Genetic Testing for FMR1 Variants (Including Fragile X Syndrome)

Policy # 00380
Original Effective Date: 08/21/2013
Current Effective Date: 08/15/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing for fragile X mental retardation 1 (FMR1) variants to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility will be considered for fragile X mental retardation 1 (FMR1) variants for the following patient populations:

- Individuals with characteristics of fragile X syndrome (FXS) or a fragile X–associated disorder, including:
  - Individuals with intellectual disability, developmental delay, or autism spectrum disorder;
  - Women with primary ovarian insufficiency under the age of 40 in whom fragile X–associated primary ovarian insufficiency is suspected;
  - Individuals with neurologic symptoms consistent with fragile X–associated tremor or ataxia syndrome.
- Individuals who have a personal or family history of fragile X syndrome (FXS) who are seeking reproductive counseling, including:
  - Individuals who have a family history of fragile X syndrome (FXS) or a family history of undiagnosed intellectual disability;
  - Affected individuals or relatives of affected individuals who have had a positive cytogenetic fragile X test result who are seeking information on carrier status;
  - Prenatal testing of fetuses of known carrier mothers.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

The use of genetic testing for fragile X mental retardation 1 (FMR1) variants when patient selection criteria are not met or for all other uses is considered to be **investigational.***

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Policy Guidelines
Physical and behavioral characteristics of FXS include typical facial features, such as an elongated face with prominent forehead, protruding jaw, and large ears. Connective tissue anomalies include hyperextensible finger and thumb joints, hand calluses, velvet-like skin, flat feet, and mitral valve prolapse. The characteristic appearance of adult males includes macroorchidism. Patients may show behavioral problems including autism spectrum disorder, sleeping problems, social anxiety, poor eye contact, mood disorders, and hand-flapping or biting. Another prominent feature of the disorder is neuronal hyperexcitability, manifested by hyperactivity, increased sensitivity to sensory stimuli, and a high incidence of epileptic seizures.

TESTING STRATEGY
Detection of CGG triplet repeats in the *FMR1* gene can occur sequentially or in parallel with determination of methylation status:

1. In sequential testing, detection of CGG triplet repeats in *FMR1* is performed first. If a large number of repeats (eg, >55) is detected, reflex methylation testing can be performed to determine methylation status
2. In parallel testing, detection methods such as methylation-specific polymerase chain reaction allow for detection of both the size of CGG triplet repeats in *FMR1* and methylation status.

CYTOGENETIC TESTING
Cytogenetic testing was used before the identification of the *FMR1* gene and is significantly less accurate than the current DNA test. The method is no longer considered an acceptable diagnostic method according to American College of Medical Genetics and Genomics standards.

GENETIC COUNSELING
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

FRAGILE X

Fragile X Syndrome
FXS is the most common cause of heritable intellectual disability, characterized by moderate intellectual disability in males and mild intellectual disability in females. FXS affects approximately 1 in 4000 males and 1 in 8000 females. In addition to intellectual impairment, patients present with typical facial features, such

as an elongated face with prominent forehead, protruding jaw, and large ears. Connective tissue anomalies include hyperextensible finger and thumb joints, hand calluses, velvet-like skin, flat feet, and mitral valve prolapse. The characteristic appearance of adult males includes macroorchidism. Patients may show behavioral problems including autism spectrum disorders, sleeping problems, social anxiety, poor eye contact, mood disorders, and hand-flapping or biting. Another prominent feature of the disorder is neuronal hyperexcitability, manifested by hyperactivity, increased sensitivity to sensory stimuli, and a high incidence of epileptic seizures.

FXS is associated with the expansion of the CGG trinucleotide repeat in the fragile X mental retardation 1 (*FMR1)* gene on the X chromosome. FXS is associated with the expansion of the *FMR1* gene CGG triplet repeat above 200 units in the 5′ untranslated region of *FMR1*, leading to hypermethylation of the promoter region followed by transcriptional inactivation of the gene. FXS is caused by a loss of the fragile X mental retardation protein, which is believed to play a key role in early brain development and brain function.

Fragile X–Associated Disorders
Patients with a premutation (55-200 CGG repeats) may develop an *FMR1*-related disorder, such as fragile X–associated tremor or ataxia syndrome or, in women, fragile X–associated premature ovarian insufficiency (FXPOI). Fragile X–associated tremor or ataxia syndrome is a late-onset syndrome, comprising progressive development of intention tremor and ataxia, often accompanied by progressive cognitive and behavioral difficulties, including memory loss, anxiety, reclusive behavior, deficits of executive function, and dementia. FXPOI is characterized by ovarian failure before the 40 years of age.

Diagnosis
DNA studies are used to test for FXS. Cytogenetic testing was used before identification of the *FMR1* gene and is significantly less accurate than the current DNA test. Genotypes of individuals with symptoms of FXS and individuals at risk for carrying the variant can be determined by examining the size of the trinucleotide repeat segment and methylation status of the *FMR1* gene. Two main approaches are used: polymerase chain reaction (PCR) and Southern blot analysis.

PCR analysis uses flanking primers to amplify a fragment of DNA spanning the repeat region. Thus, the sizes of PCR products are indicative of the approximate number of repeats present in each allele of the individual being tested. The efficiency of PCR is inversely related to the number of CGG repeats, so large mutations are more difficult to amplify and may fail to yield a detectable product in the PCR assay. This, and the fact that no information is obtained about *FMR1* methylation status, are limitations of the PCR approach. On the other hand, PCR analysis permits accurate sizing of alleles in the normal zone, the “gray zone,” and premutation range on small amounts of DNA in a relatively short turnaround time. Also, the assay is not affected by skewed X-chromosome inactivation.

The difficulty in fragile X testing is that the high fraction of GC bases in the repeat region makes it extremely difficult for standard PCR techniques to amplify beyond 100 to 150 CGG repeats. Consequently, Southern blot analysis is commonly used to determine the number of triplet repeats in FXS and methylation status.

Alternatives to Southern blotting for determining *FMR1* methylation status have been developed. They include methylation-sensitive PCR and methylation-specific melting curve analysis. One test currently available in Europe (FastFraX; TNR Diagnostics, Singapore) combines a direct triplet repeat-primed PCR with melting curve analysis for detecting CGG expansions.

In 2011, a panel of genotyping reference materials for FXS was developed and is expected to be stable over many years and available to all diagnostic laboratories. A panel of 5 genomic DNA samples (normal female, female premutation, male premutation, male full mutation, and female full mutation) was endorsed by the European Society of Human Genetics and approved as an International Standard by the Expert Committee on Biological Standardization at the World Health Organization.

Treatment
Current approaches to therapy are supportive and symptom-based. Psychopharmacologic intervention to modify behavioral problems in a child with FXS may represent an important adjunctive therapy when combined with other supportive strategies including speech therapy, occupational therapy, and special education services. Medication management may be indicated to modify attention deficits, impaired impulse control, and hyperactivity. Anxiety-related symptoms, including obsessive-compulsive tendencies with perseverative behaviors, also may be present and require medical intervention. Emotional lability and episodes of aggression and self-injury may be a danger to the child and others around him or her; therefore, the use of medication(s) to modify these symptoms also may significantly improve an affected child's ability to participate more successfully in activities in the home and school settings.

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. The Xpansion Interpreter®‡ test is available under the auspices 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.

Asuragen offers the Xpansion Interpreter test, which analyzes AGG sequences that interrupt CGG repeats and may stabilize alleles, protecting against expansion in subsequent generations.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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 sources.

INDIVIDUALS WITH CHARACTERISTICS OF A FRAGILE X SYNDROME OR A FRAGILE X–ASSOCIATED DISORDER

Clinical Context and Test Purpose

Fragile X Syndrome

Diagnosis of FXS may include a genetic test that determines the number of CGG repeats in the fragile X gene. The patient is classified as normal, intermediate ("gray zone"), premutation, or full mutation based on the number of CGG repeats (see Table 1). Approximately 1% to 3% of children initially diagnosed with autism are shown to have FXS, with expansion of the CGG trinucleotide repeat in the *FMR1* gene to full mutation length. A considerable number of children evaluated for autism have been found to have a *FMR1* premutation (55-200 CGG repeats). Fragile X-associated disorders (fragile X associated premature ovarian insufficiency [FXPOI] and fragile X-associated tremor or ataxia) are associated with a *FMR1* premutation (55-200 CGG repeats).

Table 1. Classifications of CGG Repeat Length

Mutation Classification	CGG Repeat Length	Methylation Status	Variant Classification
Full mutation	>200 to 230	Methylated	Pathogenic variant
Premutation	55 to 200	Unmethylated	Pathogenic variant
Intermediate	45 to 54	Unmethylated	Uncertain variant
Normal	5 to 44	Unmethylated	Benign variant

The purpose of *FMR1* variant testing in patients who have characteristics of FXS or a fragile X–associated disorder is to provide an accurate diagnosis and improve treatment of the associated behavioral and medical conditions.

The question addressed in this evidence review is: Does *FMR1* variant testing in patients with conditions or family history consistent with the presence of a pathogenic *FMR1* variant (eg, premutation or mutation) improve health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are:

- Individuals with characteristics of FXS or a fragile X–associated disorder, including:

- Individuals of either sex with intellectual disability, developmental delay, or autism spectrum disorder.
- Women with primary ovarian failure under the age of 40 in whom FXPOI is suspected.
- Individuals with neurologic symptoms consistent with fragile X–associated tremor or ataxia syndrome.

Interventions
The relevant interventions of interest are testing for *FMR1* variant and methylation status.

Comparators
Standard clinical evaluation without genetic testing is used to diagnose FXS or a fragile X–associated disorder.

Outcomes
The general outcomes of interest are an accurate diagnosis of patients with FXS or fragile X–associated disorders and improved management of the disorder.

Timing
This test would be performed when characteristics of FXS or fragile X–associated disorders are identified.

Setting
A number of laboratories can assess for the *FMR1* variant and methylation status.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or

adverse response. The term predictive test is often used to refer to the response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or predicting a response to therapy.

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).

Clinical sensitivity and specificity are 99% for premutation and full variant alleles. Although diagnostic errors can occur due to rare sequence variations, CGG repeat expansion full mutations account for more than 99% of cases of FXS. Therefore, tests that measure the CGG repeat region of the *FMR1* gene are clinically valid. Tests have been shown to be more than 99% sensitive. Positive results are 100% specific. There are no known forms of fragile X mental retardation protein deficiency that do not map to the *FMR1* gene.

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.

The conditions caused by abnormal CGG repeats in the *FMR1* gene—FXS, fragile X–associated tremor or ataxia syndrome, and fragile X–associated premature ovarian insufficiency—do not have specific treatments that alter the natural history of the disorders. However, because they represent relatively common causes of conditions that are often difficult to diagnose and involve numerous diagnostic tests, the capability of *FMR1* testing to obtain an accurate, definitive diagnosis and avoid additional diagnostic testing supports its clinical utility. The knowledge that the condition is caused by variants of *FMR1* provides important knowledge for offspring and for assessing the risk of disease in subsequent generations.

Also, FXS is associated with a number of medical and behavioral comorbidities. Behavioral comorbidities may include attention problems, hyperactivity, anxiety, aggression, poor sleep, and self-injury. Individuals with FXS are also prone to seizures, recurrent otitis media, strabismus, gastrointestinal disturbances, and connective tissue problems. A correct diagnosis can lead to the appropriate identification and treatment of these comorbidities.

Section Summary: Individuals With Characteristics of an FXS or a Fragile X–Associated Disorder
The evidence demonstrates that *FMR1* variant testing can establish a definitive diagnosis of FXS and fragile X–related disorders when the test is positive for a pathogenic variant. Following a definitive

diagnosis, treatment of comorbid conditions may be improved. At a minimum, providing a diagnosis eliminates the need for further diagnostic workup.

INDIVIDUALS WHO HAVE A PERSONAL OR FAMILY HISTORY OF FXS WHO ARE SEEKING REPRODUCTIVE COUNSELING

Clinical Context and Test Purpose
Premutation alleles (55-200 CGG repeats) in females are unstable and may expand to full mutations in offspring. Premutations of fewer than 59 repeats have not been reported to expand to a full mutation in a single generation. Premutation alleles in males may expand or contract by several repeats with the transmission; however, expansion to full mutations has not been reported.

Premutation allele prevalence in whites is approximately 1 in 1000 males and 1 in 350 females. Full mutations are typically maternally transmitted. The mother of a child with an *FMR1* variant is almost always a carrier of a premutation or full mutation. Women with a premutation carry a 50% risk of transmitting an abnormal gene, which contains either a premutation copy number (55-200) or a full mutation (>200) in each pregnancy.

Men who are premutation carriers are referred to as transmitting males. All of their daughters will inherit a premutation, but their sons will not inherit the premutation. Males with a full mutation usually have an intellectual disability and decreased fertility.

The purpose of *FMR1* testing in patients who have a personal or family history of FXS is to inform reproductive decision making.

The question addressed in this evidence review is: Does *FMR1* testing in this population improve health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are:

- Individuals who have a personal or family history of FXS who are seeking reproductive counseling, including:
  - Individuals seeking reproductive counseling who have a family history of FXS or a family history of undiagnosed intellectual disability.
  - Affected individuals or relatives of affected individuals who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status.
  - Prenatal testing of fetuses of known carrier mothers.

Interventions
The relevant intervention of interest is testing for *FMR1* variant status.

Comparators
Standard clinical evaluation without genetic testing is currently being used for reproductive decision making.

Outcomes
The general outcome of interest is reproductive decision making.

Timing
The timing of the test is when the individual is making reproductive decisions.

Setting
A number of laboratories can perform testing for the *FMR1* variant and methylation status.

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.

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).
The inheritance patterns of the *FMR1* gene have been well characterized, and the penetrance of the fragile X–associated disorders is very high.

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.

Hersh and Saul (2011) reported on families with an affected male and whether an early diagnosis would have influenced their reproductive decision making. After a diagnosis in the affected male was made, 73% of families reported that the diagnosis of FXS affected their decision to have another child, and 43% of the families surveyed had had a second child with a full mutation.

Section Summary: Individuals Who Have a Personal or Family History of FXS Who Are Seeking Reproductive Counseling
Testing the repeat region of the *FMR1* gene in the context of reproductive decision making may include individuals with either a family history of FXS or a family history of undiagnosed intellectual disability, fetuses of known carrier mothers, or affected individuals or their relatives who have had a positive

cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women.

SUMMARY OF EVIDENCE

For individuals who have characteristics of FXS or an FXS-associated disorder, the evidence includes studies evaluating the clinical validity of *FMR1* variant testing. Relevant outcomes are test accuracy, test validity, and resource utilization. The evidence demonstrates that *FMR1* variant testing can establish a definitive diagnosis of FXS and fragile X–related syndromes when the test is positive for a pathogenic variant. Following a definitive diagnosis, treatment of comorbid conditions may be improved. At a minimum, providing a diagnosis eliminates the need for further diagnostic workup. A chain of evidence supports improved outcomes following *FMR1* variant testing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a personal or family history of FXS who are seeking reproductive counseling, the evidence includes studies evaluating the clinical validity of *FMR1* variant testing and the effect on reproductive decisions. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. Testing the repeat region of the *FMR1* gene in the context of reproductive decision making may include individuals with either a family history of FXS or a family history of undiagnosed intellectual disability, fetuses of known carrier mothers, or affected individuals or their relatives who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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Policy History

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08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. New policy.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. No change to coverage.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. No change to coverage.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Added fragile X associated tremor/ataxia syndrome and FMR1-related primary ovarian failure to medically necessary indications.
08/09/2018	Medical Policy Committee review

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08/15/2018 Medical Policy Implementation Committee approval. Mutation changed to variant in title and body.
Next Scheduled Review Date: 08/2019

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

Code Type	Code
CPT	81243, 81244
HCPCS	No codes
ICD-10 Diagnosis	F70-F79, F80.0-F80.9, F81.0-F81.2, F81.81-F81.9, F82, F84.0, F88-F89, H93.25, Q99.2, R48.0, Z31.430, Z38.81-Z38.89, Z81.0

*****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.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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