Comparative Genomic Hybridization (CGH)/Chromosomal Microarray Analysis (CMA) for Autism Spectrum Disorders, Developmental Delay, Intellectual Disability and Congenital Anomalies

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Related Coverage Resources

Autism Spectrum Disorders/Pervasive Developmental
  Disorders: Assessment and Treatment
  Genetics

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Many benefit plans limit coverage of genetic testing and genetic counseling services. Please refer to the applicable benefit plan language to determine benefit availability and terms, conditions and limitations of coverage for the services discussed in this Coverage Policy.

Comparative genomic hybridization (CGH)/chromosomal microarray analysis (CMA) for reproductive and prenatal indications is discussed in the Cigna Coverage Policy: Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis.
Pre- and post-test genetic counseling is required for an individual undergoing genetic testing discussed in this Coverage Policy. Please refer to indications for testing* for additional information regarding genetic testing.

**Comparative Genomic Hybridization (CGH)/Chromosomal Microarray Analysis (CMA)**

**Medically Necessary**

Comparative genomic hybridization (CGH)/chromosomal microarray (CMA) genetic testing (CPT® codes 81228, 81229, S3870) is considered medically necessary when the indications for testing* listed below are met and when a recommendation for testing is confirmed by ONE of the following:

- an independent Board-Certified or Board-Eligible Medical Geneticist
- an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
- a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).

who:
- has evaluated the individual
- completed a three generation pedigree
- intends to engage in post-test follow-up counseling

*Indications for Testing

Comparative genomic hybridization (CGH)/chromosomal microarray analysis (CMA) (CPT codes 81228, 81229, S3870) is considered medically necessary for ANY of the following indications:

- autism spectrum disorder in which the phenotypic characteristics of a specific genetic disorder are absent
- non-syndromic global developmental delay or intellectual disability in which the phenotypic characteristics of a specific genetic disorder are absent
- multiple congenital anomalies not specific to a well-delineated genetic syndrome

Repeat CGH/CMA is considered medically necessary when ALL of the following criteria are met:

- Medical necessity for testing is established based on the criteria noted above.
- Results of repeat testing will directly impact clinical decision-making and/or clinical outcome for the individual being tested.
- Testing method is considered scientifically valid for identification of the genetic abnormality, disorder or syndrome.
- Request for testing uses a CGH/CMA methodology not previously employed in testing of the individual.

**Not Medically Necessary**
CGH/CMA for the purposes of genetic testing in the general population is considered not medically necessary.

Overview

This Coverage Policy addresses germline genetic testing using comparative genomic hybridization (CGH)/chromosomal microarray analysis (CMA).

CGH/CMA is a type of advanced genetic test that identifies certain types of changes in an individual's deoxyribonucleic acid (DNA) sequence. It is frequently used when there is an inability to identify a specific genetic disorder by conventional cytogenetic testing in an individual with unexplained developmental delay, autism spectrum disorders, intellectual disability and multiple congenital anomalies.

General Background

Genetic Counseling

Genetic counseling is required both before and after comparative genomic hybridization (CGH)/chromosomal microarray analysis (CMA) genetic testing to interpret family and medical histories and assess the chance of disease occurrence and recurrence. Genetic counseling also allows an opportunity to educate regarding inheritance, testing, management prevention and resources, and counsel to promote informed choices and adaptation to risk or condition.

Genetic counseling is defined as the process of helping individuals understand and adapt to the medical, psychological and familial indications of genetic contributions to disease. Genetic counseling services span the life cycle from preconception counseling to infertility evaluation, prenatal genetic screening and diagnosis, and include predisposition evaluation and genetic diagnosis (National Society of Genetic Counselors [NSGC]; Edwards, 2010).

A variety of genetics professionals provide these services: Board-Certified or Board-Eligible Medical Geneticists, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor, and genetic nurses credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC). Individuals should not be employed by a commercial genetic testing laboratory, although counseling services by these individuals are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself.

Comparative Genomic Hybridization (CGH)/Chromosomal Microarray Analysis (CMA)

Conventional cytogenetic tests identify known genetic abnormalities when a specific clinical syndrome is suspected. Conventional cytogenetic testing is used to identify balanced rearrangements (e.g., translocations or inversions), alterations in chromosome structure, sequence alterations, copy number changes (deletion, duplication and amplification), single-base pair mutation, 20% or lower level of mosaicism, and some types of polyploidy, including triploidy and tetraploidy.

A microarray is a type of technology platform that allows rapid analysis of thousands of different deoxyribonucleic acid (DNA) sequences. Comparative genomic hybridization (CGH)/chromosomal microarray analysis (CMA), also known as molecular karyotyping, is a form of array-based technology that has been proposed as an alternative testing method to conventional cytogenetic testing for a number of indications, including autism spectrum disorders, global developmental delay, intellectual disability and unspecified congenital anomalies.

CGH/CMA allows exploration of the genome to identify submicroscopic genomic copy number variations ([CNVs], e.g., deletion and duplication) for a number of indications when a specific genetic disorder has not been identified by conventional cytogenetic testing. CGH provides high resolution comparison of the differences from
one sample of DNA to another to detect copy number variations of any particular segment. The whole genome array, also known as arrayCGH (aCGH), has a wider coverage over the entire human genome and can discover new CNVs of unknown clinical significance.

Due to its ability to examine the entire genome at high resolution and specifically target copy number variations (CNVs), it is estimated that CGH provides 10%-15% more information than conventional testing in some circumstances when CNV is the etiologic mutagenic defect. ArrayCGH can identify an additional 5% of abnormalities compared to the targeted array (BlueCross BlueShield Association [BCBSA], 2009; Edelmann and Hirschhorn, 2009; Burton, 2006). When a microarray is used to identify CNVs, its sensitivity approaches 100%. However, CGH is not without limitations. In contrast to conventional cytogenetic tests, CGH does not identify balanced rearrangements (e.g., translocations or inversions), alterations in chromosome structure that are not represented on the array, sequence alterations, single-base pair mutation, 20% or lower level of mosaicism, and some types of polyploidy, including triploidy and tetraploidy. Its false positive rate has been reported to be as high as 7%. When CGH identifies a CNV of known clinical significance, conventional testing is typically used to confirm the findings of CGH.

If an unknown CNV is detected, a genomic database is accessed to see if the abnormality has been previously reported and whether or not it has been associated with a benign or proposed pathogenic condition. Evaluation of parental samples is sometimes performed to determine if the abnormality is inherited or has arisen de novo. CNVs that appear in normal individuals have been reported to be as high as 12%, making diagnostic interpretation and identification of CNVs’ clinical significance difficult. Various chromosomal microarray (CMA) platforms are currently being used and no one platform has been found to be clearly superior to all of the others for clinical purposes. There is an absence of published clinical standards for coverage and resolution which results in a lack of uniformity in arrays used in various laboratories (Novelli, et al., 2012; Miller, et al., 2010; BCBS, 2009; Pickering et al., 2008; Schaefer, et al., 2008; Burton, 2006).

**Clinical Utility**

CGH testing has been established to have clinical utility for genetic evaluations for an individual diagnosed with autism spectrum disorder, global developmental delay and intellectual disability in which the phenotypic characteristics of a specific genetic disorder are absent, and/or when multiple or unspecified congenital anomalies are not specific to a well-delineated genetic syndrome.

Developmental delay typically refers to a child younger than age six years who presents with delays in the attainment of developmental milestones at the expected age and demonstrates deficits in learning and adaptation. Global developmental delay involves a significant delay in two or more developmental domains, including gross/fine motor, speech/language, cognition, social/personal, and activities of daily living. The delays may be significant and predictive of the development of cognitive and/or intellectual disability (American Academy of Neurology, 2011; Moeschler, et al., 2014).

According to the American Association on Intellectual and Developmental Disabilities (AAIDD) intellectual disability is characterized by significant limitations both in intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills. This disability originates before the age of 18. Generally, the individual has an intelligence quotient (IQ) score of below 70–75 and is compromised in the areas of conceptual skills, social skills, and practical skills (2013). Intellectual disability can be caused by genetic abnormalities seen in various syndromes such as: Down syndrome, Edwards syndrome, Patau syndrome, Fragile X syndrome, Rett syndrome, Angelman syndrome or Prader-Willi (Prader-Labhart-Willi) syndrome (Zelden, et al., 2014).

Congenital anomalies, or birth defects, are morphologic defects present at birth, may present in various patterns, and are usually multifactorial. In 10–15% of cases, anomalies can be attributed to chromosomal aberrations (Maitra and Kumar, 2005). Examples of congenital anomalies include: cleft palate; clubfoot; spina bifida; vision and hearing impairments; and respiratory, renal and cardiac malformations. Congenital anomalies may be coupled with intellectual disability, and global developmental delay.

GCH/CMA allows exploration of the genome to identify submicroscopic genomic copy number variations (CNVs), e.g., deletion and duplication) for a number of indications when a specific genetic disorder has not been identified by conventional cytogenetic testing. The results of CGH are expected to impact the clinical
management by using gene-related information gained from CGH that would otherwise not be known to impact treatment and intervention. The clinical utility of microarray testing includes: provision of additional information leading to family reassurance, guidance for family planning, early identification of special needs, avoidance of ongoing diagnostic assessment where no clear diagnosis exists, predicted prognosis for the patient, pharmacotherapy and identification of medical risk and the need for ongoing monitoring.

Repeat Testing
As microarray technology has continued to evolve there have been improvements in the ability to detect chromosomal changes not previously identified when using a CMA testing platform with lower resolution. Repeat testing may be appropriate in selected individuals if medically necessity is established based on criteria noted in this Coverage Policy and results of the testing will directly impact clinical decision-making and management of the individual being tested. The proposed test should be scientifically validated to identify a genetic abnormality, disorder or syndrome and should not have previously been used for testing of the individual.

U.S. Food and Drug Administration (FDA)
Approval by the FDA for array comparative genomic hybridization tests is not required. CGH is a laboratory-developed test performed by various Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Array platforms, assay protocol, and analysis systems vary from laboratory to laboratory.

Literature Review

Autism Spectrum Disorder (ASD)
Siu et al. (2016) reported outcomes of a prospective study involving an adult (n=41) and pediatric (n=27) cohort of 68 Chinese individuals with ASD using array CGH. Fifteen copy number variants were detected and eight of them were clinically significant. The overall diagnostic yield was 11.8%. Diagnostic yields in the adult and pediatric groups were 12.2% and 11.1%, respectively.

Shen et al. (2010) evaluated 933 patients with a predominant diagnosis of autistic disorder (n=477) and pervasive developmental disorder-not otherwise specified (PDD-NOS) (n=454) to compare the outcomes of karyotype testing, aCGH and Fragile X testing. CGH testing was performed by 244k or 500k whole genome arrays (n=697) or v5.0 single-nucleotide polymorphism arrays (n=108). Karyotyping identified 19 of 852 patients (2.23%) with abnormal results; array CGH (aCGH) detected eight abnormalities in the 19 patients with abnormal karyotype. Ten of the 19 had balanced rearrangements that appeared normal and were not detected by aCGH. Fragile X testing identified 4 abnormalities. aCGH identified deletions or duplications in 154 of 848 patients (18.2%) with 59 being considered abnormal and possibly significant. A total of 95 abnormalities were considered of VOUS. Abnormal or possible significant results identified by CGH targeted array were 5.3% and 7.3% by whole genome array. Fifty of the abnormalities noted on aCGH were below the size range detected by karyotype. A greater number of individuals diagnosed with intellectual disability, dysmorphic features, and seizure disorders had abnormalities detected by aCGH compared to those identified by karyotype or Fragile X testing. Although aCGH detected more abnormalities, the authors noted that aCGH could not replace a G-banded karyotype in this population because of the inability of aCGH to detect balanced rearrangements. However, according to the authors, missed diagnosis may occur in 5% of ASD cases without aCGH testing. The impact of aCGH results on clinical management decisions for this patient population was not discussed. Limitations of the study noted by the authors include concerns regarding credibility of diagnosis and bias based on ascertainment of patients through tertiary care centers cannot be excluded.

To determine the benefit of CGH as a diagnostic tool, Jacquemont et al. (2006) conducted whole-genome CGH using a 1 megabase (Mb) resolution (Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK) on 29 patients with idiopathic syndromic ASD. The patients had normal high-resolution karyotype (approximately 800 bands), biochemical tests and hematological results prior to CGH testing. Thirty-three chromosome gains or losses in 22 patients were identified by CGH. Twenty-three variants were considered normal. The ten remaining abnormalities were considered possible pathogenic and were validated by at least one independent method. CHG identified eight clinically relevant abnormalities in 27.5% of the patients.

Global Developmental Delay, Intellectual Disability and Congenital Abnormalities
Several prospective and retrospective studies and systematic reviews/meta-analyses involving >18,000 individuals with developmental delay, intellectual disability and congenital anomalies have evaluated the clinical
utility of CGH testing for diagnosis and clinical management (McCormack, 2016; Lee, 2013; Barunik, 2014; Chong, 2014; Ellison, 2012; Hayashi, 2011; Sagoo, 2009; Pickering, 2008; Shao, 2008; Shevell; 2007; Baris, 2007; Engels, 2007; Subramonia-Iyer, 2007; Wong, 2005). For this subpopulation, follow-up clinical management included additional diagnostic testing, glucose monitoring, platelet count monitoring, and specialty referral. Various microarray platforms were used in testing including bacterial artificial chromosome (BAC) probes with targeted coverage of the genome, BAC-based arrays, oligonucleotide-based whole genome arrays and 135K custom designed arrays. Study limitations include heterogeneous patient population, variability in study design, variation in the microarray used for testing and high false positive rate, up to 7% in the study by Subamonia-Iyer.

The diagnostic yield of casual genetic abnormalities detected by CGH ranged from 10-20%, as reported by the systematic reviews. In the study by Ellison, 35% of all pathogenic copy number changes warranted further clinical action. Data suggest that CGH is an acceptable option for this subpopulation when other conventional cytogenetic tests are negative.

Professional Societies/Organizations
For a summary of professional society recommendations/guidelines regarding CGH/CMA genetic testing please click here.

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative (2014): No relevant statements.

Use Outside of the US
For a summary of professional society recommendations/guidelines regarding CGH/CMA genetic testing please click here.

Appendix A

PROFESSIONAL SOCIETY/ORGANIZATION RECOMMENDATIONS/GUIDELINES

Comparative Genomic Hybridization (CGH)/Chromosomal Microarray Analysis (CMA)

American College of Medical Genetics and Genomics (ACMG): The 2013 guideline update for genetic evaluation for autism spectrum disorders (ASDs) (Schaefer and Mendelsohn, 2013) lists CMA (oligonucleotide array-comparative genomic hybridization or single-nucleotide polymorphism array) as a first tier diagnostic test for the evaluation of ASDs. If the individual has a recognizable syndrome firmly documented as associated with ASDs (e.g., Angelman syndrome, Fragile X syndrome), further investigation into the etiology is not necessary. For genetic conditions that have been reported in association with ASDs for which the reported association is not convincing, ACMG recommends that an etiologic evaluation of the ASD be conducted, including CGH.

In the 2010 guidelines on array-based technology, ACMG (Manning, et al., 2010) recommended the following:

- CMA testing for copy number variations (CNV) is recommended as a first-line test in the initial postnatal evaluation of individuals with the following:
  - multiple anomalies not specific to a well-delineated genetic syndrome
  - apparently nonsyndromic developmental delay/intellectual disability
  - autism spectrum disorders
- Further determination of the use of CMA testing for the evaluation of the child with growth retardation, speech delay, and other less well-studied indications is recommended, particularly by prospective studies and aftermarket analysis.
- Appropriate follow-up is recommended in cases of chromosome imbalance identified by CMA, to include cytogenetic/FISH studies of the patient, parental evaluation, and clinical genetic evaluation and counseling.
ACMG noted that clinicians ordering the test need to be aware of the different clinical platforms (e.g., BAC versus oligo, targeted versus whole genome, and SNP), the variation in resolution among arrays and the information each provides. The College reminded clinicians that the limitations of aCGH include the inability to identify balanced chromosomal rearrangements (e.g., translocations, inversions), or differentiate free trisomies from unbalanced Robertsonian translocations. The ACMG also noted some aneuploidies and marker chromosomes may be missed; the accuracy of detecting low levels of mosaicism has been questioned; interpretation of the significance of a rare copy number change can be incomplete and that triploidy will not be detected by some forms of microarray. According to ACMG, the clinician should understand what type of follow-up tests will be performed, and on whom, in the event of abnormal results. Further, for deletions and duplications, parental studies (by fluorescence in situ hybridization [FISH] or metaphase preparations, if possible) should be conducted to rule out the presence of a chromosomal rearrangement such as an insertion or inherited duplication.

American Academy of Neurology ([AAN], 2015): On behalf of the AAN, Satya-Murti et al. published guidelines for chromosomal microarray analysis for intellectual disabilities. The Guideline notes the criteria do not represent a binding standard of care and that the criteria are proposed as clinical contexts that readily support the use of microarray testing.

Chromosomal microarray analysis is reasonable and medically necessary for diagnosing a genetic abnormality when all of the following conditions are met:

- In children with developmental delay/intellectual disability (DD/ID) or an autism spectrum disorder (ASD) according to accepted Diagnostic and Statistical Manual of Mental Disorders-IV criteria;
- If warranted by the clinical situation, biochemical testing for metabolic diseases has been performed and is negative;
- Targeted genetic testing, (for example: FMR1 gene analysis for Fragile X), if or when indicated by the clinical and family history, is negative;
- The results for the testing have the potential to impact the clinical management of the patient;
- Face-to-face genetic counseling with an appropriately trained and experienced healthcare professional has been provided to the patient (or legal guardian(s) if a minor child). Patient or legal guardians have given their consent for testing. Cognitively competent adolescent patients have given their assent for testing as well.

The Guideline notes the presence of major and minor congenital malformations and dysmorphic features should be considered evidence that microarray testing will be more likely to yield a diagnosis. However, dysmorphic and syndromic features are not required for testing.

Limitations of testing include the following:

- Absence of an appropriate and informed consent from the patient, a parent (in case of minors) or a guardian (in persons with cognitive impairment) is necessary prior to testing.
- Inadequacy of knowledge about the test and the actions required to address the results of the test.
- A lack of clear value for chromosomal microarray analysis in all instances other than those delineated above. Under these circumstances the test is considered investigational.
- Chromosomal microarray analysis would not be considered medically necessary when a diagnosis of a disorder or syndrome is readily apparent based on clinical evaluation alone.

American Academy of Neurology (AAN)/Child Neurology Society (CNS) (2011): A systematic review was conducted to determine the diagnostic yield of genetic and metabolic evaluation of children with global developmental delay or intellectual disability (GDD/ID). In their recommendations for future research, AAN/CNS noted that research is lacking on the medical, social, and financial benefits of having an accurate etiologic diagnosis in this population and the ability to rate diagnostic tests on the basis of factors other than diagnostic yield, such as the availability of effective treatment, would have a positive influence on clinical practice.
American Academy of Pediatrics ([AAP], 2014): The 2014 AAP guidance for the clinical genetic evaluation of children with intellectual disability and developmental delays notes that chromosome (genomic) microarray is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology. If diagnosis is unknown and no clinical diagnosis is strongly suspected, begin the stepwise evaluation process: chromosomal microarray should be performed in all (Moeschler, et al., 2014).

National Institute for Health and Clinical Excellence (United Kingdom) (NICE): In a 2011 guidance document on autism, NICE noted that more genetic abnormalities in autism are being identified, but their causal role in autism is not clear. Currently, the yield of abnormal genetic results using CGH array is reported to be higher in individuals with dysmorphic features and/or intellectual disability. NICE noted that it is important to have a better understanding of the diagnostic yield of CGH array testing before extending it to a wider population. It is also essential to identify any negative consequences that may result from routine testing.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
   2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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<th>CPT® Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>81228</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g., bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
</tr>
<tr>
<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
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<tr>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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<th>HCPCS Codes</th>
<th>Description</th>
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<tr>
<td>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes</td>
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<tr>
<td>S3870</td>
<td>Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability</td>
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References


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