficiency**

   G. Disorders of copper metabolism, including:
      1. **ATP7A-Related copper transport disorders** (e.g., Menkes disease, occipital horn syndrome (OHS), ATP7A-related distal motor neuropathies)
      2. **Wilson disease**

   H. Disorders of fatty acid oxidation, including:
      1. **Medium-chain acyl-coenzyme A dehydrogenase deficiency (MCAD deficiency)**

   I. Disorders of galactose metabolism, including:
      1. **Galactosemia**

   J. Disorders of glucose transport, including:
      1. **Glucose transporter type 1 deficiency syndrome (Glut1 DS)**

   K. Disorders of phenylalanine or tyrosine metabolism, including:
      1. **Alkaptonuria**
      2. **Phenylalanine hydroxylase deficiency**
L. Disorders of porphyrin and heme metabolism, including:
   1. Acute intermittent porphyria
M. Fibrous Dysplasia/McCune-Albright Syndrome
N. Glycogen storage disorders, including:
   1. Glycogen Storage Disease Type I (GSDI)
   2. Pompe disease (GSDII)
O. Hypophosphatasia
P. Kallmann syndrome (GnRH deficiency)
Q. Lysosomal storage disorders, including:
   1. Gaucher disease
   2. Krabbe disease
   3. MPS-Type I (Hurler syndrome)
   4. MPS-Type II (Hunter syndrome)
   5. Mucolipidosis IV
R. Urea cycle disorders, including
   1. Ornithine Transcarbamylase (OTC) deficiency
S. Malignant hyperthermia
T. SHOX deficiency disorders

II. Genetic testing to establish or confirm the diagnosis of all other metabolic, endocrine, and mitochondrial disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in General Approach to Genetic Testing (see policy for coverage criteria).

*Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly source.

NOTES AND DEFINITIONS

1. Close relatives include first, second, and third degree blood relatives on the same side of the family:
   a. First-degree relatives are parents, siblings, and children
   b. Second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
c. Third-degree relatives are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

2. Mitochondrial disease refers to a heterogenous group of disorders caused by dysfunctional mitochondria, the organelles responsible for oxidative phosphorylation within the cell.

BACKGROUND AND RATIONALE

Known Familial Variant Analysis for Metabolic, Endocrine, and Mitochondrial Disorders

Genetic Support Foundation

The Genetic Support Foundation’s Genetics 101 information on inheritance patterns says the following about testing for familial pathogenic variants:

Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members/enrollees of the family to see who is also at risk.

MTHFR Variant Analysis

American College of Medical Genetics and Genomics (ACMG)

ACMG published a practice guideline for MTHFR polymorphism testing (2013) with the following recommendations:

- MTHFR polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss
- MTHFR polymorphism genotyping should not be ordered for at-risk family members
- A clinical geneticist who serves as a consultant for a patient in whom an MTHFR polymorphism(s) is found should ensure that the patient has received a thorough and appropriate evaluation for his or her symptoms
- If the patient is homozygous for the “thermolabile” variant c.665C to T, the geneticist may order a fasting total plasma homocysteine, if not previously ordered, to provide more accurate counseling
MTHFR status does not change the recommendation that women of childbearing age should take the standard dose of folic acid supplementation to reduce the risk of neural tube defects as per the general population guidelines (p. 154)

**Maturity-Onset Diabetes of the Young (MODY) Panel**

*American Diabetes Association*

In 2021, the American Diabetes Association made the following recommendations:

- All children diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. (Category A)
- Children and those diagnosed in early adulthood who have diabetes not characteristic of type 1 or type 2 diabetes that occurs in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young. (Category A)
- In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of these mutations and how best to approach further evaluation, treatment, and genetic counseling. (Category E) (p. 525)

*GeneReviews: Maturity-Onset Diabetes of the Young Overview*

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. Their recommendations are as follows:

A clinical diagnosis of MODY can be suspected in individuals with:

- Early-onset diabetes in adolescence or young adulthood (typically age less than 35 years)
- Features atypical for type 1 diabetes mellitus including the following:
  - Absence of pancreatic islet autoantibodies
  - Evidence of endogenous insulin production beyond the honeymoon period (i.e., 3 to 5 years after the onset of diabetes)
  - Measurable C-peptide in the presence of hyperglycemia (C-peptide of at least 0.60 ng/mL or 0.2 nmol/L)
  - Low insulin requirement for treatment (i.e., less than 0.5 U/kg/d)
  - Lack of ketoacidosis when insulin is omitted from treatment
- Features atypical for type 2 diabetes mellitus including the following:
  - Onset of diabetes before age 45 years
● Lack of significant obesity
● Lack of acanthosis nigricans
● Normal triglyceride levels and/or normal or elevated high-density lipoprotein cholesterol (HDL-C)
● Mild, stable fasting hyperglycemia that does not progress or respond appreciably to pharmacologic therapy
● Extreme sensitivity to sulfonylureas
● Extrapancreatic features (e.g., renal, hepatic, gastrointestinal)
● A personal history or family history of neonatal diabetes or neonatal hypoglycemia
● A family history of diabetes consistent with autosomal dominant inheritance that contrasts with type 1 diabetes and type 2 diabetes in the following ways:
  ○ Type 1 diabetes can run in families but is often sporadic: only 2% to 6% of individuals with type 1 diabetes have an affected parent.
  ○ Type 2 diabetes often runs in families: shared risk alleles and shared environment can lead to occurrence of type 2 diabetes in multiple family members. Family history that helps distinguish between type 2 diabetes and MODY are onset of diabetes after age 45 years in association with obesity (type 2 diabetes) versus onset of diabetes before age 35 years and lack of obesity (MODY)

**Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Genes**

*Mitochondrial Medicine Society*

The Mitochondrial Medicine Society (2015) published the following consensus recommendations for DNA testing for mitochondrial disorders:

1. Massively parallel sequencing/NGS of the mtDNA genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations.

2. Patients with a strong likelihood of mitochondrial disease because of a mtDNA mutation and negative testing in blood, should have mtDNA assessed in another tissue to avoid the possibility of missing tissue-specific mutations or low levels of heteroplasmy in blood; tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and to guide genetic counseling.

3. Heteroplasmy analysis in urine can selectively be more informative and accurate than testing in blood alone, especially in cases of MELAS due to the common m. 3243A>G mutation.
4. mtDNA deletion and duplication testing should be performed in cases of suspected mitochondrial disease via NGS of the mtDNA genome, especially in all patients undergoing a diagnostic tissue biopsy.
   a. If a single small deletion is identified using polymerase chain reaction–based analysis, then one should be cautious in associating these findings with a primary mitochondrial disorder.
   b. When multiple mtDNA deletions are noted, sequencing of nuclear genes involved in mtDNA biosynthesis is recommended.

5. When a tissue specimen is obtained for mitochondrial studies, mtDNA content (copy number) testing via real-time quantitative polymerase chain reaction should strongly be considered for mtDNA depletion analysis because mtDNA depletion may not be detected in blood.
   a. mtDNA proliferation is a nonspecific compensatory finding that can be seen in primary mitochondrial disease, secondary mitochondrial dysfunction, myopathy, hypotonia, and as a by-product of regular, intense exercise.

6. When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no known mutation is identified via known NGS gene panels, then whole exome sequencing should be considered. (p. 692 through 693)

GeneReviews: Primary Mitochondrial Disorders Overview

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. Their recommendations are as follows:

Common clinical features of mitochondrial disorders include:

- ptosis
- external ophthalmoplegia
- proximal myopathy
- exercise intolerance
- cardiomyopathy
- sensorineural deafness
- optic atrophy
● pigmentary retinopathy
● diabetes mellitus
● fluctuating encephalopathy
● seizures
● dementia
● migraine
● stroke-like episodes
● ataxia
● spasticity
● chorea
● high incidence of mid- and late-pregnancy loss

When a patient’s clinical picture is nonspecific but highly suggestive of a mitochondrial disorder, the clinician should start with measurement of plasma or CSF lactic acid concentration, ketone bodies, plasma acylcarnitines, and urinary organic acids.

Traditionally, the diagnosis of mitochondrial disorders has been based on demonstrating mitochondrial dysfunction in a relevant tissue biopsy (e.g., a skeletal muscle or liver biopsy, or skin fibroblasts), with the particular pattern of biochemical abnormality being used to direct targeted molecular genetic testing of mtDNA, specific nuclear genes, or both.

However, the more widespread availability of molecular diagnostic techniques and the advent of exome and genome sequencing has changed the diagnostic approach.

One important caveat arises from the fact that many mtDNA pathogenic variants are heteroplasmic, and the proportion of mutated mtDNA in blood may be undetectable. This can be circumvented by analyzing mtDNA from another tissue – typically skeletal muscle or urinary epithelium – in which the level of heteroplasmy tends to be higher. Some common mtDNA pathogenic variants (e.g., large-scale deletions causing CPEO) may only be detected in skeletal muscle.

In individuals with a specific clinical phenotype (e.g., MELAS, LHON, POLG-related disorders) it may be possible to reach a diagnosis with targeted analysis of specific mtDNA pathogenic variants or single-gene testing of a nuclear gene.

A mitochondrial disorders multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. Such testing includes exome sequencing, genome sequencing, and mitochondrial sequencing which can simultaneously analyze nuclear DNA and mtDNA.
REFERENCES

1. Hickey SE, Curry CJ, Toriello H V. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. Published online 2013. doi:10.1038/gim.2012.165


11. Inborn Errors Classification: A Hierarchical Classification for Inborn Errors of Metabolism (Updated 2012). Society for the Study of Inborn Errors of Metabolism website. Available at: https://www.ssiem.org/resources/resources/inborn-errors-classification

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to
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**Note: For Medicaid members/enrollees**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**Note: For Medicare members/enrollees**, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at [http://www.cms.gov](http://www.cms.gov) for additional information.

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