BLUE CROSS OF NORTHEASTERN PA "BCNEPA" MEDICAL POLICY BULLETIN	**MANUAL:** MEDICAL POLICY
	REFERENCE NO.: MPO-083-0022
EFFECTIVE DATE June 1, 2014	**SUBJECT:** Genetic Testing, Including Chromosomal Microarray Analysis and Next-Generation Sequencing Panels, for the Evaluation of Patients with Developmental Delay/Intellectual Disability or Autism Spectrum Disorder

Blue Cross of Northeastern Pennsylvania ("BCNEPA") Medical Policy

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical policy and claims payment policy are applied. Policies are provided for informational purposes only and are developed to assist in administering plan benefits and do not constitute medical advice.

Treating providers are solely responsible for medical advice and treatment. Policies are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease.

Medical practices and information are constantly changing and BCNEPA may review and revise its medical policies periodically. Also, due to the rapid pace of changing technology and the advent of new medical procedures, BCNEPA may not have a policy to address every procedure.

In those cases, BCNEPA may review other sources of information including, but not limited to, current medical literature and other medical resources, such as Technology Evaluation Center Assessments (TEC) published by the Blue Cross Blue Shield Association. BCNEPA may also consult with health care providers possessing particular expertise in the services at issue.

DESCRIPTION:

Chromosomal microarray (CMA) testing has been proposed for detection of genetic imbalances in infants or children with characteristics of developmental delay/intellectual disability (DD/ID) or autism spectrum disorder (ASD). G-banded karyotyping has for many years been the standard first-line test for this purpose. G-banded karyotyping allows visualization and analysis of chromosomes for chromosomal rearrangements including genomic gains and losses. CMA analysis performs a similar, although nonvisual, analysis at a much higher resolution. As a result, CMA has the potential to increase the diagnostic yield in this population and change clinical interpretation in some cases.

Next-generation sequencing (NGS) panel testing allows for simultaneous analysis of a large number of genes and has been proposed as a way to identify single gene causes of syndromes that have autism as a significant clinical feature, in patients with normal CMA testing.

BENEFIT POLICY STATEMENT:

BCNEPA makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on product line, group or contract, therefore, Member benefits must be verified. In the event of a conflict between the Member's benefit plan document and topics addressed in Medical Policy Bulletins (i.e., specific contract exclusions), the Member's benefit plan document always supersedes the information in the Medical Policy Bulletins.

BCNEPA determines medical necessity only if the benefit exists and no contract exclusions are applicable.

Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

BACKGROUND:

Children with signs of neurodevelopmental delays or disorders in the first few years of life may eventually be diagnosed with intellectual disability or autism syndromes, serious and lifelong conditions that present significant challenges to families and to public health. Cases of DD/ID and of ASD may be associated with genetic abnormalities. For children with clear, clinical symptoms and/or physiologic evidence of syndromic neurodevelopmental disorders, diagnoses are based primarily on clinical history and physical examination, and then may be confirmed with targeted genetic testing of specific genes associated with the diagnosed syndrome. However, for children who do not present with an obvious syndrome, who are too young for full expression of a suspected syndrome, or who may have an atypical presentation, genetic testing may be used as a basis for establishing a diagnosis.

Current guidelines for these patients, such as those published by the American Academy of Pediatrics (AAP) and the American Academy of Neurology (AAN), recommend cytogenetic evaluation to look for certain kinds of chromosomal abnormalities that may be causally related to their condition. AAN guidelines note that only in occasional cases will an etiologic diagnosis lead to specific therapy that improves outcomes but suggest the more immediate and general clinical benefits of achieving a specific genetic diagnosis from the clinical viewpoint, as follows (1):

- limit additional diagnostic testing;
- anticipate and manage associated medical and behavioral comorbidities;
- improve understanding of treatment and prognosis; and
- allow counseling regarding risk of recurrence in future offspring and help with reproductive planning.

AAP and AAN guidelines also emphasize the importance of early diagnosis and intervention in an attempt to ameliorate or improve behavioral and cognitive outcomes over time.

Most commonly, genetic abnormalities associated with neurodevelopmental disorders are deletions and duplications of large segments of genomic material, called copy number variants, or CNVs. For many well-described syndromes, the type and location of the chromosomal abnormality has been established with the study of a large number of cases and constitutes a genetic diagnosis; for others, only a small number of patients with similar abnormalities may exist to support a genotype-phenotype correlation. Finally, for some patients, cytogenetic analysis will discover entirely new chromosomal abnormalities that will require additional study to determine their clinical significance.

Conventional methods of cytogenetic analysis, including karyotyping (eg, G-banded) and fluorescence in situ hybridization (FISH), have relatively low resolution and a low diagnostic yield (ie, proportion of tested patients found to have clinically relevant genomic abnormalities), leaving most cases without identification of a chromosomal abnormality associated with the child's condition. CMA analysis is a newer cytogenetic analysis method that increases the chromosomal resolution for detection of CNVs, and, as a result, increases the genomic detail beyond that of conventional methods. CMA results are clinically informative in the same way as results derived from conventional methods, and thus CMA represents an extension of standard methods with increased resolution.

NGS has been proposed to detect single gene causes of autism and possibly identify a syndrome that involves autism in patients with normal array-based testing.

CMA analysis to determine genetic etiology

CMA analysis detects CNVs by comparing a reference genomic sequence ("normal") with the corresponding patient sequence. Each sample has a different fluorescent label so that they can be distinguished, and both are cohybridized to a sample of a specific reference (also normal) DNA fragment of known genomic locus. If the patient sequence is missing part of the normal sequence (deletion) or has the normal sequence plus additional genomic material within that genomic location (eg, a duplication of the same sequence), the sequence imbalance is detected as a difference in fluorescence intensity. For reason, standard CMA (non-single nucleotide polymorphisms (SNP), see following) cannot detect balanced CNVs (equal exchange of material between chromosomes) or sequence inversions (same sequence is present in reverse base pair order) because the fluorescence intensity would not change.

CMA analysis uses thousands of cloned or synthesized DNA fragments of known genomic locus immobilized on a glass slide (microarray) to conduct thousands of comparative reactions at the same time. The prepared sample and control DNA are hybridized to the fragments on the slide, and CNVs are determined by computer analysis of the array patterns and intensities of the hybridization signals. Array resolution is limited only by the average size of the fragment used and by the chromosomal distance between loci represented by the reference DNA fragments on the slide.

There are some differences in CMA technology, most notably in the various types of microarrays. They can differ first by construction; earliest versions were used of DNA fragments cloned from bacterial artificial chromosomes. These have been largely replaced by oligonucleotide (oligos; short, synthesized DNA) arrays, which offer better reproducibility. Finally, arrays that detect hundreds of thousands of SNPs across the genome have some advantages as well. Oligo/SNP hybrid arrays have been constructed to merge the advantages of each. Regardless of the array components used, all microarrays allow the deposition of many thousands of short, DNA probe sequences on a small, solid surface in an orderly fashion. The location of each known probe sequence allows the identification of the test sequence bound to it, and when compared with a control sequence, the identification of missing sequences or sequences with extra copies (ie, copy number variants).

Microarrays may be prepared by the laboratory utilizing the technology, or, more commonly by commercial manufacturers, and sold to laboratories that must qualify and validate the product for use in their assay, in conjunction with computerized software for interpretation. The proliferation of in-house developed and commercially available platforms prompted the American College of Medical Genetics (ACMG) to publish guidelines for the design and performance expectations for clinical microarrays and associated software in the postnatal setting. (2)

Targeted CMA analysis provides high-resolution coverage of the genome primarily in areas containing known, clinically significant CNVs. The ACMG guideline for designing microarrays recommends probe enrichment in clinically significant areas of the genome to maximize detection of known abnormalities but also recommends against the use of targeted arrays in the postnatal setting. Rather, a broad genomic screen is recommended to identify atypical, complex, or completely new rearrangements, and to accurately delineate breakpoints.

Whole-genome CMA analysis has allowed the characterization of several new genetic syndromes, with other potential candidates currently under study. However, the whole-genome arrays also have the disadvantage of potentially high numbers of apparent false-positive results, because benign CNVs are also found in phenotypically normal populations; both benign and pathogenic CNVs are continuously cataloged and to some extent made available in public reference databases to aid in clinical interpretation. Additionally, some new CNVs are neither known to be benign nor causal; these CNVs may

require detailed family history and family genetic testing to determine clinical significance and/or may require confirmation by subsequent accumulation of similar cases and so, for a time, may be considered a CNV of undetermined significance (some may eventually be confirmed true positives or causal, others false positives or benign).

To determine clinical relevance (consistent association with a disease) of CNV findings, the following actions are taken:

- CNVs are confirmed by another method (eg, FISH, multiplex ligation-dependent probe amplification, polymerase chain reaction,).
- CNVs detected are checked against public databases and, if available, against private databases maintained by the laboratory. Known pathogenic CNVs associated with the same or similar phenotype as the patient are assumed to explain the etiology of the case; known benign CNVs are assumed to be nonpathogenic. (3-5)
- A pathogenic etiology is additionally supported when a CNV includes a gene known to cause the phenotype when inactivated (microdeletion) or overexpressed (microduplication). (4)
- The laboratory may establish a size cut-off; potentially pathogenic CNVs are likely to be larger than benign polymorphic CNVs; cut-offs for CNVs not previously reported typically range from 300 kb to 1 Mb. (5-8)
- Parental studies are indicated when CNVs of appropriate size are detected and not found in available databases; CNVs inherited from a clinically normal parent are assumed to be benign polymorphisms whereas those appearing de novo are likely pathogenic; etiology may become more certain as other similar cases accrue. (3, 9)

ACMG has also published guidelines for the interpretation and reporting of CNVs in the postnatal setting, to promote consistency among laboratories and CMA results. (10) Three categories of clinical significance are recommended for reporting: pathogenic, benign, and uncertain clinical significance.

In 2008, the International Standards for Cytogenomic Arrays (ISCA) Consortium was organized (Available online at: https://www.iscaconsortium.org/index.php); it has established a public database containing de-identified whole genome microarray data from a subset of the ISCA Consortium member clinical diagnostic laboratories. Array analysis was carried out on subjects with phenotypes including intellectual disability, autism, and developmental delay. As of November 2011, there were over 28,500 total cases in the database. Additional members are planning to contribute data; participating members use an opt-out, rather than an opt-in approach that was approved by the National Institutes of Health (NIH) and participating center institutional review boards. The database is held at NCBI/NIH (National Center for Biotechnology Information/NIH) and curated by a committee of clinical genetics laboratory experts.

A 2012 update from the ISCA summarizes their experience as a model for ongoing efforts to incorporate phenotypic data with genotypic data to improve the quality of research and clinical care in genetics. (11)

Use of the database includes an intralaboratory curation process, whereby laboratories are alerted to any inconsistencies among their own reported CNVs or other mutations, as well as any not consistent with the ISCA “known” pathogenic and “known” benign lists. The intralaboratory conflict rate was initially about 3% overall; following release of the first ISCA curated track, the intralaboratory conflict rate decreased to about 1.5%. A planned interlaboratory curation process, whereby a group of experts curates reported CNVs/mutations across laboratories, is currently in progress.

The Consortium recently proposed “an evidence-based approach to guide the development of content on chromosomal microarrays and to support interpretation of clinically significant copy number variation.” The proposal defines levels of evidence (from the literature and/or the ISCA and other public databases) that describe how well or how poorly detected mutations or CNVs are correlated with phenotype. The

consortium will apparently coordinate a volunteer effort to describe the evidence for targeted regions across the genome.

The consortium is also developing vendor-neutral recommendations for standards for the design, resolution, and content of cytogenomic arrays using an evidence-based process and an international panel of experts in clinical genetics, clinical laboratory genetics, genomics, and bioinformatics.

Commercially available tests

CMA:
CMA testing is commercially available through many laboratories. The following list is not comprehensive. Signature genomics offers a postnatal microarray (SignatureChip®OS) and a prenatal microarray (Signature PrenatalChip®TE). Both microarrays target over 245 clinically recognized genetic syndromes; these syndromes are listed on their website. SNP microarray analysis can be ordered to run concurrently with either the prenatal or postnatal microarray.

GeneDx's GenomeDx is a whole genome array intended for postnatal cases. It also contains SNP probes and also targets at the exon level 65 genes associated with neurodevelopmental disorders.
GeneDx has a Prenatal Targeted Array, enriched in 100 regions associated with common or novel microdeletion and microduplication syndromes, and also contains SNP probes.

NGS:
Emory Genetics Laboratory offers a NGS ASD panel of 61 genes that target genetic syndromes that include autism or autistic features. These genes have been associated with nonsyndromic autism and genes associated with conditions involved in the differential diagnosis of Rett syndrome and/or Angelman syndrome. The panel is offered as tier 2 testing after tier 1 cytogenetics, molecular and biochemical testing which includes array testing, fragile X CGG repeat analysis and biochemical testing for some metabolic conditions.

Greenwood Genetics Center offers a NGS panel that includes 62 genes and flanking introns. The panel includes autosomal and X-linked genes that represent the most common single gene etiologies associated with a syndrome that includes autism as a significant clinical feature. The test is offered as an option for patients with syndromal autism and normal cytogenetic/array-based testing, or as a 2nd tier test for patients with a phenotype that resembles Rett or Angelman syndrome.

Both the Emory and Greenwood Genetics panels use RainDance technology, and the Greenwood Lab panel was developed jointly with Emory.

The Department of Genetics and Genomic Sciences at the Mount Sinai School of Medicine offers a 30-gene sequencing panel.

MEDICAL POLICY STATEMENT:

BCNEPA will provide coverage for chromosomal microarray analysis when medically necessary.

Testing in children:

Chromosomal microarray analysis may be considered medically necessary for diagnosing a genetic abnormality in children with apparent nonsyndromic cognitive developmental delay/intellectual disability (DD/ID) or autism spectrum disorder (ASD) according to accepted Diagnostic and Statistical Manual of Mental Disorders-IV criteria when all of the following conditions are met (see Guidelines for definitions):

- Any indicated biochemical tests for metabolic disease have been performed, and results are non-diagnostic, and

- *FMR1* gene analysis (for Fragile X), when clinically indicated, is negative, and
- In addition to a diagnosis of nonsyndromic DD/ID or ASD, the child has one or more of the following:
  - o two or more major malformations, or
  - o a single major malformation or multiple minor malformations, in an infant or child who is also small-for-dates, or
  - o a single major malformation and multiple minor malformations, and
- The results for the genetic testing have the potential to impact the clinical management of the patient, and
- Testing is requested after the parent(s) have been engaged in face-to-face genetic counseling with a healthcare professional who has appropriate genetics training and experience.

Chromosomal microarray analysis is considered investigational in all other cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder.

Chromosomal microarray analysis to confirm the diagnosis of a disorder or syndrome that is routinely diagnosed based on clinical evaluation alone (see Guidelines) is not medically necessary.

Panel testing using next-generation sequencing is considered investigational in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder.

Prenatal testing:

Chromosomal microarray analysis is considered investigational for prenatal genetic testing.

GUIDELINES:

Definitions, from the American College of Medical Genetics Guideline, Evaluation of the Newborn with Single or Multiple Congenital Anomalies (12):

- A malformation refers to abnormal structural development.
- A major malformation is a structural defect that has a significant effect on function or social acceptability. Example: ventricular septal defect or a cleft lip.
- A minor malformation is a structural abnormality that has minimal effect on function or societal acceptance. Examples: preauricular ear pit or partial syndactyly (fusion) of the second and third toes.
- A syndrome is a recognizable pattern of multiple malformations. Syndrome diagnoses are often relatively straightforward and common enough to be clinically recognized without specialized testing. Examples include Down syndrome, neural tube defects and achondroplasia. However, in the very young, or in the case of syndromes with variable presentation, confident identification may be difficult without additional testing.

In some cases of CMA analysis, the laboratory performing the test confirms all reported CNVs with an alternative technology such as FISH analysis.

Diagnosis of developmental delay/intellectual disability or autism spectrum disorder

The diagnosis of developmental delay (DD) is reserved for children younger than age 5 years who have significant delay in 2 or more of the following developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living. (15) The diagnosis implies DD

that may be significant and may predict life-long disability, although not all children diagnosed with DD will later be diagnosed with intellectual disability (ID).

ID is a life-long disability diagnosed at or after age 5 years when intelligence quotient (IQ) testing is considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-IV), defines patients with ID as having an IQ less than 70, onset during childhood, and dysfunction or impairment in more than 2 of areas of adaptive behavior or systems of support.

According to the DSM-IV, pervasive developmental disorders (PDD) encompass 5 conditions: autistic disorder, Asperger disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS), childhood disintegrative disorder, and Rett syndrome. While the term autism spectrum disorder (ASD) is not mentioned in the DSM-IV, it is now accepted to include the first 3 in this list. However, ASD, PDD, and autism are often used interchangeably. (16) These conditions are characterized by varying degrees of restrictions in communication and social interaction, and atypical behaviors.

Some children present with features of both DD/ID and of autism. For example, Yeargin-Allsopp et al (17) reported that nearly 70% of children with a validated diagnosis of ASD, sampled from 5 metropolitan Atlanta counties, had cognitive impairment. The evaluation pathway depends on the pediatrician, consulting specialists, and their consensus on the primary neurodevelopmental diagnosis.

RATIONALE:

Postnatal CMA analysis:

Chromosomal microarray analysis (CMA) offers a higher resolution approach to detecting the presence of chromosomal alterations that have been associated with cases of developmental delay/intellectual disability (DD/ID) or autism spectrum disorder (ASD) compared with karyotyping and ancillary testing. However, the diagnostic yield remains low in unselected populations without accompanying signs and/or symptoms. In individuals with apparent nonsyndromic DD/ID, or suspected ASD and accompanying malformations, the diagnostic yield is much higher and is higher than the yield of karyotype testing.

Evidence on the clinical benefit of CMA testing is largely anecdotal. Cases have been documented in which the information derived from testing ends a long diagnostic odyssey, aids in planning for surveillance or management of associated comorbidities, and assists in future reproductive decision making. While systematic studies of the impact of CMA analysis on patient outcomes is lacking, the improvement in diagnostic yield has been well-demonstrated, and feedback from physician specialty societies, academic medical centers, and in respected guidelines is consistent in supporting the clinical benefit of CMA testing for defined populations. As a result, CMA may be considered medically necessary in individuals with developmental delay or ASDs who meet the clinical criteria defined the policy statement.

Prenatal CMA analysis:

When used in prenatal cases where there is an abnormality detected on ultrasound and a normal karyotype, CMA testing will detect clinically relevant abnormalities in a small percentage of cases. However, the incremental benefit in health outcomes that results from detecting such abnormalities in the prenatal period is not clear. For routine screening of pregnant women, the yield of abnormal findings is less and the clinical utility of CMA in detecting chromosomal abnormalities in prenatal specimens is unknown. The potential risk for findings of uncertain clinical significance may result in parental anxiety and challenges in genetic counseling. Therefore, the use of CMA analysis in the prenatal setting is considered investigational.

NGS panels:

Published data on analytic and clinical validity, clinical utility and variants of unknown significance using next-generation sequencing (NGS) panels in this setting are lacking, and therefore, panel testing using NGS is considered investigational in all cases of suspected genetic abnormality in children with DD/ID or ASD.

Practice Guidelines and Position Statements

American Congress of Obstetricians and Gynecologists Committee Opinion 581, 2013**:**
The College and the Society for Maternal-Fetal Medicine offer the following recommendations for the use of CMA in prenatal diagnosis:

- In patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis, chromosomal microarray analysis is recommended. This test replaces the need for fetal karyotype.
- In patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed.
- Most genetic mutations identified by chromosomal microarray analysis are not associated with increasing maternal age; therefore, the use of this test for prenatal diagnosis should not be restricted to women aged 35 years and older.
- In cases of intrauterine fetal demise or stillbirth when further cytogenetic analysis is desired, chromosomal microarray analysis on fetal tissue (ie, amniotic fluid, placenta, or products of conception) is recommended because of its increased likelihood of obtaining results and improved detection of causative abnormalities.
- Limited data are available on the clinical utility of chromosomal microarray analysis to evaluate first-trimester and second-trimester pregnancy losses; therefore, this is not recommended at this time.

(There is controversy as to the sensitivity of routine ultrasound in detecting fetal anomalies. A review of 36 studies involving more than 900,000 fetuses found an overall sensitivity of 40.4% [range, 13.3%-82.4%]. (41) Studies on the use of ultrasound to detect prenatal anomalies vary with regard to the definition of major versus minor fetal anomalies, the level of risk in the study population [high vs low risk], the expertise of the ultrasound operators and the ascertainment of anomalies).

The American Academy of Neurology and the Practice Committee of the Child Neurology Society updated their guideline regarding the evaluation of unexplained global DD/ID with information on genetic and metabolic (biochemical) testing in order to accommodate advances in the field. (1) The guidelines conclude that CMA testing has the highest diagnostic yield in children with DD/ID, that the often complex results require confirmation and careful interpretation, often with the assistance of a medical geneticist and that CMA should be considered the first-line test. The guidelines acknowledge that “Research is sorely lacking on the medical, social, and financial benefits of having an accurate etiologic diagnosis.”

The American College of Medical Genetics (ACMG) published guidelines on array-based technologies and their clinical utilization for detecting chromosomal abnormalities. (42) Chromosomal microarray testing for copy number variation is recommended as a first-line test in the initial postnatal evaluation of individuals with the following:

A. Multiple anomalies not specific to a well-delineated genetic syndrome
B. Apparently non-syndromic developmental delay/ intellectual disability
C. Autism spectrum disorders

ACMG also recommends against use of CMA in cases of multiple miscarriages.

Additional ACMG guidelines have been published for the design and performance expectations for clinical microarrays and associated software (2) and for the interpretation and reporting of CNVs, (10) both intended for the postnatal setting (see Description). A 2013 update includes recommendations for validation of microarray methodologies for both prenatal and postnatal specimens. (43)

The International Standard Cytogenomic Array Consortium published a Consensus Statement in which they recommend offering CMA as the first-tier genetic test, in place of G-banded karyotype, for patients with unexplained DD/ID, ASD, or multiple congenital anomalies (MCA). “Except in special cases, such as those involving family history of multiple miscarriages, a karyotype is not cost effective in a child with DD/ID, ASD, or MCA and a negative array study. CMA testing is not inexpensive, but the cost is less than the cost of a G-banded karyotype plus a customized FISH test such as subtelomeric FISH, and the yield is greater.” (6)

A 2013 guidelines update from the ACMG states that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of autism spectrum disorder is recommended, with the recommendation being for first-tier to include FXS [fragile X syndrome] and CMA, and second tier to include MECP2 and PTEN testing. (44) The guideline states that “this approach will evolve with continued advancements in diagnostic testing and improved understanding of the ASD phenotype. Multiple additional conditions have been reported in association with an ASD phenotype, but none of these has been evaluated in a large prospective cohort. Therefore, a future third tier of evaluation is a distinct possibility. Further studies would be needed to elevate the evidence to the point of recommended testing. Alternatively, advances in technology may permit bundling of individual tests into an extended, more readily accessible, and less expensive platform”. The accumulating evidence using next-generation sequencing (third tier testing) “will increase the diagnostic yield even more over the next few years.”

Medicare National Coverage

None

DEFINITIONS:

N/A

CODING:

- **The identification of a code in this section does not denote coverage or separate reimbursement.**
- Covered procedure codes are dependent upon meeting criteria of the policy and appropriate diagnosis code.
- The following list of codes may not be all-inclusive, and are subject to change at any time.
- Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

PROCEDURE CODES

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SOURCES:

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APPROVALS:

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