THE IMPACT OF MEDICAL MANAGEMENT ON QUALITY OF LIFE IN BRUGADA SYNDROME PATIENTS

by

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Sarah Richards, M.S.

University of Pittsburgh, 2012

PURPOSE: Brugada syndrome is an inherited cardiac arrhythmia disorder characterized by ST segment elevation in leads V1-V3 on an electrocardiogram (ECG). The main symptoms of this condition are syncope and sudden cardiac death. Medical management for symptomatic patients is an implantable cardioverter defibrillator (ICD). Research has shown that cardiac patients who have an ICD experience a decreased quality of life. However, limited studies have been done on the impact of Brugada syndrome on patient quality of life let alone the impact of medical management in this patient population. The purpose of this study was to understand how Brugada syndrome affects quality of life and if there is any difference between those with an ICD and those without one. The public health significance of this project is to further the understanding of the impacts of medical management in a specific patient population.

METHODS: Participants were recruited from a multigenerational family with Brugada syndrome where a mutation has been identified in the gene \textit{GPD1L}. A questionnaire was developed to ascertain medical management decisions. Additionally, the 36-Item Short Form Health Survey (SF-36v2) was used to assess quality of life.

RESULTS: A total of 17 participants agreed to enroll in the study with an age range of 36-89 years. Ten of the seventeen had the family mutation in \textit{GPD1L} with seven of these ten displaying the Brugada phenotype on an ECG. Only three participants had an ICD and one participant was considering the option in the near future. The main reasons for choosing an ICD were either due
to a sense of inevitability and necessity or for family benefit. There was no difference in quality of life between those with the familial mutation and those without. There was also no difference observed between asymptomatic and symptomatic individuals with the mutation. Those with an ICD had a lower MCS than those without an ICD (p-value 0.013) with no other significant differences observed.

**CONCLUSION:** Reasons underlying ICD decision-making are similar to those seen in other studies, indicating that Brugada patients’ experiences are similar to other patient groups with an ICD. There was no statistical difference in quality of life between those with and those without a genetic diagnosis or those with and without symptoms. The difference between those with and without an ICD indicates that medical management does impact quality of life, adding more evidence to support there is a significant psychosocial aspect to Brugada syndrome management. Additional research is needed to better address the specific needs of this patient population.
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PREFACE

This project could not have come to fruition without the family members who so willingly and happily participated in this study. This family has always been the first to volunteer for anything that would benefit the understanding of Brugada syndrome both in the medical community and for others living with the condition.

I would also like to thank my family and friends for all of their support during my graduate studies. I could not have made it these past two years without my biggest fan and supporter, Justin Richards. Thank you for letting me pursue my dreams and holding down the fort. To quote the student before me, here’s to a lifetime of weekends! To my dear friend Meagan Smith, I could not have made it through this without you. Here’s to the continuation of a lifelong friendship. To my families back in Ohio, thank you for all the phone calls, visits, and prayers. By His grace, I have made it through this season of my life.

To Dr. Barry London and his research nurse, Rebecca Gutmann, thank you for taking me under your wing and instilling within me a new found love of cardiovascular genetics. It was a little overwhelming at first, but in the end it was one of the best experiences of my life. To my program directors, Robin Grubs and Betsy Gettig, thank you for recognizing the potential inside of me and granting me the honor of being in this program. Here’s to the celebration of a new colleague.
1.0 INTRODUCTION

Brugada syndrome is a cardiac condition characterized by a structurally normal heart but abnormal heart beats (arrhythmias). The hallmarks of Brugada syndrome are right bundle branch block (RBBB) and persistent ST segment elevation in the precordial leads V1-V3 of an electrocardiogram (ECG)\(^1,2\). It is estimated that approximately 1 in 1,000 individuals has the condition\(^3\). Due to the increased risk for arrhythmias, patients with Brugada syndrome are at an increased risk for syncope and sudden cardiac death\(^4\). Approximately 30% of individuals with Brugada syndrome have an identifiable genetic mutation in one of eight currently known genes\(^5\). The majority of mutations are identified in \(SCN5A\) which was the first gene shown to be associated with the condition\(^6\).

The only proven therapy for preventing sudden cardiac death in these patients is an implantable cardioverter defibrillator\(^4\). Current management recommendations are that any individual with Brugada syndrome who has a past history of syncope or aborted sudden cardiac death receive an ICD\(^4\). However, controversy surrounds recommendations for patients with the condition who have the characteristic ECG pattern but have never had clinical symptoms\(^7\).

ICDs are used to treat patients with a variety of underlying heart issues such as heart failure, prior history of myocardial infarction, ischemic cardiomyopathy and Brugada syndrome among many others. Research has shown that living with an ICD can have a significant impact
on quality of life. While the ICD may provide a sense of comfort to some, others experience anxiety and depression leading to a lower quality of life overall. The relationship between ICDs and quality of life in Brugada syndrome patients has only been studied by one research group in France at the time this thesis document was written.

The purpose of this study was to evaluate the impact of an ICD on the quality of life in patients affected with Brugada syndrome and what factors influence a patient’s decision making to accept or decline an ICD. To this end, the 36-Item Short Form Health Survey (SF36v2) was administered to a multigenerational family with Brugada syndrome and an identifiable mutation in GPD1L to assess quality of life between three groups: those with and without the genetic mutation, those with the mutation who have symptoms and those who do not, and those with the mutation and symptoms who have an ICD and those without one. A questionnaire was developed and implemented to assess reasons for choosing or declining an ICD as well as demographic information.
2.0 BACKGROUND

2.1 BRUGADA SYNDROME HISTORY

Brugada syndrome is an inherited cardiac arrhythmia disorder that was first characterized by Pedro and Josep Brugada in 1992\(^1\). These patients have structurally normal hearts with ventricular arrhythmias characterized by right bundle branch block and persistent ST segment elevation in the precordial leads V1-V3 of an electrocardiogram (ECG)\(^1,2\). In 1998, the first underlying genetic mechanism of the disease was identified as mutations in the sodium channel, voltage-gated, type V, alpha subunit (\(SCN5A\))\(^{10}\). Since that time, mutations in eight different genes have been shown to cause Brugada syndrome and there is now a clearer understanding of both the molecular genetics and cellular mechanisms of disease.
2.2 CLINICAL FEATURES

2.2.1 Electrocardiographic Findings

The hallmark of Brugada syndrome is the characteristic patterns observed on an electrocardiogram. An electrocardiogram is a medical test used to record the electrical activity of the heart. Electrodes are placed at precise locations on the body including both arms, both legs, and the chest. There are usually ten of these electrodes in the standard 12-lead ECG. Each lead represents a tracing of the voltage between two or more of the electrodes. For Brugada syndrome, the electrodes or leads V1 through V3 are important for diagnosing the condition. V1 is placed in the fourth intercostal space between the fourth and fifth ribs just to the right of the sternum. V2 is also placed in the fourth intercostal space just to the left of the sternum. V3 is placed between V2 and V4, which is in the fifth intercostal space in the midclavicular line. Placing V1 and V2 one intercostal space higher (in the third intercostal space) increases the sensitivity of the ECG in detecting the Brugada phenotype.

![Figure 1: Cardiac Electrical Cycle](image)

Figure 1: Cardiac Electrical Cycle
Each beat of the heart on an ECG can be broken down into five deflections: P, Q, R, S and T (see Figure 1). The cardiac cycle begins with a P wave followed by a QRS complex and ending with a T wave. The ST segment represents the period of zero potential between ventricular depolarization and repolarization. On the ECG, it is the time from when the QRS complex ends and the T wave begins.

The Brugada ECG pattern was first reported as right bundle branch block (RBBB) and persistent ST segment elevation in the precordial leads V1-V3 of an ECG. More specifically, when the QRS complex ends, there is positive deflection known as prominent J wave. This is followed by an elevated down-sloping ST segment with a negative T wave and normal to short QT intervals. Although this is the typical description of a Brugada type ECG, there are in fact three patterns of Brugada syndrome each characterized by distinctive ECG findings (Figure 2).

The Type 1 ECG is the classic Brugada pattern as described by Brugada et al in 1992. In this pattern, there is a $\geq 2$mm J point elevation followed by a downsloping or coved ST segment.
and a negative (inverted) T wave\textsuperscript{13}. The Type 2 pattern is also referred to as the saddleback type\textsuperscript{4}. It also shows a $\geq 2\text{mm}$ J point elevation but has a gradually descending ST segment that does not reach the baseline and is elevated $\geq 1\text{mm}$ which causes the saddleback appearance\textsuperscript{4,15}. It also is characterized by a positive (upward) or biphasic T wave. Finally, the Type 3 pattern is characterized by a smaller magnitude of ST segment elevation $\leq 1\text{mm}$, with either a saddleback or coved type appearance and J point elevation $\geq 2\text{mm}$\textsuperscript{4,13,16}. Table 1 lists each type of Brugada ECG pattern and characteristic ECG findings in leads V1-V3\textsuperscript{17}.

<table>
<thead>
<tr>
<th>J-point</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2mm</td>
<td>≥2mm</td>
<td>≥2mm</td>
<td></td>
</tr>
<tr>
<td>T-wave</td>
<td>Negative</td>
<td>Positive or biphasic</td>
<td>Positive</td>
</tr>
<tr>
<td>ST-T configuration</td>
<td>Coved type</td>
<td>Saddleback</td>
<td>Saddleback or coved</td>
</tr>
<tr>
<td>ST segment</td>
<td>Downsloping/gradually descending</td>
<td>Elevated $\geq 1\text{mm}$</td>
<td>Elevated $\leq 1\text{mm}$</td>
</tr>
</tbody>
</table>

In addition to ECG abnormalities discussed, RBBB is also associated with Brugada syndrome. The presence of RBBB was at one time necessary for the diagnosis of the condition, however, not all individuals have RBBB and thus it is no longer a necessary factor for diagnosis\textsuperscript{4,17}. Right bundle branch block is an interference in the electrical conduction of the heart\textsuperscript{11}. Other ECG abnormalities that may be seen in Brugada syndrome include: QRS axis deviation, P wave enlargement, PQ prolongation, atrioventricular (AV) node dysfunction, sinus node dysfunction, and occasionally QTc prolongation\textsuperscript{15}. All of these features represent signs of conduction defects.
Brugada syndrome is not usually associated with structural heart disease\textsuperscript{1,2}. All symptoms and manifestations of the disease are due to cardiac arrhythmias. The ST segment elevation in Brugada syndrome is associated with a high risk for ventricular arrhythmias\textsuperscript{1,2,13}. This includes both ventricular tachycardia (VT) and ventricular fibrillation (VF). VT is a rapid but regular heartbeat originating in the ventricles. VF is a rapid and irregular heartbeat. When the arrhythmia occurs for a few seconds before spontaneously resolving, it can lead to the clinical symptoms of Brugada syndrome. These symptoms are the same as individuals in the general population who experience VT/VF: palpitations, lightheadedness and dizziness, and syncope\textsuperscript{13–15,18}. If the arrhythmia does not spontaneously resolve, it can lead to sudden cardiac death. In addition to VT and VF, supraventricular arrhythmias such as atrial fibrillation can occur in 15 to 20\% of patients with Brugada syndrome\textsuperscript{15}.

Most patients with Brugada syndrome never experience any symptoms\textsuperscript{15}. In those who do, the most common symptoms are syncope and sudden cardiac death\textsuperscript{19}. The percentage of clinically affected individuals with at least one cardiac arrest before age 60 is 10-15\%, supporting the fact that the majority of patients remain asymptomatic\textsuperscript{3}. The first symptoms usually occur in the third and fourth decade of life\textsuperscript{4}. It is not common for symptoms to appear in childhood, however, some studies indicate that this early onset of symptoms correlates with a more aggressive form of the disease\textsuperscript{3}. Many patients with Brugada syndrome are identified after an aborted sudden cardiac death and screening of at risk family members\textsuperscript{20}. A study in 1998 by Brugada et al. on long-term outcome of patients with Brugada syndrome demonstrated that both symptomatic and asymptomatic patients had a similar risk for sudden cardiac death (34\% versus...
27% respectively\textsuperscript{20}. Since then, many Brugada registries have been created with the purpose of identifying the annual incidence of life-threatening arrhythmias. However, many of these registries disagree about the annual incidence. Table 2 below summarizes the findings of the different Brugada registries\textsuperscript{21}.

![Table 2: Comparison of Brugada Syndrome Registries (Adapted from Priori et al. 2012)](image)

<table>
<thead>
<tr>
<th></th>
<th>Brugada et al. 2003\textsuperscript{22}</th>
<th>FINGER\textsuperscript{23}</th>
<th>PRELUDE\textsuperscript{21}</th>
<th>Delise et al. 2011\textsuperscript{24}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>443</td>
<td>967</td>
<td>308</td>
<td>320</td>
</tr>
<tr>
<td>Number with syncope before enrollment</td>
<td>100 (23%)</td>
<td>313 (32%)</td>
<td>64 (21%)</td>
<td>105 (34%)</td>
</tr>
<tr>
<td>Number with aborted Sudden Cardiac Death (SCD) before enrollment</td>
<td>80 (18%)</td>
<td>62 (6.4%)</td>
<td>Not available</td>
<td>Excluded from the study</td>
</tr>
<tr>
<td>Number with Spontaneous Type 1 ECG</td>
<td>391 (71%)</td>
<td>437 (45%)</td>
<td>171 (56%)</td>
<td>174 (54%)</td>
</tr>
<tr>
<td>Arrhythmic events at follow-up</td>
<td>65 (14.7%)</td>
<td>51 (5.2%)</td>
<td>14 (4.5%)</td>
<td>17 (5.3%)</td>
</tr>
<tr>
<td>Annual arrhythmic event rate in symptomatic patients</td>
<td>4.1%</td>
<td>7.7% in patients with aborted SCD; 1.9% in patients with syncope</td>
<td>1.5%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Annual arrhythmic event rate in asymptomatic patients</td>
<td>Not available</td>
<td>0.5%</td>
<td>Not available</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

### 2.2.3 Risk Factors

For some of the inherited cardiac arrhythmia conditions like Long QT syndrome, clear risk factors have been linked to increased risk for symptoms and avoidance of these factors decreases risks. In Brugada syndrome, arrhythmias typically occur at rest or during sleep and as such no clear prevention strategies exist. There have been reports of avoidable risk factors such as cocaine use, large meals, and excessive alcohol consumption\textsuperscript{4}. In addition, some medications
such as class 1C antiarrhythmic drugs and tricyclic antidepressants have also been shown to induce arrhythmias in Brugada syndrome patients (more information in section 2.6.4 Agents and Circumstances to Avoid). Fevers also increase the risk of arrhythmia in Brugada syndrome patients and precautions should be taken during periods of illness.\(^{25}\)

Perhaps one of the largest risk factors associated with Brugada syndrome is male gender. It is estimated that 80% of Brugada patients in Western countries and 90% of patients in Asian countries are male.\(^{26}\) Furthermore, the clinical phenotype is 8 to 10 times more prevalent in males than in females.\(^{27}\) Possible explanations for this phenomenon revolve around the sex hormone testosterone and modulation of cardiac potassium currents (\(I_{to}\))\(^{26,27}\).

### 2.3 EPIDEMIOLOGY

Sudden cardiac death is a major public health burden. Each year in the United States, approximately 300,000 deaths are a result of sudden cardiac death.\(^{28}\) The overall number of cases of sudden death in young people (e.g. under the age of 40) is not well known as no clear unifying diagnoses exists to allow these numbers to be tracked. Most cases of sudden cardiac death in the young occur in men who die during sleep or at rest.\(^{29}\) Where sudden cardiac death in individuals over age 40 is largely attributed to coronary artery disease, sudden cardiac death in young people remains largely unexplained as most cases do not have an explanation that can be found by autopsy. Up to 40% of these autopsy-negative sudden cardiac deaths can be attributed to sudden arrhythmic death syndromes including Brugada syndrome.\(^{30}\) Brugada syndrome itself is
estimated to be responsible for anywhere from 4% to 20% of sudden deaths in individuals with no evidence of structural heart disease\textsuperscript{4}.

There is also a link between Brugada syndrome and sudden infant death syndrome (SIDS). SIDS is defined as the death of an infant under the age of 1 year that remains unexplained after a thorough case investigation including medical autopsy, death scene investigation and detailed review of the clinical history\textsuperscript{31}. Approximately 10% of SIDS cases can be attributed to sudden arrhythmic death syndromes including Brugada syndrome\textsuperscript{31}. Of these cases, about half involve mutations in \textit{SCN5A}\textsuperscript{31}. The first report of the connection between Brugada syndrome and SIDS was in 2000 where a mutation in \textit{SCN5A} was found to be associated with SIDS and sudden cardiac death in young children in one family\textsuperscript{32}. For these reasons, Brugada syndrome as well as any of the inherited arrhythmia syndromes should be considered in any case of sudden unexplained death especially in children and young adults\textsuperscript{30,32}.

The overall prevalence of Brugada syndrome is unknown but is estimated to be 0.10% or 1 individual per 1,000 worldwide with a lower frequency in Western countries and higher frequency in Southeast Asia\textsuperscript{3,13}. Due to the variable expressivity and reduced penetrance in Brugada syndrome, more precise estimates of prevalence are difficult to obtain for most countries\textsuperscript{4}. Brugada syndrome is endemic in Thailand and the Philippines where it is the second cause of death in young men occurring particularly during sleep\textsuperscript{13,33}. The average age of diagnosis or sudden death in Brugada syndrome is 41 ± 15 years\textsuperscript{4}. However, the youngest patient diagnosed with Brugada syndrome was 2 days old and the oldest patient was 84 years old\textsuperscript{4}.
2.4 GENETICS

The first gene identified as being causative of Brugada syndrome was \( SCN5A \)\(^{10} \). To date, there are currently eight confirmed genes associated with Brugada syndrome that demonstrates locus heterogeneity (Table 3). The majority of the genes associated with Brugada syndrome encode for ion channel proteins hence why Brugada syndrome is often described as an inherited channelopathy.

Table 3: Brugada Syndrome Genes

<table>
<thead>
<tr>
<th>Brugada Type</th>
<th>Gene Symbol</th>
<th>Chromosomal Locus</th>
<th>Protein Name</th>
<th>Effect of Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrS1</td>
<td>SCN5A</td>
<td>3p22.2</td>
<td>Cardiac sodium channel alpha subunit</td>
<td>Loss of function</td>
</tr>
<tr>
<td>BrS2</td>
<td>GPD1L</td>
<td>3p22.3</td>
<td>Glycerol-3-phosphate dehydrogenase 1-like</td>
<td>Loss of function</td>
</tr>
<tr>
<td>BrS3</td>
<td>CACNA1C</td>
<td>12p13.3</td>
<td>Voltage-dependent L-type calcium channel subunit alpha-1C</td>
<td>Loss of function</td>
</tr>
<tr>
<td>BrS4</td>
<td>CACNB2</td>
<td>10p12.33-p12.31</td>
<td>Voltage-dependent L-type calcium channel subunit beta-2</td>
<td>Loss of function</td>
</tr>
<tr>
<td>BrS5</td>
<td>SCN1B</td>
<td>19q13.1</td>
<td>Sodium channel subunit beta-1</td>
<td>Loss of function</td>
</tr>
<tr>
<td>BrS6</td>
<td>KCNE3</td>
<td>11q13.4</td>
<td>Potassium voltage-gated channel subfamily E member 3</td>
<td>Gain of function</td>
</tr>
<tr>
<td>BrS7</td>
<td>SCN3B</td>
<td>1q23.3</td>
<td>Sodium channel subunit beta-3</td>
<td>Loss of function</td>
</tr>
<tr>
<td>BrS8</td>
<td>HCN4</td>
<td>15q24.1</td>
<td>Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4</td>
<td>Loss of function</td>
</tr>
</tbody>
</table>

Mutations in these genes lead to Brugada syndrome by altering the electrical potential of cardiac myocytes\(^34\). Mutations in \( SCN5A, GPD1L, SCN1B \) and \( SCN3B \) lead to a reduction in sodium current (\( I_{Na} \))\(^{34,35} \). Mutations in \( KCNE3 \) lead to an increase in potassium current (\( I_{Ko} \)) which increases total cellular charge and leads to Brugada syndrome\(^36\). Mutations in \( CACNA1C \) and \( CACNB2 \) lead to a reduction in the calcium current (\( I_{CaL} \) and \( I_{Ca} \) respectively). In addition, mutations in these two calcium channel subunits can cause a decreased QT interval on the ECG\(^37\). Thus patients with mutations in these genes are often considered to have both Brugada
syndrome and Short QT syndrome\textsuperscript{34,37}. Mutations in $HCN4$ may induce Brugada syndrome by altering potassium current ($I_{f}$)\textsuperscript{38}.

Mutations in $SCN5A$ are also associated with Long QT syndrome type 3. However, these mutations tend to be gain of function rather than loss of function\textsuperscript{19}. There is clinical overlap in the presenting symptoms (e.g. syncope and sudden cardiac death); however the findings on an ECG are the distinguishing features. In Long QT syndrome, there is a prolongation of the QT interval that is usually not seen in Brugada syndrome. There are families with both Long QT and Brugada syndrome with one $SCN5A$ mutation.

All known genes associated with Brugada syndrome are inherited in an autosomal dominant fashion. There have been no descriptions of de novo mutations or germline mosaicism and as such extensive evaluation of the family for disease is recommended\textsuperscript{14}. Siblings of an affected individual have a 50\% risk to have also inherited the disease-causing mutation. Likewise, children of an affected individual have a 50\% chance of inheriting the mutation and being at risk for Brugada syndrome. There is a 50\% chance that either parent has the disease causing mutation. It is important to determine which parent has the mutation as his or her family members would also be at risk.

Brugada syndrome also demonstrates reduced penetrance and variable expressivity. Not every person with a mutation will show signs or symptoms of the condition and there can be variability in the phenotype within a family.
### 2.5 Diagnosis

#### 2.5.1 Clinical Diagnosis

The following table lists the diagnostic criteria for a clinical diagnosis of Brugada syndrome\textsuperscript{4,14,17}:

**Table 4: Clinical Diagnosis of Brugada Syndrome**

<table>
<thead>
<tr>
<th>Definitive diagnosis of Brugada syndrome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG Finding</td>
</tr>
<tr>
<td>Type 1 Pattern (elevation of the J wave ≥2mm with a negative T wave and coved type/gradually descending ST segment) in more than one right precordial lead (V1 to V3) in the presence or absence of sodium channel blocker. No confounding factors accounting for ECG abnormality.</td>
</tr>
<tr>
<td><strong>AND</strong></td>
</tr>
<tr>
<td>At least one of the following:</td>
</tr>
<tr>
<td>• Documented VF</td>
</tr>
<tr>
<td>• Polymorphic VT</td>
</tr>
<tr>
<td>• Family history sudden cardiac death &lt;45 years old</td>
</tr>
<tr>
<td>• Coved-type ECGs in family members</td>
</tr>
<tr>
<td>• Inducibility of VT with programmed electrical stimulation</td>
</tr>
<tr>
<td>• Syncope or nocturnal agonal respiration</td>
</tr>
<tr>
<td><strong>AND/OR</strong></td>
</tr>
<tr>
<td>Mutation in:</td>
</tr>
<tr>
<td><em>SCN5A, GDP1L, CACNA1C, CACNB2, SCN1B, KCNES, SCN3B</em>, or HCN4*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suspected diagnosis of Brugada syndrome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG Finding</td>
</tr>
<tr>
<td>Type 2 ECG Pattern (elevation of the J wave ≥2 mm with a positive or biphasic T wave and saddleback ST segment elevated ≥1 mm) in more than one right precordial lead under baseline conditions with conversion to Type 1 pattern following challenge with a sodium channel blocker</td>
</tr>
<tr>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>ECG Finding</td>
</tr>
<tr>
<td>Type 3 ECG Pattern (elevation of J wave ≥2 mm with a positive T wave and coved/saddleback ST segment elevated ≤1 mm) in more than one right precordial lead under baseline conditions with conversion to Type 1 pattern following challenge with a sodium channel blocker</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inconclusive for diagnosis of Brugada syndrome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG Finding</td>
</tr>
<tr>
<td>Type 3 ECG Pattern in more than one right precordial lead under baseline conditions with conversion to Type 2 ECG pattern following challenge with a sodium channel blocker</td>
</tr>
</tbody>
</table>
2.5.2 Use of Sodium Channel Blockers to Unmask Brugada Syndrome

Sodium channel blockers have been shown to amplify or unmask the Brugada Type 1 ECG pattern\textsuperscript{4,17,39,40}. These drugs are usually prescribed to treat arrhythmias through impairment of conduction of sodium ions through sodium channels. However, when given to patients with Brugada syndrome, sodium channel blockers can provoke typical ST segment elevation\textsuperscript{15}. They work by producing strong use-dependent blocking of fast sodium current ($I_{Na}$) secondary to their slow dissociation from the sodium channels\textsuperscript{13}.

Many patients in whom a diagnosis of Brugada syndrome has previously been made do not show consistent characteristic findings on an ECG. With this in mind, it can be difficult to identify at risk family members or infer if an individual with a Type 2 or Type 3 ECG pattern really has Brugada syndrome when those with the condition do not consistently display the Type 1 pattern. In these situations, a diagnostic challenge with a sodium channel blocker may be used to induce the Type 1 pattern\textsuperscript{4,40}. The types of drugs used include class 1A and class 1C antiarrhythmic drugs such as flecainide, procainamide, ajmaline, and pilsicainide\textsuperscript{4}. Descriptions of the protocol and precautions have been described elsewhere\textsuperscript{4,17,40–42}.

2.5.3 Genetic Testing

Genetic testing for Brugada syndrome is not necessary to establish the diagnosis. However, genetic testing can be used to confirm the diagnosis and is useful for the identification of at-risk family members\textsuperscript{5,13,14}. In 2011, the Heart Rhythm Society published a set of consensus guidelines
on the role of genetic testing for channelopathies and cardiomyopathies, including Brugada syndrome. The recommendations for Brugada syndrome genetic testing are as follows:

1. **Comprehensive or BrS1 (SCN5A) targeted Brugada syndrome (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.

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

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

These recommendations took into consideration the low yield of genetic testing at this time. On average, genetic testing for Brugada syndrome yields a disease causing mutation 30% of the time. The remaining 70% of Brugada syndrome cases remain unexplained genetically. Table 5 illustrates the eight current known genes involved with Brugada syndrome and the percentage of disease caused by each gene.

**Table 5: Frequency of Genetic Mutations Causing Brugada Syndrome**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN5A</td>
<td>15-30%</td>
</tr>
<tr>
<td>GPD1L</td>
<td>Rare</td>
</tr>
<tr>
<td>CACNA1C</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>CACNB2</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>SCN1B</td>
<td>Rare</td>
</tr>
<tr>
<td>KCNE3</td>
<td>Rare</td>
</tr>
<tr>
<td>SCN3B</td>
<td>Rare</td>
</tr>
<tr>
<td>HCN4</td>
<td>Very Rare</td>
</tr>
</tbody>
</table>
The majority of patients with a genotype positive case of Brugada syndrome have a mutation in \(SCN5A\). For this reason, the proposed testing strategy is to start with sequence analysis of \(SCN5A\). If no mutation is found, sequence analysis of \(CACN1C, SCN1B, KCNE3\), and \(SCN3B\) may be considered with the underlying expectation of low yield\(^{14}\). \(HCN4\) genetic testing is currently not available in the United States. GeneDx currently offers a Brugada syndrome panel that screens for \(SCN5A, CACN1C, CACNB2, GPD1L, SCN1B, KCNE3\), and \(SCN3B\) with a quoted detection rate of 26-41%.

### 2.5.4 Identification of At-Risk Family Members

If there is a known mutation causing Brugada syndrome in the index case, cascade screening of first degree family members to identify those who also carry the mutation and are at risk of developing symptoms\(^{5,44}\). This method allows accurate identification of which family members are at risk for Brugada syndrome. Further testing such as an electrocardiogram or provocative drug-testing may be useful in risk stratification.

In the absence of a known genetic mutation, the only methods available for the identification of at-risk family members include ECG and provocative drug testing\(^{40}\). Since Brugada syndrome is inherited in an autosomal dominant pattern of inheritance, first-degree relatives have up to a 50% chance of being affected.
2.6 MANAGEMENT

2.6.1 Risk Stratification

Management of Brugada syndrome depends on accurate risk stratification and the ability to identify patients at high risk for an arrhythmic event. Unfortunately, this area remains a source of debate among medical professionals. All studies agree that patients at the highest risk for an arrhythmic event are those with a prior history of symptoms: aborted sudden cardiac death, syncope or documented history of VT. Controversy ensues when discussing risk stratification of asymptomatic patients with a Type 1 ECG pattern. Brugada et al. described it well in a 2011 publication in *Heart Rhythm*: “In all series, [asymptomatic patients with a Type 1 ECG] has a risk between 0.5% and 3% per year of having an arrhythmic event. This event will occur in about 50% of cases as a ventricular fibrillation without previous syncopal warning. Mean age at which symptoms occur is 40 years. Accepting even the lowest published risk, a 10% event rate at 20-year follow-up in otherwise healthy patients is unacceptable. Waiting for a syncopal episode in order to react is condemning at least 50% of these patients to death.”

Brugada et al. proposed that electrophysiologic (EP) testing can be a useful tool to predict which asymptomatic patients are at high risk. In contrast, Priori et al. in the PRELUDE study found that EP testing was unable to identify those patients at high risk and proposed instead that other features such as QRS fragmentation and ventricular effective refractory period <200 ms as tools to identify high risk patients. The FINGER study also reached a similar conclusion as PRELUDE as their study population showed no correlation between EP testing and prediction of life-threatening events at follow-up. In addition, the FINGER study showed that factors such
as family history of SCD and presence of a \(SCN5A\) mutation were not predictive of arrhythmic events. Despite the controversy, EP testing may still be an effective tool for risk stratification and selection of patients for ICD implantation\(^4\).

2.6.2 Treatment of Manifestations: ICD

The only effective therapy in Brugada syndrome is an implantable cardioverter defibrillator (ICD)\(^4\). The Second Consensus Report about Brugada syndrome established the recommendations for ICD implantation in patients\(^4\). Currently, only individuals with a past history of aborted sudden death are considered to be at risk for another event and are recommended to have an ICD. Also, any individual with a history or syncope and a spontaneous type 1 ECG pattern should have an ICD. Situations where evidence weighs in favor of an ICD include history of syncope and a type 1 ECG pattern revealed by sodium channel blocker drug testing or spontaneous type 1 ECG pattern with no history of symptoms and inducible for ventricular fibrillation or tachycardia. As discussed in section 2.6.1, EP testing for risk stratification remains controversial but can be useful to identify asymptomatic patients most likely to experience an arrhythmic event and benefit from an ICD. There is much debate on management for asymptomatic individuals who do not meet recommendation criteria for an ICD.

Several studies have examined the outcome of Brugada patients treated with an ICD\(^48–51\). These studies demonstrate that in addition to proper risk stratification, the potential for adverse effects of an ICD are significant. One of the most important adverse effects to consider is the rate of inappropriate shocks. The following table was adapted from Veltman et al. and demonstrates the annual rates of inappropriate ICD shock from different studies\(^49\).
Table 6: Appropriate and Inappropriate ICD therapy in Patients with Brugada Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Patients with appropriate ICD therapy (%)</th>
<th>Annual rate of appropriate ICD therapy (%/year)</th>
<th>Patients with inappropriate ICD therapy (%)</th>
<th>Annual rate of inappropriate ICD therapy (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bordachar et al.</td>
<td>29</td>
<td>3 (10.5%)</td>
<td>3.9%</td>
<td>Not available</td>
</tr>
<tr>
<td>Daoulah et al.</td>
<td>25</td>
<td>3 (12%)</td>
<td>3.5%</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Kharazi et al.</td>
<td>12</td>
<td>2 (17%)</td>
<td>7.2%</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>Holst et al.</td>
<td>35</td>
<td>9 (26%)</td>
<td>6.6%</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Sacher et al.</td>
<td>220</td>
<td>18 (8%)</td>
<td>2.5%</td>
<td>45 (20%)</td>
</tr>
<tr>
<td>Sarkozy et al.</td>
<td>47</td>
<td>7 (15%)</td>
<td>3.8%</td>
<td>17 (36%)</td>
</tr>
<tr>
<td>Veltmann et al.</td>
<td>61</td>
<td>7 (12%)</td>
<td>2.9%</td>
<td>5 (8%)</td>
</tr>
</tbody>
</table>

Causes of inappropriate ICD shocks in this patient population can be attributed to supraventricular tachycardia, lead malfunction, double counting, external noise detection, and younger age of patients. The physical activity of younger patients is higher and therefore the occurrence of sinus tachycardia is increased in this population which can lead to inappropriate ICD discharge. Veltmann et al. recommended programming Brugada syndrome patients’ ICDs at a single, high-rate VF zone to reduce inappropriate shocks related to supraventricular tachycardia.

2.6.3 Prevention of Primary Manifestations: Anti-Arrhythmic Medication

Brugada syndrome is an inherited channelopathy caused by genetic alterations to ion channels, and as such pharmacological treatment is focused on rebalancing the ion channel current. As described previously, class 1A and class 1C antiarrhythmic drugs such as flecainide can unmask the Brugada ECG pattern and induce VT/VF and are not an effective treatment for these patients. Other common antiarrhythmic medicines such as beta-blockers and amiodarone have been shown to be ineffective. In one study, quinidine has been shown to prevent VF induction in
patients with Brugada syndrome\textsuperscript{56}. This medicine works by depressing outward potassium current ($I_{to}$). There are some concerns related to quinidine therapy as some of the side effects include the potential for QT prolongation and torsade de pointes\textsuperscript{56,57}. There is not enough long-term data at this point in time to support quinidine therapy alone instead of ICD placement in Brugada syndrome patients.

### 2.6.4 Agents and Circumstances to Avoid

Several different agents and circumstances have been demonstrated to unmask the Brugada ECG manifestations and may cause VT/VF. These include sodium channel blockers, a febrile state, vagotonic agents, $\alpha$-adrenergic agonists, $\beta$-adrenergic blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin, hyperkalemia, hypokalemia, hypercalcemia, and alcohol and cocaine toxicity\textsuperscript{4}. A comprehensive list of medications to be avoided by Brugada syndrome patients can be found at [www.brugadadrugs.org](http://www.brugadadrugs.org). This website is maintained by the University of Amsterdam Academic Medical Center, Department of Cardiology, and is updated regularly\textsuperscript{58}.

### 2.7 PSYCHOSOCIAL CONSIDERATIONS

There are limited studies that focus specifically on psychosocial aspects of Brugada syndrome. Many papers elude to decreased quality of life, anxiety, and depression in this patient population but have focused on other issues such as disease prevalence and ICD complications\textsuperscript{21,47,49,50}.
There have been studies focused on quality of life and other psychosocial implications of inherited heart disease such as Long QT syndrome and Hypertrophic Cardiomyopathy and the results of these studies can be used as a point of reference to draw correlations to Brugada syndrome patients\textsuperscript{59–62}.

### 2.7.1 Disease Burden

Brugada syndrome is diagnosed at an average age of 40 years old and is more likely to be diagnosed in a man than in a woman. At-risk family members can be identified based on ECG analysis, provocative drug testing or genetic testing if there is a known family mutation. Patients identified as having Brugada syndrome face a risk of arrhythmic events of up to 4.1% per year\textsuperscript{22}. An arrhythmic event can include syncope and sudden cardiac death.

Patients with Long QT and Hypertrophic cardiomyopathy also face a significant risk of arrhythmic events and sudden cardiac death. These patients often present for genetic counseling services with high levels of general anxiety. A study by Hamang et al. found that approximately 25% of the patients in their study had clinical anxiety symptoms\textsuperscript{60}. This anxiety tends to be heart focused and can manifest as cardio-protective avoidance, heart-focused attention and fear of sudden cardiac death and heart sensations. Anxiety tends to be increased in these inherited heart conditions independent of demographic covariates such as age and gender as well as clinical variables such as a recent sudden cardiac death in the family\textsuperscript{60}.

This same research group conducted a one year follow up on their patient population and found continued evidence to support their claims\textsuperscript{61}. In addition, they found that heart-focused anxiety was higher in patients with a clinical diagnosis of Long QT syndrome or Hypertrophic
Cardiomyopathy as compared to patients at genetic risk for these conditions\textsuperscript{61}. Hamang et al. hypothesized that the reason for this increased anxiety may be due to the fact that these patients live with the genetic risk of a life-threatening disorder and the uncertainty regarding cardiac symptoms\textsuperscript{60}. The same set of criteria applies to Brugada syndrome and it is reasonable to anticipate the same concerns in that patient population.

A study by Andersen et al. examined psychosocial aspects of living with Long QT syndrome including their daily life challenges and coping strategies\textsuperscript{59}. Sources of worry and anxiety identified in this study were unresolved emotions and worry on behalf of family members. In agreement with Hamang et al. this study also identified uncertainty about their condition and cardiac symptoms as sources of anxiety. Another theme identified by Andersen et al. was a sense of loneliness and isolation caused by having a rare condition. Few people in the general population are familiar with Long QT syndrome and as a result those with the condition felt that they had no close friends who could understand their perspective. This sense of isolation is common in other rare genetic conditions as well and Brugada patients may experience the same sentiment. Referral to a support group or online discussion forum may be of benefit to these patients to allow them to communicate with those who also have the condition.

Another theme identified by Andersen et al. was that fear of something happening to their children or grandchildren is often the largest concern patients with Long QT syndrome experience\textsuperscript{59}. These participants favored early genetic testing and informing their children about their genetic status and risk for arrhythmic events and felt that this information would not induce unnecessary anxiety or worry for their children. A study by Smets et al. investigated the potential negative impact of informing children about their genetic risk status\textsuperscript{62}. The results of their study showed that there was no difference in quality of life of carrier children as compared to a
representative sample of peers. They offered some caution as these results may be reassuring to those who express concern for informing children about their risk status yet it is possible that some may still experience problems and proper counseling and attention should be given to these patients.

Patients with inherited cardiovascular disease are at risk for depression. In the Long QT symptomatic patient population, depression has been associated with arrhythmic events. Interestingly, the study by Hintsa et al. did not show a relationship between asymptomatic carriers of a disease causing mutation and depression. General cardiovascular research has identified an association between depression and increased probability of various cardiac events such as VT and VF. There may be a connection between altered autonomic nervous system function and arrhythmias. This phenomenon may also apply to Brugada syndrome patients and medical professionals should take care to identify and assist those patients with signs of anxiety and depression. A study by Daoulah et al. that focused on assessing outcome after ICD placement in Brugada patients documented that five of their patients were diagnosed with depression.

### 2.7.2 Genetic Testing

Genetic testing for Brugada syndrome only identifies a disease causing mutation in 30% of symptomatic individuals. The remaining 70% still have the clinical diagnosis but have no genetic explanation for the condition. In addition, if a mutation is not identified then it becomes more difficult to assess family members and determine who is and is not at risk. Research has shown that in families where a mutation is already known, patients coming in for genetic testing have a
lower level of heart-focused attention and monitoring of cardiac activity than patients who are uncertain whether genetic testing has been performed in the family\textsuperscript{61}. Medical professionals performing genetic testing should bear in mind that genetic testing is both an individual and a family affair\textsuperscript{43}.

Many parents with inherited cardiovascular disease express concern for their children’s well being\textsuperscript{61}. In other genetic conditions, parents have experienced guilt related to having passed on a disease causing mutation to their children\textsuperscript{65–67}. Brugada syndrome is inherited in an autosomal dominant manner and children of an affected parent have a 50\% chance of inheriting the disease causing allele. Strategies for dealing with guilt in this type of situation revolve around effective communication that there is nothing that the parent could have done or not done to prevent this from happening. In fact, genetic testing can help alleviate anxiety as those who test negative for the family mutation are not at risk for arrhythmic events.

2.7.3 Implications of an ICD

There have been several research studies that have focused on the psychosocial implications of having an ICD\textsuperscript{8,68–71}. In Brugada syndrome, an ICD is recommended for all patients with a past history of aborted sudden cardiac death or syncope. For asymptomatic patients, the recommendations are less clear as more research is needed for proper risk stratification. This creates a dilemma for the asymptomatic patient and the physician. To quote Brugada et al., current methods “condemn patients to an individual approach based more on the personal experience of the treating physicians with other Brugada syndrome patients and the fear of dramatic events…This might lead to unnecessary overtreatment with devices.”\textsuperscript{47}”
Regardless of risk stratification, the final decision on whether or not to place an ICD rests on the patient. Motivators to accept an ICD include awareness of sudden cardiac death risks and the physician’s recommendations. Factors such as trust in the physician, social influences, and health state influence the decision making process the most. Most patients begin their decision making process after a health-related “trigger”. For Brugada patients, this could be either an aborted sudden cardiac death or syncope. In asymptomatic patients, the trigger could be a history of sudden cardiac death in a family member or palpitations leading to a fear of sudden cardiac death. The decision process can take a few moments for some patients and up to two years in others.

To assist patients with their decision making process, it is important to discuss all the benefits and limitations of the device. In particular to Brugada syndrome, the limitations of the device and complications should be addressed. As described previously in this document, there is concern for a high rate of inappropriate shocks in Brugada patients. The rate of inappropriate shocks is often greater than appropriate therapy and the annual risk of inappropriate shocks has been reported to be as high as 18% per year. An incidental finding by Daoulah et al. was depression in Brugada patients with an ICD. Two of their patients suffered from insomnia due to phobia after receiving inappropriate shocks. In addition, Brugada patients often receive an ICD at a younger age compared to other patients with an ICD. This results in higher rates of complications such as device change out surgery and lead malfunction.

It is rare for Brugada syndrome to affect children, but there have been reports of adolescents being affected and having an ICD. Less than 1% of ICD patients are under 21 years of age and this population may have a unique set of psychosocial considerations. There can be negative stigma associated with body image, inability to do some activities, and increased
frequency of doctors’ appointments. An interesting theme that emerged from the study by Rahman et al. was that parents often viewed their children as being “normal” but the adolescents described themselves as being “not normal” or “different”\textsuperscript{69}. One adolescent with Brugada syndrome in the study described his life after placement of the device as follows: “…that I am limited more um [pause] that I have to be careful what I do, that I’m not as able as I was beforehand but am a lot more aware now. \textsuperscript{69}.”
3.0 AIMS OF THE STUDY

3.1 SPECIFIC AIM 1: ASSESSMENT OF BRUGADA MANAGEMENT

To assess the factors that determine management decisions for Brugada syndrome patients.

3.2 SPECIFIC AIM 2: ASSESSMENT OF QUALITY OF LIFE

To determine how Brugada syndrome patient management impacts quality of life and if any differences exist between symptomatic, asymptomatic, those with an ICD and those without an ICD. Three different hypotheses were generated:

1. Is there a difference in quality of life between those with a genetic mutation that causes Brugada syndrome and those without one?

2. In individuals who have a genetic mutation that causes Brugada syndrome, is there a difference in quality of life between those who are symptomatic and those who asymptomatic?

3. In symptomatic individuals with a genetic mutation that causes Brugada syndrome, is there a difference in quality of life between those who have an ICD and those who do not?
4.0 MATERIALS AND METHODS

4.1 STUDY POPULATION

The Institutional Review Board at the University of Pittsburgh approved all human studies. The study population chosen for this investigation is a large multigenerational family with Brugada syndrome. The full history of this family has been described previously in a research study by Weiss et al. 72. To summarize, the proband was referred to the University of Pittsburgh Medical Center after a syncopal event in 1996. At-risk family members were enrolled in a research study to elucidate the genetic cause of Brugada syndrome in the family. All family members have a brief clinical history and a 12-lead ECG on file. Some members participated in additional cardiac testing which included 24-hour holter monitors, echocardiograms, procainamide drug testing, and cardiac MRIs. Serial ECGs have been obtained on most family members every 6 months to a year when possible.

When this family was first enrolled in the research study, the underlying genetic etiology of Brugada syndrome was not known. Family members were considered affected or not based on the findings of their ECGs. Brugada syndrome was diagnosed in any family member who had at least a single ECG with a RBBB pattern (RSR’ in leads V1 or V2) and greater than 1 mm of J-point elevation and ST elevation (measured 80 ms after the J-point) in the right precordial leads.
V1 through V3. However, it is well established that due to reduced penetrance of Brugada syndrome not every person with the condition will have characteristic findings on ECG.

In 2007, the underlying genetic etiology was identified as an A280V mutation in \(GPD1L\)\(^{35}\). All family members were then tested to see if they carried the familial mutation or not, even those who were considered to be unaffected based on ECG findings. Genetic testing allowed the identification of at risk individuals as well as the ability to define those who were truly affected and unaffected.

### 4.2 ASSESSMENT OF PATIENT ICD AND GENETIC STATUS

A questionnaire was created to assess patient demographic information and medical management decisions. The document can be found in Appendix B. The questionnaire was divided into four sections.

#### 4.2.1 Part I: General Information

This section was designed to better understand the participant’s demographics. The questions focused on age, gender, ethnicity, education, marital status, occupation, and living arrangements.

#### 4.2.2 Part II: Diagnosis History

The purpose of this section was to assess the participant’s understanding of his or her personal diagnosis and family history. The questions dealt with whether or not the participant had a
diagnosis of Brugada syndrome, genetic status, and clinical symptoms. Participants were also asked to identify other family members diagnosed with Brugada syndrome.

4.2.3 Part III: Device History

The third section of the questionnaire focused on whether or not the participant had an ICD. It also provided an opportunity for the participants to share their personal reasons as to why they did or did not choose an ICD.

4.2.4 Part IV: Follow Up History

The last portion of the questionnaire was designed to assess how compliant the participants were in following with a cardiologist and/or an electrophysiologist based on ICD status.

4.3 ASSESSMENT OF QUALITY OF LIFE

The Medical Outcome Study 36-item short-form health survey version 2.0 (SF-36v2) was used to assess each participants quality of life. The SF-36v2 is a validated instrument for assessing quality of life that utilizes eight health domains: physical functioning, role limitation caused by physical problems, bodily pain, general health perception, vitality, social functioning, role limitation caused by emotional problems and mental health. The eight scales are scored from 0 to 100. The survey uses norm-based scoring which allows comparisons among different populations. The SF-36v2 also provides two summary measures, physical component summary
(PCS) and mental component summary (MCS), to further characterize quality of life. The figure below qualitatively depicts how the eight different scales are combined to form the PCS and the MCS.

![Diagram showing the SF36v2 scales and their relationship to the component summaries.]

Figure 3: The SF36v2 Scales and Their Relationship to the Component Summaries

### 4.4 DATA COLLECTION

For this study, all participants were contacted in person. Informed consent was obtained and each participant filled out a Long Term Follow Up Questionnaire (Appendix B) and the Medical Outcome Study 36-item short-form health survey version 2.0 (SF-36v2). The questionnaires
were stored with the participants’ original research files containing their medical histories and cardiac testing information.

4.5 STATISTICAL ANALYSIS

The SF-36v2 questionnaire was analyzed using the SF Health Outcomes™ Scoring Software (Quality Metric Inc., Lincoln, USA), as already described. Additional statistical tests were used to evaluate the significance of the results including two-sample t test and regression analysis.
5.0 RESULTS

5.1 POPULATION DEMOGRAPHICS

As described in Materials and Methods, the family approached for this research study is a large, multigenerational family. Over two hundred family members are enrolled in the larger research study that this thesis project is a part of. Clinical follow-up of the family has been continued for the past fifteen years with annual visits for updated ECGS and status reports. The family is of Italian ethnicity with no known consanguinity. There are no other known genetic conditions in this family. A pedigree of the entire family is presented below (Figure 4).
Seventeen total participants were enrolled in the research study. One family member was approached and declined to participate in the study. The mean age of the study population was 57 years old with a range from 36 to 89 years old. Twelve of the participants were male (71%) and five were female (29%). Ten of the participants had the familial A280V GPD1L mutation (59%). Of those with the GPD1L mutation, seven (70%) were affected and had an identifiable Brugada ECG pattern with or without clinical symptoms. The remaining three participants with a mutation have had no clinical symptoms or identifiable Brugada ECG pattern to date. Table 7 summarizes the general characteristics of this study population.

Table 7: General Characteristics of Study Population

<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>Gender</th>
<th>Genetic Status*</th>
<th>Affected†</th>
<th>ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>M</td>
<td>A280V</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>M</td>
<td>A280V</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>M</td>
<td>WT</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>F</td>
<td>A280V</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>M</td>
<td>A280V</td>
<td>Yes</td>
<td>Plan on getting one</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>M</td>
<td>A280V</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>39</td>
<td>M</td>
<td>A280V</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>F</td>
<td>A280V</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>89</td>
<td>M</td>
<td>A280V</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>M</td>
<td>A280V</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>M</td>
<td>WT</td>
<td>No</td>
<td>No, had one in the past</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>M</td>
<td>WT</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>63</td>
<td>M</td>
<td>WT</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>75</td>
<td>M</td>
<td>A280V</td>
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<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>85</td>
<td>F</td>
<td>WT</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>38</td>
<td>F</td>
<td>WT</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>43</td>
<td>F</td>
<td>WT</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*GPD1L
† Past history of syncope, palpitations, or dizziness/lightheadedness and/or Brugada ECG Pattern
Seven of the participants with the familial mutation have experienced clinical symptoms or have a documented Brugada ECG pattern (Table 8). None of the participants have experienced an aborted sudden cardiac death, and there is no history of sudden cardiac death in this family overall. All seven of these participants have an identifiable Brugada ECG pattern. Three have a history of syncope and have received an ICD due to this clinical symptom. Five report having experienced palpitations as well as feeling dizzy/lightheaded.

Table 8: Clinical Symptoms of Participants with the GPD1L Mutation

<table>
<thead>
<tr>
<th>Participant</th>
<th>Clinical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (proband)</td>
<td>Brugada ECG Phenotype, syncope, dizzy/lightheaded, palpitations</td>
</tr>
<tr>
<td>2</td>
<td>Brugada ECG Phenotype</td>
</tr>
<tr>
<td>5</td>
<td>Brugada ECG Phenotype, palpitations, dizzy/lightheaded</td>
</tr>
<tr>
<td>6</td>
<td>Brugada ECG Phenotype, syncope, dizzy/lightheaded, palpitations</td>
</tr>
<tr>
<td>9</td>
<td>Brugada ECG Phenotype</td>
</tr>
<tr>
<td>10</td>
<td>Brugada ECG Phenotype, palpitations, dizzy/lightheaded</td>
</tr>
<tr>
<td>14</td>
<td>Brugada ECG Phenotype, syncope, dizzy/lightheaded, palpitations</td>
</tr>
</tbody>
</table>

Three of the family members with a mutation and clinical symptoms have an ICD, one of which is the proband (Table 9). The average age of ICD placement was 56 years old with a range from 39-75. Two of the individuals with an ICD have received shocks from their device. Participant 1 (proband) has had two episodes of polymorphic ventricular tachycardia that were terminated by appropriate ICD shocks. Participant 6 has received four shocks from the device; all four were consistent with inappropriate shocks due to a low monitoring threshold. Although participant 14 has not received a shock, there is a documented 20-beat episode of ventricular flutter that self-terminated and did not require a shock from the ICD.
Table 9: Characteristics of Participants with ICDs

<table>
<thead>
<tr>
<th>Participant</th>
<th>Current Age</th>
<th>Gender</th>
<th>Age at Device Placement</th>
<th>Shocked</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>M</td>
<td>56</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>M</td>
<td>39</td>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>75</td>
<td>M</td>
<td>75</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

One family member, participant 11, had an ICD in the past but has since had it removed. Brugada syndrome was diagnosed in this family in 1997; however, the genetics underlying the condition in were not discovered until 2007. Until the mutation in \textit{GPD1L} was discovered, the only means of identifying at risk family members were an ECG and drug testing. Based on nonspecific ECGs and a history of syncope, participant 11 was believed to have Brugada syndrome and be at risk for arrhythmias. He chose to have an ICD placed to protect against fatal arrhythmias. However, once the familial mutation was discovered and the family revisited, it was discovered that participant 11 did not have the A280V \textit{GPD1L} mutation and was thus not at risk for arrhythmias due to Brugada syndrome. As a consequence, this family member chose to have the ICD removed as it was no longer necessary.

Participant 5 reported that he plans on getting an ICD in the future. In addition to the Brugada ECG phenotype, he has experienced palpitations and felt dizzy/lightheaded before but denies syncope.

Only two patients are regularly following with a local cardiologist and both are clinically affected and have ICDs. None of the clinically affected, gene positive individuals without a mutation are currently seeing a local cardiologist. Additionally, none of the participants who have the familial mutation but no clinical symptoms see a local cardiologist.
5.2 REASONS FOR CHOOSING AN ICD

The Long Term Follow Up Questionnaire was designed to evaluate the reasons and motivations Brugada syndrome patients choose or decline an ICD. In this study, three individuals with the A280V \textit{GPD1L} had an ICD. An open-ended question on the questionnaire gave the participants an opportunity to share the reason why they choose to have an ICD placed. Their responses are listed below:

- “I needed it.” –Participant 1, proband
- “No choice.” –Participant 6
- “To help my children to be to know what to look for with their heart. Get regular check up, also because of family history.” –Participant 14

Participant 5 reported that he plans on getting an ICD in the future. His response to the open-ended question of why he will get one in the future is as follows:

- “If symptoms should appear at some point, then I don’t have much of a choice.”
  –Participant 5

A follow up question asked why the participant did not have an ICD currently to which participant 5 responded:

- “I do not need one yet.” –Participant 5

As previously mentioned, participant 11 was incorrectly identified as having Brugada syndrome and had an ICD in the past. An open-ended question was designed to ascertain the reason for choosing to have an ICD removed. His response was:

- “Do not have Brugada syndrome.” –Participant 11
Although not marked on the questionnaire as planning to get an ICD in the future, participant 2 answered the opened ended question regarding why he will choose to get an ICD in the future. He wrote:

- “If I ever need one. For the kids for my wife – for longevity.” –Participant 2

He also answered the follow up question about why he chose not to have an ICD currently with:

- “I do not need one yet.” –Participant 2

5.3 RESPONSES TO THE SF-36V2 HEALTH SURVEY

The participants were divided into four separate groups to facilitate data analysis (Table 10). Group 1 consists of the two participants who carry the GPD1L mutation but have no clinical symptoms and is referred to as the “Gene Positive Asymptomatic”. Participant 8 was excluded from data analysis as she was recently diagnosed with Crohn’s disease and her responses to the SF36v2 Health Survey were reflective of that health condition and not Brugada syndrome. Group 2 consists of the four participants who carry the GPD1L mutation and are clinically affected but do not have an ICD and is referred to as “Gene Positive Symptomatic”. Group 3 consists of the three participants who carry the GPD1L mutation, are clinically affected, and have an ICD. Group 3 is referred to as “Gene Positive Symptomatic ICD.” The last group, Group 4, consists of the seven participants who do not carry the family mutation in GPD1L and is referred to as “Gene Negative”.

38
Table 10: Group Classifications of Participants

<table>
<thead>
<tr>
<th>Group</th>
<th>Size (n)</th>
<th>Participants</th>
<th>Age</th>
<th>Gender</th>
<th>Symptoms</th>
<th>ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
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<td>4</td>
<td>54</td>
<td>F</td>
<td>None</td>
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<td>Asymptomatic</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>4</td>
<td>2</td>
<td>43</td>
<td>M</td>
<td>Brugada ECG Phenotype, palpitations, dizzy/lightheaded</td>
<td>No</td>
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<td>Gene Positive</td>
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<td>36</td>
<td>M</td>
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<td></td>
<td>10</td>
<td>72</td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>3</td>
<td>1 (proband)</td>
<td>70</td>
<td>M</td>
<td>Brugada ECG Phenotype, syncope, dizzy/lightheaded, palpitations</td>
<td>Yes</td>
</tr>
<tr>
<td>Gene Positive</td>
<td></td>
<td>6</td>
<td>45</td>
<td>M</td>
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<td></td>
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<tr>
<td>Symptomatic ICD</td>
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<td>14</td>
<td>75</td>
<td>M</td>
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<td></td>
</tr>
<tr>
<td>Group 4</td>
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<td>3</td>
<td>63</td>
<td>M</td>
<td>None</td>
<td>No</td>
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<td>Gene Negative</td>
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<td>M</td>
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<tr>
<td></td>
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<td>60</td>
<td>M</td>
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<td>63</td>
<td>M</td>
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<td></td>
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<td>17</td>
<td>43</td>
<td>F</td>
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</tbody>
</table>

5.3.1 General Responses of All Groups within the Study Population

The SF36v2 scores all eight scales from 0-100. These eight scales are physical functioning (PF), role limitation caused by physical problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitation caused by emotional problems (RE) and mental health (MH). The software package normalizes the raw scores (0-100) to a mean of 50 and a standard deviation of 10 referred to as norm based scoring (NBS). In addition, US general population norms from 1998 are built into the algorithm. Thus the NBS allows accurate comparison between the eight scales and is already compared with general population data. For this reason, the NBS values were used for data analysis. There were no missing responses on any of the surveys.

Overall, the average for each scale and summary component fell within one standard deviation of the mean. The NBS for each group and the average NBS for the groups are
compared in Table 11. The average score for the PCS in Group 1 was 44.64; Group 2 was 50.86; Group 3 was 57.91; and Group 4 was 48.41. The average MCS score for each group was as follows: 57.31 for Group 1, 60.23 for Group 2, 50.13 for Group 3, and 55.34 for Group 4. The lowest scale group average was found in the BP scale in Group 1 (39.30). The highest scale group average was observed in the VT mean for Group 2.

### Table 11: SF36v2 Norm Based Scores for All Participants

<table>
<thead>
<tr>
<th>Participant</th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
<th>VT</th>
<th>SF</th>
<th>RE</th>
<th>MH</th>
<th>PCS</th>
<th>MCS</th>
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</tr>
<tr>
<td>4</td>
<td>46.51</td>
<td>56.85</td>
<td>41.41</td>
<td>48.17</td>
<td>64.58</td>
<td>56.85</td>
<td>55.88</td>
<td>61.27</td>
<td>44.49</td>
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</tr>
<tr>
<td>7</td>
<td>52.82</td>
<td>56.85</td>
<td>37.18</td>
<td>45.78</td>
<td>45.85</td>
<td>56.85</td>
<td>55.88</td>
<td>44.38</td>
<td>48.42</td>
<td>50.50</td>
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<td>49.67</td>
<td>56.85</td>
<td>39.30</td>
<td>46.98</td>
<td>55.22</td>
<td>56.85</td>
<td>55.88</td>
<td>52.83</td>
<td>46.46</td>
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<tr>
<td>2</td>
<td>57.03</td>
<td>56.85</td>
<td>55.36</td>
<td>44.83</td>
<td>67.70</td>
<td>56.85</td>
<td>55.88</td>
<td>61.27</td>
<td>52.64</td>
<td>61.13</td>
</tr>
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<td>50.29</td>
<td>52.93</td>
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<td>51.13</td>
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<td>64.09</td>
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</tr>
<tr>
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<td>55.88</td>
<td>41.56</td>
<td>58.33</td>
<td>50.73</td>
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<tr>
<td><strong>Group Average</strong></td>
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<td>47.21</td>
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<td>58.78</td>
<td>52.95</td>
<td>53.10</td>
<td>51.62</td>
<td>48.41</td>
<td>55.34</td>
</tr>
</tbody>
</table>

5.3.1.1 Adjustment for Age – PCS

The data was first evaluated to see if there was any affect of age on the physical scales and component summary. Regression analysis identified the following trends (Figure 5). When looking at the PCS, there was a trend toward lower physical quality of life and increasing age
although it was not statistically significant (p-value = 0.259). When looking at each physical scale individually, the same trend was observed for all four. None of these regression analyses were statistically significant either. The PF and RP scales showed the strongest correlation with age with a p-value of 0.085 and 0.079 respectively.
Figure 5: PCS and Related Summary Measures Correlation with Age
5.3.1.2 Adjustment for Age – MCS

Figure 6: MCS and Related Summary Measures Correlation with Age

MCS

\[
y = 0.0497x + 52.97
\]

\[
R^2 = 0.0207
\]

\[
p\text{-value} = 0.595
\]
Regression analysis was also used to evaluate age variation for the mental health scales and summary component (Figure 6). The mental quality of life tended to increase with older age but was not statistically significant (p-value = 0.595). Each of the four scales that comprise the MCS was evaluated separately for age variation. VT and MH showed a weak trend toward increased quality of life with older age, however, it was not statistically significant (p-value 0.423 and 0.432 respectively). Of interest, SF and RE showed a trend toward decreased mental quality of life and older age. These trends were also not statistically significant (SF p-value = 0.267; RE p-value = 0.118).

5.3.1.3 Adjustment for Gender – PCS

Two-sample t test for unequal variance was used to evaluate the data for variation according to gender. There were twelve total males in this study and four females. For the PCS, males had a higher average score than females (Figure 7). The average score for the males was 52.77 and the average score for the females was 43.94. This difference was not statistically significant (p-value 0.226).
Each of the four physical scales was also analyzed for variation with gender. Similarly to PCS, all four scales had higher averages in the males than females (Table 12). These differences were not statistically significant.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td>12</td>
<td>53.87</td>
<td>54.61</td>
<td>50.32</td>
<td>53.77</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>4</td>
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<td>49.51</td>
<td>43.95</td>
<td>42.57</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td></td>
<td>0.168</td>
<td>0.370</td>
<td>0.281</td>
<td>0.083</td>
</tr>
</tbody>
</table>

### 5.3.1.4 Adjustment for Gender – MCS

MCS was also analyzed using a two-sample t test for unequal variance to evaluate gender variation (Figure 8). The MCS average in males was 56.44 and in females 54.02. The mental health quality of life was higher in the males similar to the physical quality of life; however this difference was also not statistically significant (p-value = 0.556).

![Figure 8: MCS Variation with Gender](image.png)
Each of the four mental scales was also analyzed for variation with gender (Table 13). In general, these scores were all higher in males than in females although none reached statistical significance.

<table>
<thead>
<tr>
<th>n</th>
<th>VT</th>
<th>SF</th>
<th>RE</th>
<th>MH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>12</td>
<td>59.90</td>
<td>56.40</td>
<td>53.29</td>
</tr>
<tr>
<td>Females</td>
<td>4</td>
<td>56.00</td>
<td>50.03</td>
<td>51.02</td>
</tr>
<tr>
<td>p-value</td>
<td>0.514</td>
<td>0.220</td>
<td>0.544</td>
<td>0.370</td>
</tr>
</tbody>
</table>

5.3.2 Hypothesis 1: Gene Negative vs. Gene Positive

To assess the difference in quality of life between participants with A280V *GPD1L* mutation (Gene Positive) and those without it (Gene Negative), a two-sample t test for unequal variance was performed (Table 14). Overall, there was no significant difference in any of the eight scales between those with and without the mutation.

<table>
<thead>
<tr>
<th>n</th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
<th>VT</th>
<th>SF</th>
<th>RE</th>
<th>MH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene Negative Group 4</td>
<td>7</td>
<td>49.51</td>
<td>50.21</td>
<td>47.21</td>
<td>50.62</td>
<td>58.78</td>
<td>52.95</td>
<td>53.10</td>
</tr>
<tr>
<td>Gene Positive Groups 1-3</td>
<td>9</td>
<td>53.52</td>
<td>55.76</td>
<td>49.91</td>
<td>51.24</td>
<td>59.03</td>
<td>56.24</td>
<td>52.42</td>
</tr>
<tr>
<td>p-value</td>
<td>0.323</td>
<td>0.108</td>
<td>0.584</td>
<td>0.900</td>
<td>0.955</td>
<td>0.257</td>
<td>0.836</td>
<td>0.238</td>
</tr>
</tbody>
</table>

The summary component scores, PCS and MCS, were also evaluated to see if any differences existed by genetic status (Figure 9). The scores were higher for participants who had the mutation for both PCS and MCS. However, neither one had a significant difference.
5.3.3 **Hypothesis 2: Asymptomatic vs. Symptomatic**

The data was analyzed with a two-sample t test for unequal variance to assess differences in quality of life in participants who had the genetic mutation and either had symptoms or did not (Group 1 versus Group 2-3). In general, the physical scales (PF, BP, and GH) were on average higher in the symptomatic group (Table 15). The average for BP in the asymptomatic group was 39.30 and the average in the symptomatic group was 52.94. This difference reached statistical significance with a p-value of 0.017. However, there was a small number of participants in Group 1 (n=2).

In the mental scales, there was no general trend observed as some averages were higher in symptomatic participants (VT and MH) and others were lower (SF and RE). None of the mental scale differences were significant (p-values 0.231 – 0.718).
<table>
<thead>
<tr>
<th>Symptom Status</th>
<th>n</th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
<th>VT</th>
<th>SF</th>
<th>RE</th>
<th>MH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>2</td>
<td>49.67</td>
<td>56.85</td>
<td>39.30</td>
<td>46.98</td>
<td>55.22</td>
<td>56.85</td>
<td>55.88</td>
<td>52.83</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>7</td>
<td>54.63</td>
<td>55.45</td>
<td>52.94</td>
<td>52.46</td>
<td>60.12</td>
<td>56.07</td>
<td>51.44</td>
<td>56.85</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td></td>
<td>0.321</td>
<td>0.356</td>
<td>0.017</td>
<td>0.091</td>
<td>0.693</td>
<td>0.356</td>
<td>0.231</td>
<td>0.718</td>
</tr>
</tbody>
</table>

The MCS and PCS summaries were analyzed as well (Figure 10). The PCS mean was higher in the symptomatic group (53.88 versus 46.46). This difference was almost significant with a p-value of 0.065. The differences in MCS were reversed as compared to PCS scores. The mean was higher in the asymptomatic group (57.31 versus 55.90), yet this difference did not reach statistical significance (p-value = 0.872).

**Figure 10: PCS and MCS Differences by Brugada Symptom Status**

### 5.3.4 Hypothesis 3: No ICD vs. ICD

The final data analysis was a two-sample t test for unequal variance to evaluate differences between symptomatic patients with and without a device (Group 2 versus Group 3). All
participants in these two groups were male. When comparing the eight scales, none of the differences were significant. PF, RP, and BP were higher in those with and ICD whereas VT, RE, and MH were lower (Table 16).

Table 16: SF26v2 Mean Responses by ICD Status

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
<th>VT</th>
<th>SF</th>
<th>RE</th>
<th>MH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ICD</td>
<td></td>
<td>4</td>
<td>52.82</td>
<td>54.40</td>
<td>50.71</td>
<td>53.29</td>
<td>62.24</td>
<td>55.49</td>
<td>53.94</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td>3</td>
<td>57.03</td>
<td>56.85</td>
<td>55.92</td>
<td>51.34</td>
<td>57.29</td>
<td>56.85</td>
<td>48.11</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.391</td>
<td>0.391</td>
<td>0.270</td>
<td>0.755</td>
<td>0.479</td>
<td>0.391</td>
<td>0.535</td>
<td>0.168</td>
</tr>
</tbody>
</table>

PCS was higher in those with an ICD, similar to the results found with the physical scales PF, RP, and BP (Figure 11). This difference was almost significant with a p-value of 0.069. The difference between MCS means was significant with a p-value of 0.013. The mean MCS in ICD participants was 50.13 as compared to 60.23 in the symptomatic patients without an ICD.

Figure 11: PCS and MCS Differences by ICD Status
6.0 DISCUSSION

6.1 SPECIFIC AIM 1

The purpose of the Long Term Follow Up Questionnaire was to evaluate the reasons a patient with Brugada syndrome chooses or declines an ICD. In this sample, three participants chose to get an ICD and one reported planning to get one. All four of these participants answered an open-ended question about the reason they made their decision. In addition, one participant does not plan on getting an ICD in the future but still answered the question. The responses are listed in the Results section of this document and described again below.

When evaluating the responses, two themes emerged. The first theme identified was ICD decision making due to a sense of inevitability or necessity. Three of the responses fell into this category. The first two were from participants who had an ICD already and the last was from the participant who plans to get an ICD in the future:

- “I needed it.” – Participant 1 (proband)
- “No choice.” – Participant 6
- “If symptoms should appear at some point then I don’t have much of a choice.” – Participant 5
These responses indicate that the patients’ decision making to accept an ICD was more of a necessity and not an option. These findings are similar to a study by Agard et al. that looked at the decision making process regarding ICD therapy in patients with heart failure and prior history of arrhythmias. In their study, patients who survived a cardiac arrest felt that the offer of an ICD could not be refused. This decision reflects a belief that doctors know what is best for the patient and a trust in their decision for the patient. It also reflects a belief that life is valuable and that any precautions should be taken to preserve and prolong it.

The second theme that emerged was the decision to choose an ICD for family or spouse benefit. Two responses fell into this category, one from a participant with an ICD and one from a participant who does not plan on getting an ICD in the near future but answered the question regardless:

- “To help my children to be to know what to look for with their heart. Get regular check up, also because of family history.” –Participant 14
- “If I ever need one. For the kids for my wife – for longevity.” –Participant 2

These participants may have also felt a sense of necessity and/or inevitability but they did not report it in their responses. Instead, their responses highlight that the main reason for choosing an ICD was or would be for the benefit and reassurance of a spouse or family member. Brugada syndrome carries a risk for sudden cardiac death that can be difficult for both the patient and their family to come to terms with and accept. An ICD can intervene should a serious arrhythmia occur and prevent sudden death. In these patients, the ability to provide a sense of relief and safety to their spouses and family was reason enough to choose an ICD.

Based on these responses, medical professionals working with Brugada syndrome patients may find it useful to take time to carefully explain the benefits, risks, and limitations of
an ICD to those considering one. Although it is difficult to estimate the exact risk of arrhythmia and sudden cardiac death in this patient population, there have been several studies that estimate the risk and the differences observed between these groups can be presented to the patients as a range of risks. Hopefully in the future more research will become available to clarify the risks and provide more accurate information to aid patients in their decision-making process.

6.2 SPECIFIC AIM 2

The SF36v2 health survey was used to evaluate quality of life in this patient sample. The NBS values were used for comparison as these values have all been scored to have the same mean (50) and standard deviation (10). The algorithm also incorporates general population norms for the general United States Population circa 1998. An individual score below 45 or a group mean below 47 can be interpreted as being below the average range for the general population.

Only 16 participants were used for the data analysis; Participant 8 was excluded due to a recent diagnosis of Crohn’s disease. When evaluating the responses overall for each participant, eleven participants had scores lower than 45 in at least one scale. The most common scale with a score lower than 45 was bodily pain (BP) and general health (GH). These lower scores are reflected in the score for PCS, which was below 45 in six of the participants. None of the MCS scores were below 45, indicating no differences in mental quality of life as compared to the general population.

The majority of the group means were above 47, however, there were three scales that were below the cut-off of 47 and all were in Group 1. The BP, GH and PCS means were 39.30,
46.98, and 46.46 respectively. As BP and GH are used in the calculation of PCS, it follows that a lower quality of life in those physical scales would lead to a lower physical component summary.

In this data set, a trend was observed that as age increased, the physical quality of life decreased. Even though the correlation was not significant, this overall trend has been observed and reported on for the SF-36v2. The MCS component for this sample showed a positive correlation between increasing age and increased quality of life. However, when examining each of the four scales that comprise MCS (VT, SF, RE, and MH), the trend varied. These trends also were comparable to reported age variation within these scales. Thus overall, the variation with respect to age matched what is typically seen in the US population.

The data set was also analyzed for variation with gender. Across the board, the males’ responses were higher. None of the scales or component summaries reached statistical significance. However, like age variation, the SF36v2 responses tend to be higher in males and lower in females. In short, gender variation observed in this population also correlates with the trend in the US population.

The first hypothesis sought to identify any differences in quality of life between family members with the A280V GPD1L mutation and those without it. There were no statistical differences in quality of life between the two groups when comparing the summary scores and the eight individual scales. In general, the scores were higher in the Gene Positive group. This data indicates that those with the genetic diagnosis of Brugada syndrome in this family in general have a good quality of life.

The second hypothesis was to determine if any differences due to symptom status existed in those with the genetic diagnosis of Brugada syndrome. The PCS was higher in those with symptoms while their MCS scores were lower. A similar pattern was seen in the eight scales.
with those contributing to PCS being higher and those contributing to MCS being lower. Only the difference between BP scores reached statistical significance; the rest had p-values greater than 0.05. In summary, symptomatic Brugada syndrome patients have a comparable quality of life to asymptomatic patients with a tendency toward better physical quality of life.

The third and final hypothesis was to evaluate differences in quality of life due to ICD status in symptomatic Brugada patients. None of the eight scales were significant on their own. PCS was higher in those with and ICD with a p-value of 0.069. The MCS score, in contrast, was lower in those with an ICD and the p-value was 0.013. This data indicates that Brugada patients with an ICD in this family experience a higher physical quality of life but a lower mental quality of life.

With respects to physical quality of life, those with an ICD may experience less physical limitations as they feel dependent and protected by their ICD whereas those without an ICD may limit their physical activities due to fear of an arrhythmic event. Even though a trend was noticed, the means for both groups were above 50, the US population mean, and indicate that both have a good quality of life. An explanation of the difference in MCS due to ICD status could be explained by a fear of ICD shock leading to anxiety as has been reported in other patient populations with these devices.

A study by Probst et al. also looked at the impact of ICD implantation on quality of life in Brugada patients. In their study population, they did not identify any difference in responses to the SF36 (the first version the 36-item short form health survey) between Brugada patients with or without a device. However, they also implemented a questionnaire to the participants that showed 48% of Brugada patients felt that the diagnosis had a negative impact on their quality of life. 55% of participants with an ICD reported no difficulties with their physical activities, which
is comparable to this research with a high physical quality of life in those with an ICD. Sixty-two percent of the participants in the study by Probst et al. felt that having an ICD was detrimental to their social quality of life, citing difficulties with obtaining insurance and obstacles in their career. These same difficulties could be possible explanations for the lower mental component summary in ICD patients observed in this research study.

In conclusion, Brugada syndrome patients in this family enjoy a good quality of life as compared to both the US population and family members without the condition. Symptomatic Brugada patients also experience a good quality of life; however, those with an ICD in this study had a lower mental quality of life. As discussed in relation to decision-making and ICD status earlier, medical professionals, especially genetic counselors, should bear this information in mind when discussing the option of ICD placement with these patients.

6.3 LIMITATIONS AND FUTURE DIRECTIONS

6.3.1 Limitations

This study was conducted in a small sample (seventeen total participants but only sixteen used for data analysis). Gender and age distribution was not equal in the different sub-groups. It is possible that these may account for some of the differences observed in this study. All of the participants in this study were from the same multigenerational family. The differences in quality of life may be unique to this family and may not be reproducible in other populations. As all the participants came from a single family, there may be shared values, attitudes, perspectives, and
environmental factors that affect world-views regarding quality of life and medical treatment. Additional studies will confirm if the conclusions drawn from this family have universal applications.

The SF36v2 was not specifically created for use in the Brugada syndrome patient population. Another survey may be able to better identify differences in quality of life in these patients.

The way the Long Term Follow Up Questionnaire, Part II: Diagnosis History was worded failed to assess patient understanding of their genetic status. There was not an option for participants to choose “No” for diagnosis and still continue on to answer if they had participated in genetic testing. The information reported on from this questionnaire regarding genetic status was taken from their medical record. All other responses to the questionnaires were used directly as reported by the patient.

6.3.2 Future Directions

This study demonstrated that there is a difference in quality of life in Brugada syndrome patients with an ICD versus those who do not. Future research should be aimed at enrolling a larger sample size and focusing on Brugada patients with and without a known genetic mutation as well as those with or without an ICD. It would also be worthwhile either to continue this study in the same family and attempt to administer the SF36v2 to all family members with the condition and reassess the differences or to enroll other families and compare the quality of life between families to assess for differences in coping mechanisms.
APPENDIX A

INSTITUTIONAL REVIEW BOARD CONSENT FORM
ADDENDUM

CONSENT TO ACT AS A SUBJECT IN A CLINICAL STUDY

TITLE: FAMILIAL STUDIES IN CARDIOVASCULAR DISEASE

PRINCIPAL INVESTIGATOR
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Graduate Student Researcher
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Research Nurse Coordinator
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Pittsburgh PA 15213
(412) 383-7339

SOURCE OF SUPPORT: National Institute of Health

RESEARCH PURPOSE
You or your child are currently a participant in a research study because you or a family member has a history of abnormal electrocardiograms (ECG’s) and sudden cardiac death. In your family, the cause of these events is due to an inherited heart condition called Brugada syndrome or Long QT syndrome. Because you or your child have been diagnosed with one of these syndromes, we are asking you to complete two questionnaires about your experiences and choices related to these syndromes as well as your overall health and wellbeing. These questionnaires will take about 30 minutes total to complete, and contain questions about how you or your family member were diagnosed, treatment received (if any), and current health status. We are asking 25 people who are enrolled in the main study to complete this questionnaire. We hope to obtain a better understanding of the choices about implantable cardioverter defibrillators and overall health and wellbeing in families with Brugada syndrome or Long QT syndrome.

POTENTIAL BENEFITS
There are no direct benefits to you by taking part in this research study. By answering the questions in these questionnaires you will help us identify information that we can provide that would help you to better understand these syndromes. The information from the study may help educate other families with either Brugada syndrome or Long QT syndrome.
POTENTIAL RISKS
The risks of completing the questionnaires include potential discomfort answering personal questions and the possibility of a breach of confidentiality. Any information about you obtained from this research will be kept as confidential as possible. All records related to your involvement in this research study will be stored in locked file cabinets in the Cardiovascular Institute of the University of Pittsburgh. Your identity on these records will be indicated by a code number rather than by your name and the information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by name in any publication of research results unless you sign a separate consent form giving your permission (release).

ALTERNATIVES
This research study involves no medical therapy or treatment. The alternative to participating in this study is to not participate.

VOLUNTARY CONSENT:
All of the above has been explained to me by one of the Co-investigators in the research study and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study and that the researchers listed on the first page of this form will answer such future questions. Any questions I have about my rights as a research participant will be answered by the Human Subjects Protection Advocate at the University of Pittsburgh IRB Office 1-866-212-2668.

A copy of this consent form will be given to me, my signature below means that I have freely agreed to participate in this research study.

Subject’s Signature Date

CERTIFICATION OF INFORMED CONSENT
I certify that I have explained the nature and purpose of this research study to the above named individual(s), and have discussed the potential benefits and possible risks of study participation.

Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise.

Printed Name of Person Obtaining Consent Role in Research Study

Signature of Person Obtaining Consent Date
APPENDIX B

LONG-TERM FOLLOW UP QUESTIONNAIRE
**Part I: General Information**

1. **ID Number:**

2. **Current Age:**

3. **Gender:** Male or Female

4. **Ethnicity:**
   - a. African-American
   - b. Asian
   - c. Hispanic
   - d. Native American
   - e. White
   - f. Other:

5. **What is the highest level of education you have completed:**
   - a. Some high school
   - b. Graduated High School/GED
   - c. Some college/vocational school
   - d. Graduated college/vocational school
   - e. Some professional/grad school
   - f. Graduated professional/grad school

6. **What is your current marital status:**
   - a. Single
   - b. Engaged
   - c. Living Together
   - d. Married
   - e. Divorced
   - f. Separated
   - g. Widowed

7. **Are you currently employed outside the home?**
   - a. Yes – full time
   - b. Yes – part time
   - c. Yes – seasonal
   - d. No – but looking for a job
   - e. No – receive social security benefits or disability benefits
   - f. No – not looking for a job
   - g. Retired
8. Which one of the following best describes your current living arrangements?
   a. Living alone
   b. Living with spouse/partner
   c. Living with spouse/partner and children
   d. Living with parents
   e. Living with a roommate who is not a family member
   f. Other: ____________________________

**Part II: Diagnosis History**

1. Have you been diagnosed with one of the following heart conditions?
   a. Brugada Syndrome
   b. Long QT Syndrome
   c. None of the above (Skip to question 6, page 3)

2. If you have one of these heart conditions, when did you find out?
   a. Date: ______/______/_______
   b. Age: __________

3. If you have one of these heart conditions, how did you find out?
   a. In a hospital/doctor's office due to symptoms
   b. In a hospital/doctor's office due to abnormal electrocardiogram (ECG)
   c. From screening due to family history

4. Did you participate in genetic testing?
   a. No
   b. Yes, and a mutation was found
   c. Yes, but no mutation was found

5. Have you ever experienced any of the following symptoms? Circle all that apply.
   a. Feeling lightheaded or dizzy
   b. Fainting
   c. Irregular heart beat (e.g., skipped or racing)
   d. Survived cardiac arrest

6. Does anyone in your family have one of the following heart conditions?
   a. Brugada Syndrome
   b. Long QT Syndrome
   c. Neither
7. If yes, how are they related to you? Circle all that apply
   a. Mother
   b. Father
   c. Brother
   d. Sister
   e. Son
   f. Daughter
   g. Grandmother
   h. Grandfather
   i. Uncle
   j. Aunt
   k. Cousin
   l. Other

Part III: Device History
1. Were you told by a doctor that you might need an implantable cardioverter defibrillator (ICD)?
   a. Yes
   b. No (skip to Part IV, page 6)

2. Do you currently have an ICD?
   a. Yes
   b. No, but I plan on getting one. (skip to question 6, page 4)
   c. No and I do not plan on getting one (skip to question 7, page 5)
   d. No, but I had one in the past (skip to question 8, page 5)

3. If you currently have an ICD or had one in the past, when was it placed?
   a. Date Placed: _________/_________/____________
   b. Age: ______________

4. If you have an ICD, have you ever been shocked?
   a. Yes
   b. No (skip to question 6, page 4)

5. If you have been shocked:
   a. How many times have you been shocked?
      i. Number: ______________________
   b. When were you shocked? List the date for each shock (approximate date and month is acceptable)
      i. Dates: _______________________________________________________
      _______________________________________________________
   c. Did you go to the hospital or doctor’s office when you were shocked?
      i. Yes, Hospital/Doctor’s Name: _________________________
      ii. No
6. If you have an ICD or plan on getting an ICD, what was the main reason you decided to get one?

__________________________________________________________________

__________________________________________________________________

__________________________________________________________________

__________________________________________________________________

__________________________________________________________________

__________________________________________________________________

7. If you do not have an ICD, what was the main reason for choosing not to get one?

__________________________________________________________________

__________________________________________________________________

__________________________________________________________________

__________________________________________________________________

__________________________________________________________________

__________________________________________________________________
8. If you had an ICD in the past and no longer have one, why did you decide to get it removed?

Part IV: Follow Up History
1. Do you currently see a cardiologist on a regular basis?
   a. Yes   b. No   c. Plan to do so

2. If yes, please answer the following questions:
   a. What is the name of your cardiologist?
      i. ____________________________________________
   b. How often do you see them?
      i. ____________________________________________
   c. What is the primary reason for seeing the cardiologist?
      i. ____________________________________________

3. Do you currently see an electrophysiologist?
   a. Yes   b. No   c. Plan to do so

4. If yes, please answer the following questions:
   a. What is the name of your electrophysiologist?
      i. ____________________________________________
   b. How often do you see them?
      i. ____________________________________________
   c. What is the primary reason for seeing the electrophysiologist?
      i. ____________________________________________

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BIBLIOGRAPHY


