I. POLICY

Genetic testing for *FMR1* mutations may be considered medically necessary for the following patient populations:

- Individuals of either sex with intellectual disability, developmental delay, or autism spectrum disorder (see Policy Guidelines section*).

- Individuals seeking reproductive counseling who have a family history of fragile X syndrome or a family history of undiagnosed intellectual disability (see Policy Guidelines section*).

- Prenatal testing of fetuses of known carrier mothers (see Policy Guidelines section*).

- 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 (see Policy Guidelines section**).

Genetic testing for *FMR1* mutations is investigational for all other uses as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

**American College of Medical Genetics Recommendations***

According to the American College of Medical Genetics (ACMG), the following is the preferred approach to testing:

- DNA analysis is the method of choice if one is testing specifically for fragile X syndrome and associated trinucleotide repeat expansion in the FMR1 gene.
For isolated cognitive impairment, DNA analysis for fragile X syndrome should be performed as part of a comprehensive genetic evaluation that includes routine cytogenetic evaluation. Cytogenetic evaluation is important in these circumstances because constitutional chromosome abnormalities have been identified as frequently as or more frequently than fragile X mutations in mentally retarded patients referred for fragile X testing.

Fragile X testing is not routinely warranted for children with isolated attention-deficit/hyperactivity. (see Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, 2011).

For individuals who are at risk due to an established family history of fragile X syndrome, DNA testing alone is sufficient. If the diagnosis of the affected relative was based on previous cytogenetic testing for fragile X syndrome, at least 1 affected relative should have DNA testing.

Prenatal testing of a fetus should be offered when the mother is a known carrier to determine whether the fetus inherited the normal or mutant FMR1 gene. Ideally DNA testing should be performed on cultured amniocytes obtained by amniocentesis after 15 weeks’ gestation. DNA testing can be performed on chorionic villi obtained by chorionic villus sampling at 10 to 12 weeks’ gestation, but results must be interpreted with caution because the methylation status of the FMR1 gene is often not yet established in chorionic villi at the time of sampling. Follow-up amniocentesis may be necessary to resolve an ambiguous result.

If a woman has ovarian failure before the age of 40, DNA testing for premutation size alleles should be considered as part of an infertility evaluation and before in vitro fertilization.

If a patient has cerebellar ataxia and intentional tremor, DNA testing for premutation size alleles, especially among men, should be considered as part of the diagnostic evaluation.

The ACMG Professional Practice and Guidelines Committee made recommendations regarding diagnostic and carrier testing for fragile X syndrome to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the FMR1 gene. These recommendations include testing of individuals of either sex who have intellectual disability, developmental delay, or autism, especially if they have any physical or behavioral characteristics of fragile X syndrome. (See Sherman et al, 2005).

Physical and behavioral characteristics of fragile X syndrome 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 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.

**Cytogenetic Testing**
Cytogenetic testing was used before the identification of the FMR1 gene and is significantly less accurate than the current DNA test. DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women (see Sherman et al, 2005).

**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.

**Cross-reference:**

**II. Product Variations**

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

BlueJourney HMO* BlueJourney PPO* FEP PPO**
* Refer to Novitas Solutions. Local Coverage Determination (LCD) L35062 Biomarkers Overview.

III. DESCRIPTION/BACKGROUND

Fragile X Syndrome
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.

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 size of 200 or more repeats.¹ A considerable number of children evaluated for autism have been found to have FMR1 premutations (55-200 CGG repeats).² In 1 author’s experience, 2% of persons ascertained through a dedicated autism clinic had either an FMR1 full mutation or premutation.

Treatment of FXS
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 home and school settings.

Genetics of FXS
FXS is associated with the expansion of the CGG trinucleotide repeat in the fragile X mental retardation 1 (FMR1) gene on the X chromosome. Diagnosis of FXS may include using a genetic test that determines the number of CGG repeats in the fragile X gene. The patient is classified as normal, intermediate (or “gray zone”), premutation, or full mutation based on the number of CGG repeats³.
Full mutations are associated with FXS, which is caused by expansion of the \textit{FMR1} gene CGG triplet repeat above 200 units in the 5' untranslated region of \textit{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.

Patients with a premutation are carriers and may develop an \textit{FMR1}-related disorder, such as fragile X–associated tremor/ataxia syndrome (FXTAS) or, in women, fragile X–associated premature ovarian insufficiency. FXTAS 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.

Premutation alleles 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 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 \textit{FMR1} mutation is almost always a carrier of a premutation or full mutation. Women with a premutation are at risk of premature ovarian insufficiency and at small risk of FXTAS; they 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 intellectual disability and decreased fertility.

\textbf{Regulatory Status}

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Genotyping tests for \textit{FMR1} mutations are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

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

**Analytic Validity and Clinical Validity**

Analytic validity refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent. Clinical validity refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease.

For FXS, analytic and clinical validity are the same because the diagnosis of FXS is based on detection of an alteration in the FMR1 gene.

According to a large reference laboratory, analytic sensitivity and specificity of FMR1 screen with reflex to FMR1 diagnostic, FMR1 diagnostic, and FMR1 fetal diagnostic is 99%. Clinical sensitivity and specificity is 99% for premutation and full mutation alleles. Diagnostic errors can occur due to rare sequence variations.

DNA studies are used to test for FXS. Genotypes of individuals with symptoms of FXS and individuals at risk for carrying the mutation 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.

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.

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.3,10

Unlike PCR, Southern blotting is time-consuming and requires large amounts of DNA. Alternatives to Southern blotting for determining FMR1 methylation status are in development. These include methylation-sensitive PCR and methylation-specific melting curve analysis.11-14 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.15 For detecting expansions of more than 55 CGG repeats in FMR1, sensitivity and specificity were 100% (95% confidence interval [CI], 91 to 100) and 100% (95% CI, 99 to 100), respectively.
Quality assessment schemes have shown wide disparity in allele sizing between laboratories. Therefore, 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 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. Patient blood samples were collected from 6 consenting donors; 1 donor was a normal female, and the remainder had been identified after previous molecular genetic investigation. Classifications of these patients were: female premutation, male premutation, male full mutation, and female full mutation. In all, 38 laboratories were invited to take part in the study, 23 laboratories agreed to participate, and results were returned by 21 laboratories. The participating 21 laboratories evaluated the samples (blinded, in triplicate) using their routine methods alongside in-house and commercial controls. Seventeen countries were represented among participating laboratories: 13 from Europe, 4 from North America, 3 from Australasia, and 1 from Asia. Collaborative validation study participants were requested to test 18 coded samples on 3 separate days using different lots of reagents or different operators if possible. A total of 18 nonconsensus results were reported, giving an overall rate of nonconcordance of 4.9% (21 laboratories × 18 samples – 7 samples not tested), although these were clustered in 3 laboratories. There was no correlation between nonconcordant results and any particular sample or a specific method. One laboratory reported 12 of the 18 nonconcordant results. This laboratory was contacted, and their testing protocol was changed.

CGG-repeat expansion full mutations account for more than 99% of cases of FXS. Therefore, tests that effectively detect and measure the CGG repeat region of the FMR1 gene are 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.

**Clinical Utility**

Clinical utility refers to how results of the diagnostic test will be used to change patient management and whether these changes in management lead to clinically important improvements in health outcomes.

Evidence on the clinical benefit of testing for FXS is largely anecdotal. Clinical utility of genetic testing can be considered in the following clinical situations: (1) individuals with a clinical diagnosis of intellectual disability, developmental delay, or autism, especially if they have any physical or behavioral characteristics of FXS, a family history of FXS, or male or female relatives with undiagnosed intellectual disability, and (2) individuals seeking reproductive counseling.

Clinical utility for these patients depends on the ability of genetic testing to make a definitive diagnosis and for that diagnosis to lead to management changes that improve outcomes. No studies were identified that described how a molecular diagnosis of FXS changed patient management. Therefore there is no direct evidence for clinical utility of genetic testing in these patients.
Because there is no specific treatment for FXS, making a definitive diagnosis will not lead to treatment that alters the natural history of the disorder. There are several potential ways in which adjunctive management might be changed after confirmation of the diagnosis by genetic testing. The American Academy of Pediatrics (AAP)\(^5\) and the American Academy of Neurology (AAN)\(^17\) recommend cytogenetic evaluation in individuals with developmental delay to look for certain 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 more immediate and general clinical benefits of achieving a specific genetic diagnosis from the clinical viewpoint, as follows:

- 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. Guidelines from AAP recommend against routine fragile X testing for children with isolated attention-deficit/hyperactivity disorder.\(^18\)

Hersh et al (2011) reported on families with an affected male and whether an early diagnosis would have influenced their reproductive decision making.\(^5\) 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.

Testing the repeat region of the \textit{FMR1} gene in the context of reproductive decision making may include testing 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. (Cytogenetic testing was used before identification of the \textit{FMR1} gene and is significantly less accurate than the current DNA test. DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women.)

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in May 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

**Summary of Evidence**

The evidence for \textit{FMR1} mutation testing in individuals with intellectual disability, developmental delay, or autism spectrum disorder or in affected individuals or at-risk relatives in whom testing will affect reproductive decision making includes studies evaluating the analytic and clinical validity of \textit{FMR1} mutation testing and a chain of indirect evidence for demonstration
of clinical outcome improvements. Relevant outcomes are test accuracy, test validity, resource utilization, and changes in reproductive decision making. Analytic sensitivity and specificity for diagnosing these disorders has been demonstrated to be sufficiently high. The evidence demonstrates that \textit{FMR1} mutation testing can establish a definitive diagnosis of FXS when the test is positive for a pathogenic mutation. Following a definitive diagnosis, there are a variety of ways management may change. Providing a diagnosis can eliminate the need for further clinical workup. For certain mutations, results may aid in management of psychopharmacologic interventions, assist in informed reproductive decision making, or both. Although direct evidence for improved outcomes is insufficient, there is a chain of indirect evidence that supports improvements in outcomes following \textit{FMR1} mutation testing. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

\textbf{Practice Guidelines and Position Statements}

\textbf{American College of Medical Genetics}

American College of Medical Genetics’s (ACMG) Professional Practice and Guidelines Committee makes the following recommendations regarding diagnostic and carrier testing for FXS.\textsuperscript{10} The purpose of these recommendations is to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the \textit{FMR1} gene.

- Individuals of either sex with intellectual disability, developmental delay, or autism, especially if they have (a) any physical or behavioral characteristics of fragile X syndrome, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed intellectual disability.
- Individuals seeking reproductive counseling who have (a) a family history of fragile X syndrome or (b) a family history of undiagnosed intellectual disability.
- Fetuses of known carrier mothers.
- Affected individuals or their relatives in the context of a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. The cytogenetic test was used before the identification of the \textit{FMR1} gene and is significantly less accurate than the current DNA test. DNA testing on such individuals is warranted to accurately identify premutation carriers and to distinguish premutation from full mutation carrier women.

In the clinical genetics evaluation to identify the etiology of autism spectrum disorders, ACMG recommends testing for FXS as part of first tier testing.\textsuperscript{1}

\textbf{Academy of Pediatrics}

The Academy of Pediatrics recommends that, because children with FXS may not have apparent physical features, any child who presents with developmental delay, borderline intellectual abilities, or intellectual disability, or has a diagnosis of autism without a specific etiology should undergo molecular testing for FXS to determine the number of CGG repeats.\textsuperscript{5}
American Congress of Obstetricians and Gynecologists
The American Congress of Obstetricians and Gynecologists (Committee Opinion, 2010) recommends that prenatal testing for FXS should be offered to known carriers of the fragile X premutation or full mutation, and to women with a family history of fragile X–related disorders, unexplained intellectual disability or developmental delay, autism, or premature ovarian insufficiency.19

European Molecular Genetic Quality Network
In 2015, the European Molecular Genetic Quality Network issued best practice guidelines for the molecular genetic testing and reporting of FXS, fragile X–associated primary ovarian insufficiency, and fragile X–associated tremor/ataxia syndrome.20 The guidelines recommend “a method which detects the whole range of expansions when testing relatives (including prenatal diagnosis) in a family with any known fragile X disorder due to expansion.” Technical limitations of specific techniques, such as Southern blot and PCR–based methods, are described.

U.S. Preventive Services Task Force Recommendation
No U.S. Preventive Services Task Force recommendations for genetic testing for FMR1 mutations have been identified.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

V. DEFINITIONS

N/A

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.
VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

<table>
<thead>
<tr>
<th>CPT Codes®</th>
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<tr>
<th>ICD-10-CM Diagnosis Codes*</th>
<th>Description</th>
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<tr>
<td>F70</td>
<td>Mild intellectual disabilities</td>
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<td>F71</td>
<td>Moderate intellectual disabilities</td>
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<td>F72</td>
<td>Severe intellectual disabilities</td>
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<td>F84.0</td>
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<td>Q99.2</td>
<td>Fragile X Chromosome</td>
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<tr>
<td>Z31.440</td>
<td>Encounter of male for testing for genetic disease carrier status for procreative management</td>
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<tr>
<td>Z36</td>
<td>Encounter for antenatal screening of mother</td>
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<tr>
<td>Z81.0</td>
<td>Family history of intellectual disabilities</td>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.
IX. REFERENCES


**MEDICAL POLICY**

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>GENETIC TESTING FOR FMR1 MUTATIONS (INCLUDING FRAGILE X SYNDROME)</th>
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<th>POLICY NUMBER</th>
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**Other Sources:**


**X. POLICY HISTORY**

| MP 2.276 | CAC 11/25/14 | New policy. BCBSA adopted. Genetic testing for FMR1 mutations is considered medically necessary for specific policy indications to include:
- Individuals of either sex with intellectual disability, developmental delay, or autism spectrum disorder
- Individuals seeking reproductive counseling who have a family history of fragile X syndrome or a family history of undiagnosed intellectual disability
- Prenatal testing of fetuses of known carrier mothers
- 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

An FEP variation was added to refer to the FEP medical policy manual. A Medicare variation was also added.
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CAC 11/24/15 Consensus review. No change to policy statements. References and rationale updated. LCD changed from L33460 to LCD L35062 due to Novitas ICD-10 update. Coding reviewed.

11/29/16 Consensus review. No change to policy statements. References and rationale updated. Variation reformatting. Coding reviewed.