Test Specific Guidelines

Brugada Syndrome Genetic Testing

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Introduction

Brugada syndrome genetic testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures address by this guideline	Procedure codes
Brugada Syndrome Deletion/Duplication Panel	81414
Brugada Syndrome Genetic Testing (SCN5A and Variants)	S3861
Brugada Syndrome Known Familial Mutation Analysis	81403
Brugada Syndrome Sequencing Multigene Panel	81413
Genomic Unity Cardiac Ion Channelopathies Analysis	0237U
SCN5A Deletion/Duplication Analysis	81479
SCN5A Sequencing	81407

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 (SCD).

Prevalence

BrS is found worldwide and its global prevalence is unknown. The prevalence in endemic areas is approximately 1:2000.[1] 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 gene, suggesting that this condition is actually

Brugada Syndrome.[2,3] In these countries, SUNDS is the second most common cause of death of men under age 40 years.[1]

Symptoms

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, as well as females.[4,5] Symptoms often occur at rest or during sleep.

BrS has variable expression and incomplete penetrance. Approximately 25% of gene positive individuals have an ECG diagnostic of BrS.[1,6] Additionally, 80% of individuals with a disease-causing mutation only present with symptoms when challenged with a sodium channel blocker.[5,7]

Cause

BrS has been associated with at least 16 different genes and >400 mutations,[1,6,8,9] 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.[1,6]

- SCN5A is responsible for the majority of BrS cases (15-30%).[1]
- There are reports that CACNA1C and CACNB2B may account for up to 11% of cases of BrS. [8,10]
- None of the additional genes comprises more than 5% of causative BrS mutations.

Inheritance

BrS is an autosomal dominant inheritance disorder with the exception of KCNE5-related Brugada syndrome, which is an X-linked disorder.[1]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

X-Linked Inheritance

In X-linked inheritance, the mutation is carried on the X chromosome. Females have two X chromosomes, and males have one. Males typically have more

severe symptoms than females. A female with a mutation has a 50% chance to pass that mutation to her children. A male with a mutation cannot pass the mutation to any sons, but will pass it to all daughters. A process called X-inactivation in females results in random inactivation of expression of one X-chromosome in each cell of the body. For females with one mutation, the percentage and distribution of cells with expression of the X chromosome carrying the mutation can influence the degree of severity.

Genetic testing 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.[11]

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.[1] Siblings would still need to be tested as germline mosaicism cannot be excluded.

Diagnosis

The diagnosis of BrS is based on ECG findings, clinical presentation and family history. Findings of either type 1, 2, or 3 ECG pattern 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 SCD, especially in an autosomal dominant inheritance pattern, can help aid in the diagnosis.[1,12]

The clinical presentation of Brugada syndrome is not always clear cut. Arrhythmia disorders with both genetic and non-genetic etiologies can present similarly. When a clear genetic etiology cannot be suspected based on EKG findings alone, molecular testing can help to clarify a cause and inform management.[1,11,13,14]

Full sequence analysis of the SCN5A gene is available through a number of commercial laboratories. About 25% of people with a clinical diagnosis of BrS will have a mutation identified by genetic testing. SCN5A accounts for the majority of mutations (15-30%)[1]. The vast majority of identified mutations are sequence changes.

Deletion/duplication testing for SCN5A is available and is typically done in reflex to a negative result from full sequence analysis. Deletions and duplications have been reported though their prevalence is unknown.

Management

Implantable cardioverter-defibrillators (ICDs) are the only definitive treatment for individuals with BrS. "Patients with suspected arrhythmic syncope with a spontaneous type I ECG are at high risk of malignant arrhythmic events (~2.3%/year) and should consider ICD implantation. Asymptomatic patients with

drug-induced type I ECG are at low risk (equal to or less than 0.4%/year) and should be managed conservatively. All BrS patients should be counselled to (i) avoid drugs that impair cardiac sodium channels (brugadadrugs.org), (ii) avoid alcohol intoxication, (iii) immediately treat fever with antipyretic drugs, and (iv) seek urgent medical attention following a syncope. The role of invasive electrophysiological testing for risk stratification remains controversial."[15]

Survival

BrS "is responsible for nearly 20% of all sudden cardiac deaths in patients with structurally normal hearts and up to 12% of all sudden cardiac deaths."[16] Survival is impacted by the identification of the disease, risk stratification for SCD, and interventions such as the use of ICDs.

Test Information

Introduction

Testing for Brugada syndrome may include known familial mutation analysis, next generation sequencing, deletion/duplication testing, and/or multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and

losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multigene Panel Testing

Multigene panel testing 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.

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

An expert consensus statement from the European Heart Rhythm Association, the Heart Rhythm Society, the Asia Pacific Heart Rhythm Society and the Latin American Heart Rhythm Society (EHRA/HRS/APHRS/LAHRS, 2022) addressed the utility and appropriateness of genetic testing for inherited cardiovascular conditions.[15] The consensus statements were categorized as follows:

- Supported by strong observational evidence and authors' consensus
- Some evidence and general agreement favor the usefulness/ efficacy of a test
- There is evidence or general agreement not to recommend a test

Regarding the choice of genetic testing and variant interpretation:

- Genetic testing should occur with genetic counseling. [Supported by strong observational evidence and authors' consensus]
- If an individual has a clear phenotype, it is appropriate to analyze genes with definite/strong evidence to support disease causation [Supported by strong observational evidence and authors' consensus] and may be appropriate to analyze genes with moderate evidence for disease causation. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
- In some cases with a clear phenotype and negative genetic testing of genes with definite/strong evidence for disease causation, broader genetic testing may be considered [Some evidence and general agreement favor the usefulness/ efficacy of a test].
- "Genetic testing for genes with (i) limited, (ii) disputed, or (iii) refuted evidence should not be performed in patients with a weak (non-definite) phenotype in the clinical setting." [There is evidence or general agreement not to recommend a test]

- "Variant interpretation in the clinical setting is greatly enhanced by the use of disease-specific, multi-disciplinary teams that could include clinical disease experts, clinical geneticists, or genetic counsellors and molecular geneticists." Standard guidelines for variant interpretation should be used. Variant interpretation "can be enhanced by gene-specific rule specifications tailored for the gene and disease under consideration. [Supported by strong observational evidence and authors' consensus]
- Variants of uncertain significance may be reclassified to likely pathogenic, pathogenic, likely benign or benign. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
- When a likely pathogenic or pathogenic variant has been identified, genetic counseling should be offered. The inheritance pattern, penetrance, and associated risks can be discussed. Additionally, cascade testing for relatives can be facilitated. [Supported by strong observational evidence and authors' consensus]
- "Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causing variant." [Supported by strong observational evidence and authors' consensus] "Predictive genetic testing in related children is recommended from birth onward (any age)." [Some evidence and general agreement favor the usefulness/ efficacy of a test]
- Some affected individuals may have had previous genetic testing that was not a comprehensive, such as prior to the use of next generation sequencing or with an incomplete testing panel. Repeat testing should be considered in these cases. [Supported by strong observational evidence and authors' consensus]

Regarding genetic testing for Brugada syndrome:

- "Genetic testing with sequencing of SCN5A is recommended for an index case diagnosed with BrS with a type I ECG in standard or high precordial leads occurring either (i) spontaneously, or (ii) induced by sodium-channel blockade in presence of supporting clinical features or family history." [Supported by strong observational evidence and authors' consensus]
- "Rare variants in genes with a disputed or refuted gene-disease clinical validity should not be reported routinely for BrS genetic testing in a diagnostic setting". [There is evidence or general agreement not to recommend a test]
- "Targeted sequencing of variant(s) of unknown significance in SCN5A with a population allele frequency $<1x10^{-5}$ identified in an index case can be considered concurrently with phenotyping for family members, following genetic counselling, to assess variant pathogenicity through co-segregation analysis." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

Heart Rhythm Society and European Heart Rhythm Association

An expert consensus statement from the Heart Rhythm Society (HRS, 2011) and the European Heart Rhythm Association (EHRA, 2011) stated:[6]

- **"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."**

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

An expert consensus statement from the Heart Rhythm Society, the European Heart Rhythm Association, and the Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS, 2013) remained silent on the indications for genetic testing in individuals affected by inherited arrhythmias and their family members, because the topic is covered elsewhere. The statement acknowledged that genetic testing can play a role for affected and unaffected individuals.[17]

Selected Relevant Publication

Regarding the use of multi-gene testing panels in Brugada syndrome, the clinical utility 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 of these additional genes account for less than 5% of cases. Therefore, the incremental mutation yield on a multi-gene panel is expected to be very low.[6]

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 that would detect the familial mutation, 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:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous sequence analysis of SCN5A, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Type 1, 2, or 3 ECG results, and
  - Documented ventricular fibrillation, or
  - Self-terminating polymorphic ventricular tachycardia, or
  - A family history of sudden cardiac death, or
  - Coved-type ECGs in family members, or
  - Electrophysiologic inducibility, or
  - Syncope, or
  - Nocturnal agonal respiration (breaths that persist after cessation of heartbeat), OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Biologic relative(s) (1st, 2nd, or 3rd degree) diagnosed with BrS clinically, and no familial mutation identified, or
  - Sudden death in biologic relative(1st, 2nd, or 3rd degree), and
  - 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:**
  - **Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND**
- **Previous Genetic Testing:(a)**
  - **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

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