Brugada Syndrome Genetic Testing

Introduction

Brugada syndrome genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What is Brugada syndrome

Definition

Brugada syndrome (BrS) is an inherited channelopathy characterized by right precordial ST elevation. This can result in cardiac conduction delays at different levels, syncope, or a lethal arrhythmia resulting in sudden cardiac death.

Onset

Although the typical presentation of BrS is sudden death in a male in his 40s with a previous history of syncope, BrS has been seen in individuals between the ages of 2 days and 85 years, \(^1\) as well as females. \(^2\)

Diagnosis

The diagnosis of BrS is based on ECG results, clinical presentation and family history. A diagnosis of either type 1, 2, or 3 ECG results with a personal history of fainting spells, ventricular fibrillation, self-terminating polymorphic ventricular tachycardia, or electrophysiologic inducibility can help identify those at risk for BrS. A family history of
syncope, coved-type ECGs, or sudden cardiac death, especially in an autosomal dominant inheritance pattern, can help aid in the diagnosis.\textsuperscript{3,4}

**Cause**

BrS has been associated with at least 16 different genes and >400 mutations,\textsuperscript{3,5-7} and is estimated to be seen in about 1 in 2000 individuals. Approximately 65-75\% of families with a clinical diagnosis of BrS do not test positive for a mutation in one of the known genes, suggesting that there are other genes that have not been identified.\textsuperscript{3,5}

- SCN5A is responsible for the majority of BrS cases (15-30\%).
- There are reports that CACNA1C and CACNB2B may account for up to 11\% of cases of BrS.\textsuperscript{6,8}
- Each of the other genes comprise less than 5\% of mutations in each case.

BrS has variable expression and incomplete penetrance. Approximately 25\% of gene positive individuals have an ECG diagnostic of BrS.\textsuperscript{3,5} Additionally, 80\% individuals with a disease-causing mutation only present with symptoms when challenged with a sodium channel blocker.\textsuperscript{2,9}

**Prevalence**

BrS is found worldwide with a prevalence of approximately 1:2000 in endemic areas.\textsuperscript{3} It seems to have a higher incidence in Southeast Asia. In countries such as Japan, the Philippines, Laos, and Thailand, a condition called Sudden Unexplained Nocturnal Death syndrome (SUNDs) has been associated with mutations in the SCN5A, suggesting that this condition is actually Brugada Syndrome.\textsuperscript{10,11} In these countries, SUNDS is the second most common cause of death of men under age 40 years.\textsuperscript{3}

**Inheritance**

BrS is inherited in an autosomal dominant inheritance pattern, with the exception of KCNE5-related Brugada syndrome, which is inherited in an X-linked manner.\textsuperscript{3} This means that an individual has a 50\% chance of passing on a mutation to their children. Additionally, parents and siblings of known carriers have a 50\% chance of being carriers of the same mutation.

When a mutation in a child is not found in the parents, it is assumed that there is a de novo mutation in the child. De novo mutations are estimated to occur in approximately 1\% of cases.\textsuperscript{3} Siblings would still need to be tested to rule out germline mutations.

A DNA test for BrS should be offered to the person who has the most obvious disease, as that individual will more likely test positive than someone without disease. At this time, population wide carrier screening for BrS is not recommended.\textsuperscript{5}
Test information

Introduction

Testing for Brugada syndrome may include full sequence analysis, deletion/duplication testing, known familial mutation analysis, or multigene panels.

Full sequence analysis

Full sequence analysis of the SCN5A gene is available through a number of commercial laboratories.

Deletion/duplication testing

Deletion/duplication testing for SCN5A is available and is typically done in reflex to a negative result from full sequence analysis.

Known familial mutation analysis

Known familial mutation analysis can be considered for individuals with a known mutation in the family. Once a deleterious mutation is identified in a family member, at-risk relatives can be tested for only that specific mutation. Testing by single site analysis is greater than 99% accurate.³

Multigene panels

Multigene panels can be considered but this test is typically not recommended.

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Brugada syndrome testing.

Heart Rhythm Society, European Heart Rhythm Association, and Asia Pacific Heart Rhythm Society

A 2013 expert consensus statement from the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), and the Asia Pacific Heart Rhythm Society is silent on the role of genetic testing in diagnosis and management.¹²

Heart Rhythm Society and European Heart Rhythm Association

A 2011 expert consensus statement from the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) recommends.⁵
“Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.” (Class IIa)

“Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.”

“Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.”

**Multigene panels**

The clinical utility of Brugada multigene panels has not been well established. Mutations in SCN5A are responsible for 15-30% of cases of Brugada Syndrome, making it the most common known genetic cause of BrS. There are other genes associated with BrS, but mutations in each gene account for <5% of cases of BrS, therefore incremental mutation yield on a multi-gene panel is expected to be very low.

**Criteria**

**Introduction**

Requests for Brugada syndrome testing are reviewed using these criteria.

**Brugada Syndrome Known Familial Mutation Analysis**

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for Brugada Syndrome, AND
- Diagnostic and Predisposition Testing:
  - Brugada Syndrome familial mutation identified in biologic relative(s), OR
- Prenatal Testing:
  - Brugada syndrome mutation identified in one biologic parent or 1st degree relative, AND
- Rendering laboratory is a qualified provider of service per the Health plan policy.
Brugada Syndrome Full Sequence Analysis of SCN5A

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous sequence analysis of SCN5A, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Type 1, 2, or 3 ECG results, and
  o Documented ventricular fibrillation, or
  o Self-terminating polymorphic ventricular tachycardia, or
  o A family history of sudden cardiac death, or
  o Coved-type ECGs in family members, or
  o Electrophysiologic inducibility, or
  o Syncope, or
  o Nocturnal agonal respiration (breaths that persist after cessation of heartbeat), OR

• Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  o Biologic relative(s) (1st, 2nd, or 3rd degree) diagnosed with BrS clinically, and no familial mutation identified, or
  o Sudden death in biologic relative(1st, 2nd, or 3rd degree), and
  o Type 1 ECG changes, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

Brugada Deletion/Duplication Analysis of SCN5A

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:(a)
  o No mutation identified with Brugada Syndrome sequence analysis of SCN5A, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.
Brugada Syndrome Multigene Panels

- Brugada syndrome multigene panels are considered investigational and/or experimental.
  - Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.
  - In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

References

Introduction

These references are cited in this guideline.


5. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace*. 2011;13(8):1077-1109.


