The BCL11A Gene and the 3D Printing of an Adjustable Hyperextension Orthotic Knee Brace for Patients with Hypotonia

By

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Abstract

The B-cell lymphoma/leukemia 11A (BCL11A) gene plays an important role in the development of the brain. A mutation of the BCL11A gene causes individuals to have developmental delays among other abnormalities. Two of the key symptoms are hypotonia and hypermobility. These two issues contribute to hyperextension of the knee joint. To help limit the hyperextension presented in the patient studied, this project utilizes rapid-prototyping technology through 3D-printing to develop an adjustable, custom knee brace that will attach to the patient's current ankle-foot orthoses (AFOs). Through a series of qualitative and quantitative assessments, the effectiveness of this patient-specific knee brace will be determined. If successful, this brace could open doors for a novel way to fabricate cost-effective, time efficient, adjustable orthotics. A BCL11A gene mutation is a rare condition and in the context of this study only one patient was tested. However, the methods presented to mitigate hyperextension go beyond this mutation, potentially impacting numerous patients living with hypermobility symptoms. While an exact number of people who suffer from hypotonia cannot be determined, those who suffer from diseases such as cerebral palsy, muscular dystrophy, Down syndrome, Tay-Sachs disease, and Multiple Sclerosis suffer from hypotonia to a certain degree. In the context of this paper, the hypotonia and hyperextension shown by our patient will be studied, along with the fabrication of a knee brace to mitigate these symptoms.

INTRODUCTION

Project Overview

This project studies the effects of a mutation of the BCL11A gene and how it has caused hypotonia and joint laxity in an eight-year-old male patient. The patient's joint laxity and low muscle tone cause him to hyperextend his knees, and as the patient grows this will become a greater problem as added stress is placed on the knee joint. The patient currently wears ankle foot orthoses (AFOs) to assist with his gait, however they do not address the hyperextension of the patient's knees. The goal of this project was to 3D print an adjustable hyperextension orthotic knee brace that will connect to the patient's current AFOs.

The brace was drawn in Autodesk Inventor and then was 3D printed using MatterHackers PRO Polylactic Acid Filament. The brace was designed to be adjustable in girth and length in order to be adjustable as the patient grows. The brace was tested using both qualitative and quantitative assessments. Surveys were administered to parents, therapists, and teachers to monitor the effectiveness of the brace. Force plate technology and MaxTRAQ software was used to gather data that was used to help evaluate the effectiveness of the brace. The design of the brace is cost-effective, time efficient, and readily available. The goal of this project is not only to improve the quality of life of individuals like our patient, but also to develop a brace that could be marketable to help others who suffer from hypotonia or joint laxity.

The BCL11A Gene

The BCL11A gene, located on chromosome two, encodes a zinc finger transcription factor and serves two main purposes, one in the hematopoietic system and the other in the development of the brain. Zinc finger transcription factors assist in protein binding and gene expression. The hematopoietic system includes the organs and tissues comprised in the production of blood. In regards to the hematopoietic system, the BCL11A gene is essential for the advancement of erythrocytes, a blood cell in bone marrow containing hemoglobin, where it facilitates the change from fetal to mature forms of hemoglobin (Estruch, 2018). In a study by Basak, it was determined that the BCL11A gene was key to neurodevelopment. The BCL11A gene plays a crucial role in the transition from fetal hemoglobin (HbF) to adult hemoglobin (HbA) shortly after birth. In patients with a mutation of the BCL11A gene, HbF production is not silenced leading to developmental delays (Basak et al., 2015). Extensive research has been conducted on the role of BCL11A in the hematopoietic system, but far less information is known as to its role in the brain. The role of BCL11A in the brain and how these neurodevelopmental disorders result in disability will be the focus of this paper.

With only twelve confirmed cases of BCL11A gene mutations in the world, finding trends between patients can be challenging. However, a mutation of the BCL11A gene has been shown to cause underdevelopment of the cerebellum, an area of the brain which regulates muscle activity and coordination (Shimbo et al., 2017). One clinical report described the case of a seven-year-old boy (Patient 1) in Western Europe who also has a mutation in the BCL11A gene. Patient 1 showed signs of intellectual disability, difficulties with speech, and hypotonia across his various motor systems. In addition to sharing similar impairments as our patient, neither of the boy’s parents had any history of neurodevelopmental disorders (Soblet et al., 2017). Like our patient, Patient 1 was enrolled in both speech and physical therapy and placed into a special education program at an early age. In a cognitive test at the age of five, Patient 1 performed poorly, especially in the area of vocabulary. Patient 1 had difficulty doing activities that would seem commonplace for most seven-year-old boys. In the clinical study, Patient 1 had delays in developing skills such as riding a bike, catching a ball, handling a fork and knife, and handwriting (Soblet et al., 2017). The traits of Patient 1 are similar to those experienced by our patient.

Haploinsufficiency of the BCL11A gene is the reason many individuals suffer from developmental disorders which range from language development to hyperactivity disorder (Chen et al., 2018). Haploinsufficiency is a condition in which having a single working copy of an allele is insufficient. In a case study by Peter, an 11-year old boy (Patient 2) with a deletion of the BCL11A gene is reported. In this study, Patient 2 has childhood apraxia of speech, dyspraxia, hypotonia, mild intellectual delays, and difficulties with attention and focus. Like our patient, Patient 2 did not show signs of cranial or skeletal irregularities, microcephaly, or internal organ defects. Mobility issues were observed in Patient 2 resulting in developmental delays such as walking. Walking was observed at 28 months (Peter et al., 2014). In the study by Soblet, Patient 1 with the same mutation did not sit unsupported until 11 months and did not walk until 24 months (Soblet et al., 2017). Our patient sat unsupported at 9 months, crawled at 12 months and did not walk until he was 18 months old. A typical child can sit unsupported at around 5 months, crawl at 8 months, and walk at 12 months (Payne, 2008).

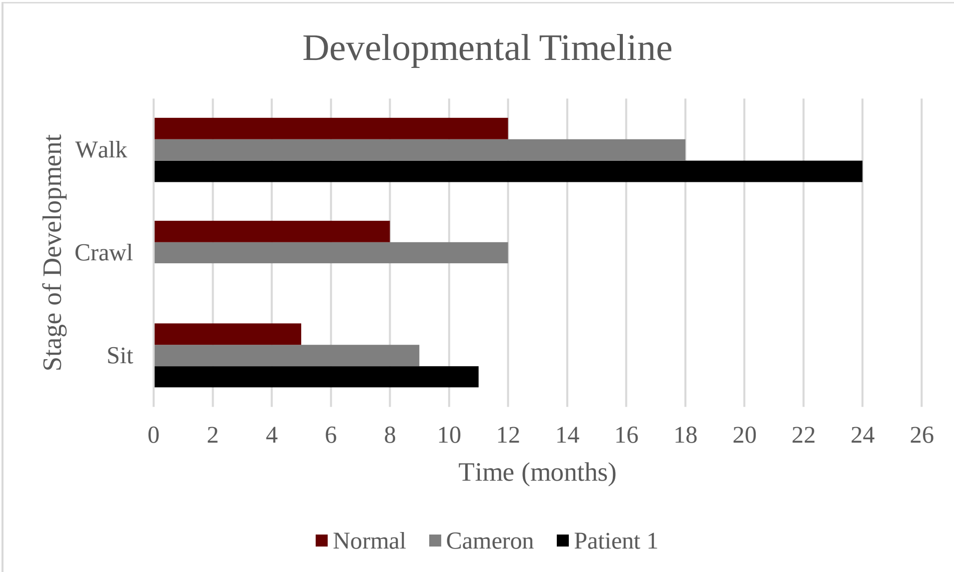

Figure 1: A timeline comparing the development of a normal child, Cameron, and Patient 1.

Most patients with a mutation of the BCL11A gene experience some degree of intellectual disability, abnormal muscle tone, delays in fine and gross motor skills, delayed growth, difficulty with speech, hypotonia, facial deformities, and even sporadic stints of epilepsy (Yoshida et al., 2017). Fine motor skills require hand-eye coordination and more precise control of one's body movements. An example of a daily fine motor skill is holding a pencil in one's hand. Gross motor skills engage large muscle groups and include more general movements such as walking. In another study, including patients that also had BCL11A mutations, these patients presented the usual signs of autism spectrum disorder, developmental delays, hypotonia, and facial abnormalities (Basak et al., 2015). Table 1, shown below, by Dias shows ten individuals who have been identified with BCL11A mutations and compares various conditions that are common among BCL11A gene mutation patients. It shows the variety of disorders that can be seen in patients with a BCL11A mutation. These features described range from global developmental delay to intellectual disability to joint hypermobility and much more (Dias et al., 2016).

Table 1. Genetic and Clinical Characteristics of Individuals with De Novo *BCL11A* Mutations

Individual	1	2	3	4	5	6[a]	7	8	9	10[b]	11[c]	Summary of Features
BCL11A mutation[d]	c.139A>C (p.Thr47Pro)	c.143G>T (p.Cys48Phe)	c.198C>A (p.His66Gln)	c.529C>T (p.Gln177Ter)	c.2035_2037delinsC (p.Ser679GlnfsTer47)	c.1545delinsGGCTTC (p.Phe515LeufsTer5)	c.1775_1776insTGG CTCAGCGG (p.Glu593GlyfsTer9)	c.154C>T (p.Gln52Ter)	c.193G>T (p.Glu65Ter)	c.1325_1325del (p.Leu442ProfsTer37)	c.792_793insC (p.Leu265ProfsTer3)	3 missense; 8 nonsense/ frameshift
Decipher ID	262471	262952	261658	268026	275695	280953	NA	NA	NA	NA	NA	
Mutation class	missense	missense	missense	loss of function	loss of function	loss of function	loss of function	loss of function	loss of function	loss of function	loss of function	
Sex	F	M	F	F	F	F	F	F	M	F	M	3 M, 8 F
Microcephaly	–[e]	–[e]	+	+	+	+	+	–[e]	–[e]	NA	NA	5/9
Intellectual disability	mild-moderate	moderate-severe	moderate	moderate	moderate	+[f]	moderate	moderate	moderate	severe	NA	10/10 (average moderate)
Developmental Milestones (Age of Achievement in Months)												
Sat independently	7	10	12	NA	11	NA	NA	14	12	NA	NA	~11
Walked independently	20	36	24	22	45	NA	NA	23	36	30	NA	~29.5
First words	22	27	36	16	NA[g] (80 words at 100 months)	24–30	NA (few words at 33 months)	60	36	NA (2 words at 6 years)	NA	~32
Craniofacial Features												
Downslanting palpebral fissures	+	–	–	+	–	NA	+	+	–	NA	NA	4/8
Epicanthus	–	–	–	–	+	NA	+	–	+	NA	NA	
Strabismus	+	+	+	+	+	NA	+	+	+	NA	NA	8/8
Blue sclera in infancy	–	–	–	+	+	+	–	–	–	NA	NA	3/9
Flat midface	+	+	+	+	+	NA	–	–	+	NA	NA	6/8
Thin upper lip	+	+	+	+	+	NA	–	+	+	NA	NA	7/8

(Continued on next page)

Table 1. *Continued*

Individual	1	2	3	4	5	6[a]	7	8	9	10[b]	11[c]	Summary of Features
Everted lower lip	+	+	–	+	–	NA	+	+	+	NA	NA	6/8
Nose	anteverted	small nares	anteverted; full tip	–	–	NA	full tip	small nares; full tip	small nares; full tip	NA	NA	4/8
Micro/ retrognathia	–	–	–	–	–	retro	–	retro	micro	NA	NA	3/9
Additional craniofacial features	frontal upsweep, cleft uvula	coarse hair	–	small mouth,[h] high palate, pointed chin	small mouth, plagiocephaly, synophrys	–	large tip of the nose, broad bridge, flared eyebrows, telecanthus	large tip of the nose, high palate	high nasal bridge	NA	NA	
External ear anomalies	–	–	+[i]	+[j]	+[k]	NA	+[l]	–	+[m]	NA	NA	5/8
Additional Physical and Neurologic Features												
Joint hypermobility	+	–	+	+	+	NA	+	+	+	NA	NA	7/8
Short stature	–	–	–	–	–	+	+	–	–	NA	NA	2/9
Gait abnormalities	broad based	broad based, truncal ataxia	–	–	–	NA	–	–	ataxia	NA	NA	3/8
Other	anteriorly placed anus, dyspraxia		fetal pads, bilateral coxa valga, valgus foot deformity		hernia repair	congenital hip dislocation, delayed bone age	GE reflux	large 2^{nd} metacarpals, scoliosis	pectus excavatum	NA	NA	
Behavioral Features												
ASD	–	+	–	–	–	NA	–	–	–	+	+	3/10
Repetitive behavior	+	+	+	+	–	NA	–	–	–	–	NA	4/9
Other behavior problems	emotional lability	recurrent hand flapping	sensory abn., self-injurious behavior	recurrent hand flapping/ biting	none reported	NA	none reported	anxiety, eating disorder	none reported	attention deficit	NA	6/9
Sleep disturbance	–	+	+	+	–	NA	–	–	–	+	NA	4/9

(Continued on next page)

Table 1. ***Continued***

Individual	1	2	3	4	5	6[a]	7	8	9	10[b]	11[c]	Summary of Features
Additional Investigations												
MRI	slightly reduced WM volume	small CV	NA	normal	VM	NA	NA	atrophy of the superior CV	mild hypoplasia of the CC	NA	NA	
Hemoglobin F %	20.8%	8%	8.7%	NA	26.3%	NA	NA	3.1%	8.6%	NA	NA	6/6

Abbreviations are as follows: GE, gastroesophageal; ASD, autism spectrum disorder; Abn, abnormalities; WM, white matter; VM, ventriculomegaly; CV, cerebellar vermis; CC, corpus callosum; NA, not available. Ascertainment: individuals 1 to 6, the DDD study (1 to 3 reported in previous DDD study,[6] 4 to 6 identified subsequently); individuals 7 and 8, clinical exome sequencing; individual 9, PARI 2011 study.
[a]Individual 6 has an additional probable pathogenic copy number variation (4.3 Mb duplication: dup15q15.3q21.1).
[b]Mutation reported by de Rubeis et al.[20]
[c]Mutation reported by Iossifov et al.[36]
[d]*BCL11A* mutations are annotated to transcript NM_022893.3, ENST00000335712 (GRCh37).
[e]OFC measured between percentiles 9 and 25.
[f]Severity unknown.
[g]No words at 28 months.
[h]Microstomia, with intercomissural distance ≤ −2 SD.
[i]Unilateral (left) flat helix, prominent anti-crus.
[j]Bilateral microtia (< −2 SD), asymmetric low-set ears, with overfolded and cupped helix, attached earlobes.
[k]Low-set ears with overfolded helixes and attached earlobes.
[l]Thick, overfolded helixes.
[m]Dysplastic, posteriorly rotated ears.

Table 1: Describes the genetic and clinical characteristics of patients with BCL11A mutations (Dias et al, 2016)

Many of the effects of a BCL11A mutation described above are seen in Cameron. In a report by the patient's geneticist, the individual was described as having hypotonia, motor delay, irregular gait, hypermobility within his joints, seizures, autistic tendencies, and an abnormal electromyography. Both of the patient's parents tested negative for the mutation (McDonald, 2018). In observing Cameron weekly, it can be seen that he does have abnormal muscle tone, hypermobile joints, and hypotonia that leads to the hyperextension of his knees. Before delving into Cameron's hyperextension the term hypotonia needs to be discussed in greater detail.

Hypotonia

In its simplest understanding, hypotonia is reduced muscle tone. However, the concept of muscle tone is vague and somewhat hard to define without defining all of the aspects that contribute to it. In a study by Martin, 300 surveys were sent out to 150 physical therapists and 150 occupational therapists in an effort to define hypotonia. The therapists were asked questions addressing strength, mobility, posture, fatigue, and flexibility. After reviewing all of the completed surveys, this study determined that a child with hypotonia is likely to show decreased strength, fatigue easily, demonstrate delayed development of motor skills, poor posture, hypermobility of joints, increased flexibility, and poor attention (Martin et al., 2005). While this study concludes by saying more research needs to be done, this description of hypotonia and what has been observed in Cameron are nearly identical from a biomechanical standpoint. Cameron's hypotonia affects his handwriting, speech, and gait, and causes his muscles to fatigue at a faster rate. As a result of his hypotonia, Cameron is also highly flexible with little resistance from his muscles, especially his hamstring and quadriceps muscles, contributing to the hyperextension of his knees. For the remainder of the paper, the focus will be placed on the lack of muscle tone that leads to hypermobile joints, specifically the knee joint.

Hypermobility and Hyperextension

Hypermobility of the knee joint and overall increased flexibility leads to hyperextension of the knee joint, which if uncorrected could be detrimental as Cameron ages. Currently, Cameron's hypermobility affects his overall gait and balance. If uncorrected, as he ages, he could one day damage ligaments of the knee such as the anterior cruciate ligament (ACL) or the medial collateral ligament (MCL) (Ramesh et al., 2005).

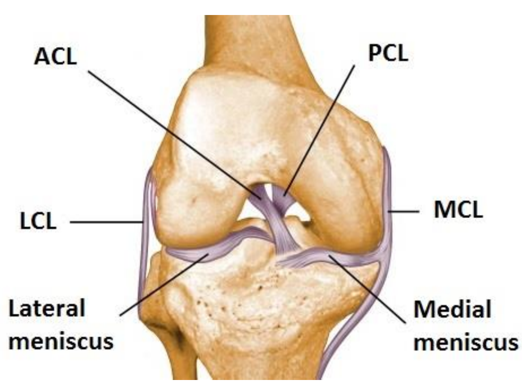

Figure 2: The picture above shows the major ligaments of the knee.

The patient could also undergo an anteromedial rim fracture of his medial tibial plateau as a result of his hypermobility and hyperextension (Chanasit et al., 2013). As he ages, he could begin to develop osteoarthritis in his knees as a product of his hypermobile joints (Beighton et al., 2012). Osteoarthritis could lead to the need for knee injections, partial or even total knee replacement.

In an effort to help Cameron's hyperextension, our Biomedical Engineering senior design team set out to 3D-print an adjustable hyperextension orthotic knee brace for Cameron. The knee brace was to be cost-effective, time efficient and easily available. Measurements of the patient were taken, the knee brace was drawn in AutoDesk Inventor, printed on the TAZ LulzBot 3D Printer, and then finally fitted to the patient. The goal of the project was to mitigate hyperextension tendencies presented by the patient during day-to-day activities.

3D Printing vs the traditional cascade cast

As stated previously, the goal of the project was to be cost-effective, time efficient, and readily available. Another goal as stated in the title was for the brace to be adjustable since the patient will be growing. All of these were made goals of the project after determining the limitations of the traditional cascade casts currently available. Cameron currently wears AFOs that run from his toe, up his heal and calf, and stop right below his knee. Figure 3 below shows a picture of his current AFOs. The current AFOs provide Cameron with greater stability when walking and slow his rate of fatigue. However, they do not provide him support surrounding his knees to prevent hyperextension. Thus, a knee brace customized to the patient was necessary to address this issue.

Figure 3: A picture of the patient's ankle-foot orthoses.

Cameron's current orthotic provider takes about one month to fit him, cast the custom mold, and fabricate the brace. This brace also costs upwards of hundreds of dollars. Having to get new braces every 3-4 months with a child that is continuing to grow becomes expensive and time-consuming. Once fitted, the 3D-printed brace can take less than 24 hours to be fabricated and the material cost of the PLA, padding, and Velcro is less than $12. In addition, the 3D printer is accessible, located in the Agricultural and Biological Engineering building on campus. With easy access, it is very easy to remodel the design and have the newly designed part printing in a number of minutes. Lastly, and most importantly for a growing child, the knee brace is adjustable in both length and girth. The notches on the 3D printed brace and the Velcro extend the lifespan of the brace as the patient grows.

Patient Information

Dr. Adam Knight and Mrs. Amy Knight's eight-year-old son, Cameron, has a pathogenic mutation of his B-cell lymphoma/leukemia 11A (BCL11A) gene. Cameron was diagnosed with this mutation in April of 2018, at the age of seven, after undergoing various different neurological and genetic tests the past four years. The Knight family was glad to finally have a diagnosis after years of testing. With only twelve reported cases of this mutation globally, there is limited research on this genetic mutation. As a result of this genetic mutation, Cameron suffers from developmental delays in his fine and gross motor skills, hypotonia, and occasional seizures. He also suffers from muscle weakness, fatigue and ataxia, also known as impaired coordination. In order to improve his quality of life, Cameron attends occupational and physical therapy sessions weekly at Kids Therapy Spot in Starkville, and has also received aquatic therapy at Columbus Orthopedic, which the family hopes to continue this summer. Additionally, he receives speech therapy, occupational therapy, and physical therapy at school. While at school, Cameron wears ankle-foot-orthoses (AFOs) and uses a wheelchair to travel long distances.

While observing Cameron, the hyperextension he exhibits in both knees, during daily activities such as walking, jumping or going up and down stairs has been a significant issue. The AFOs provide Cameron with some stability and support, however, he still hyperextends his knees. This hyperextension is not a significant problem now, however, as Cameron grows, it will become a greater problem as added stress is placed on his knee joint. The focus of this 3D-printed brace is to help with Cameron's hypotonia and overall muscle weakness and joint laxity. Targeting Cameron's biomechanical delays, it is our hope that the 3D-printed knee brace will attach to his current AFOs, reduce his overall hyperextension, and improve his gait.

MATERIALS AND METHODS OF TESTING

Materials

The knee brace was printed on the TAZ LulzBot 3D Printer, shown below, using MatterHackers White PRO Series Polylactic Acid (PLA) Filament. Plastazote Self-Adhesive Padding (1/8 inch thick) was placed on the interior of the brace to prevent rubbing and irritation. Four Velcro straps were also used to secure the brace at the top and bottom. Many iterations of the brace were created to determine the best design and size.

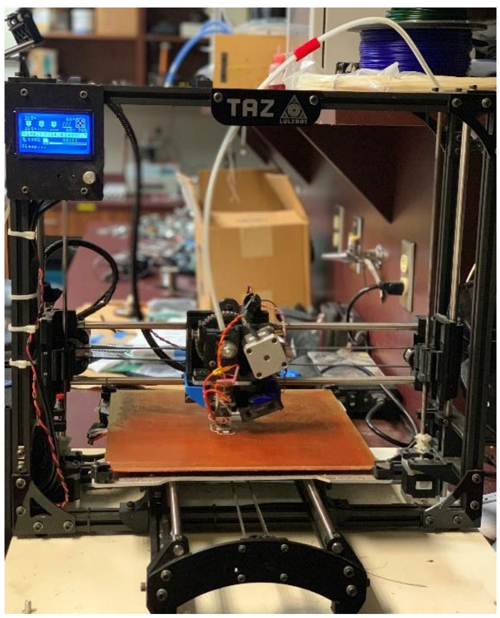

Figure 4: The 3D printer used to fabricate the brace.

Design

Several designs were generated and iterations were edited in Autodesk Inventor. First, measurements of Cameron were taken. An average child grows around three inches every year, so the brace was made adjustable to counterbalance the expected growth of the patient. The drawings of each of the final parts are shown below in Figures 5-8.

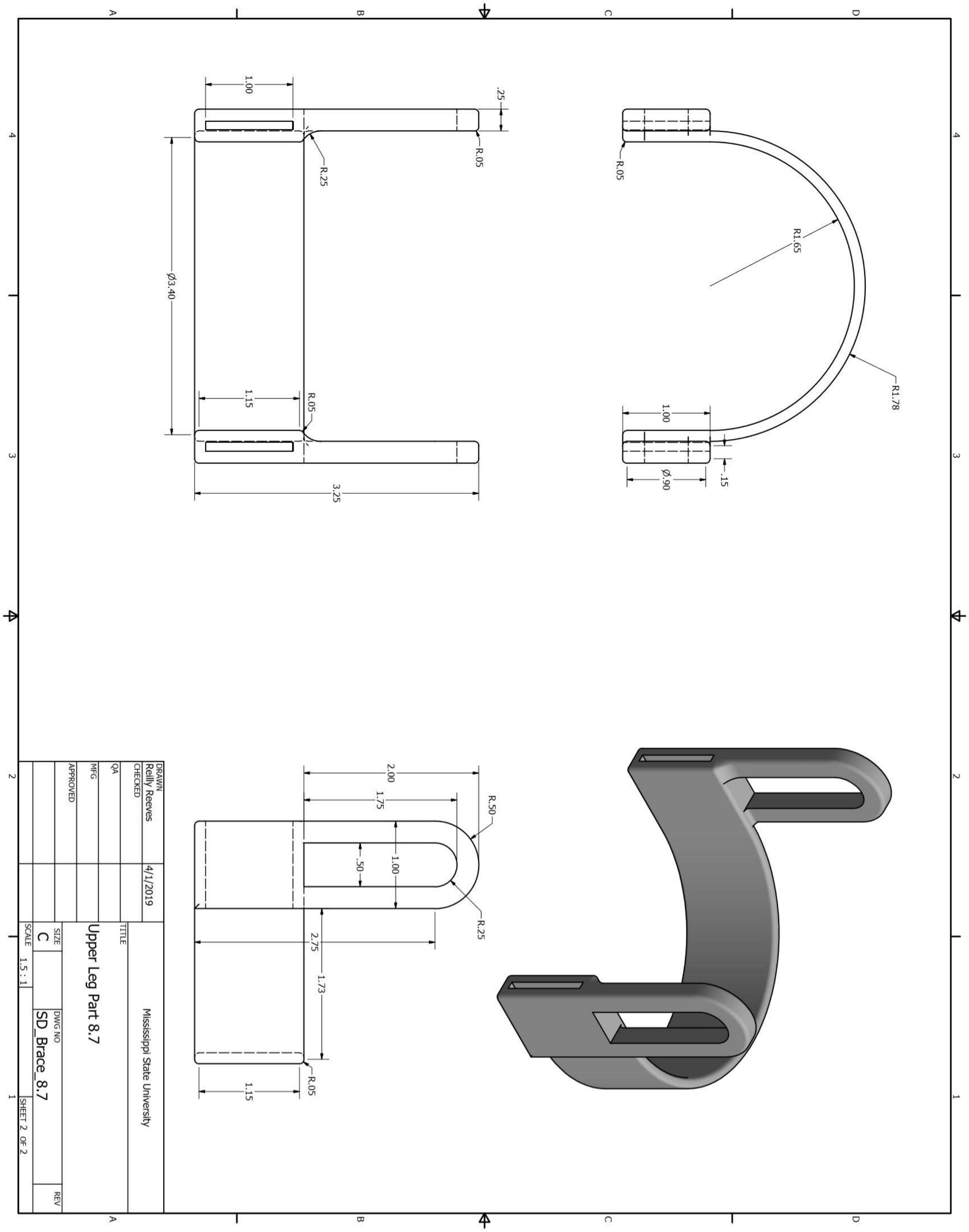

Figure 5: A drawing of the upper leg part of the final brace rendering.

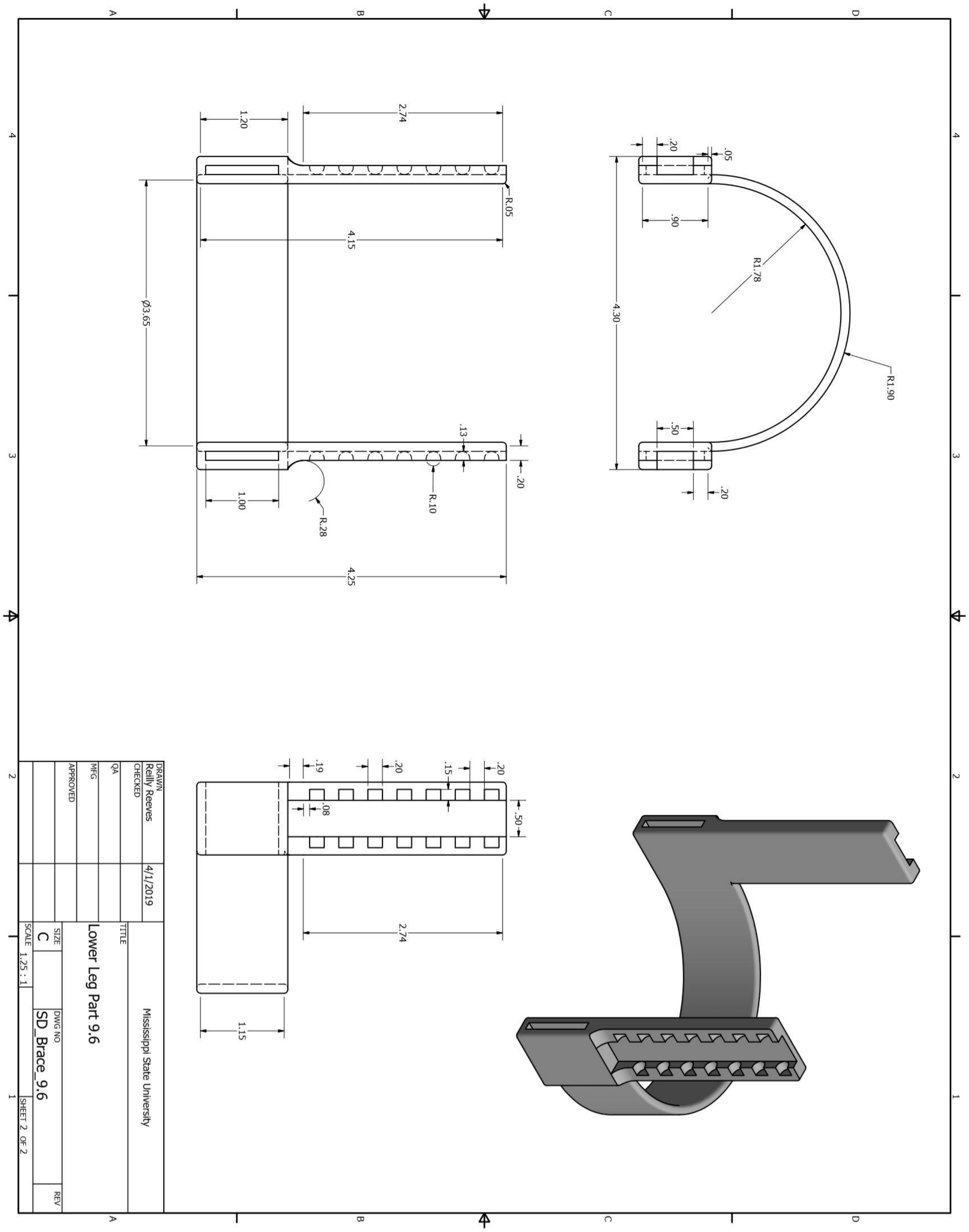

Figure 6: A drawing of the lower leg part of the final brace rendering.

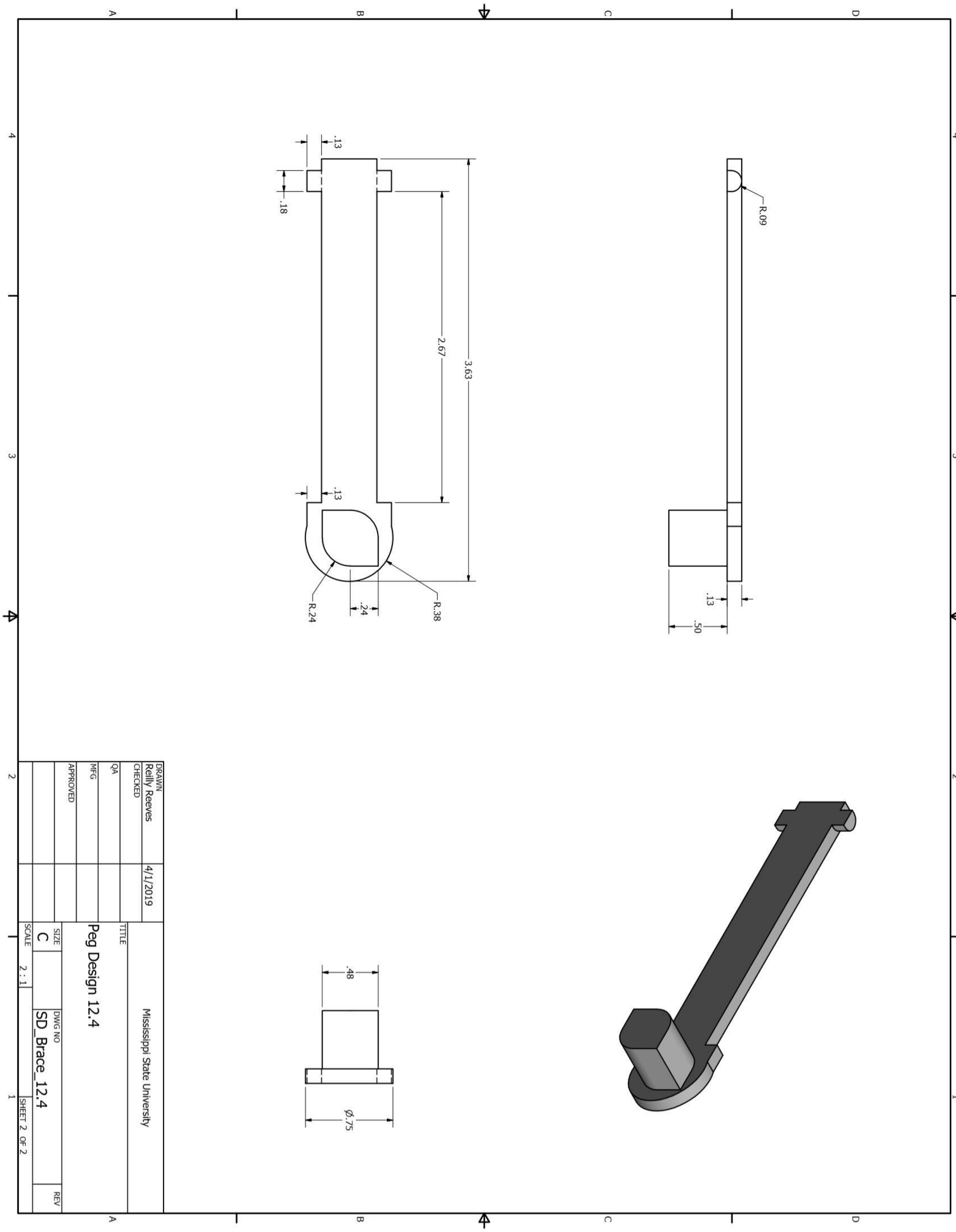

Figure 7: A drawing of peg part 12.4.

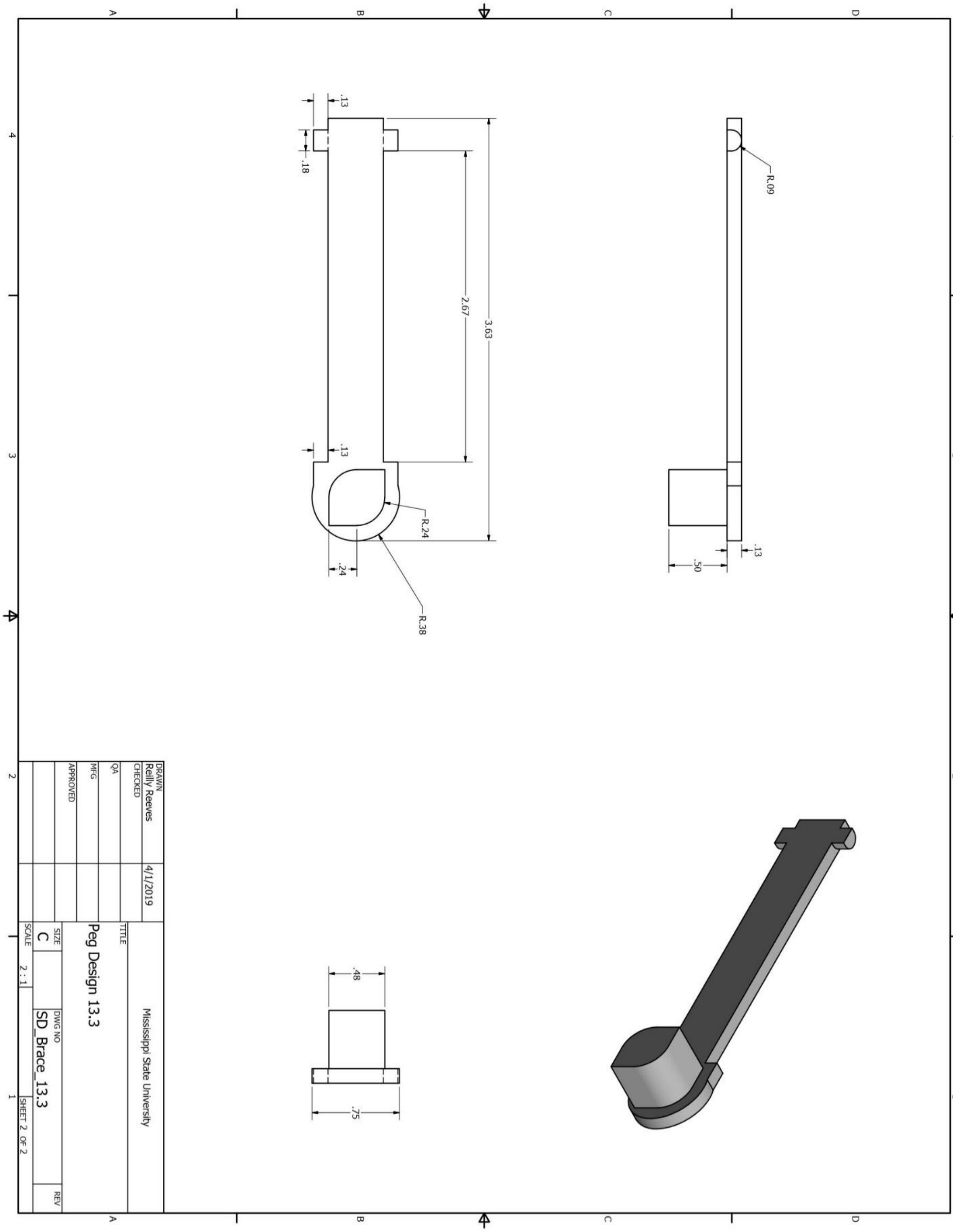

Figure 8: A drawing of peg part 13.3.

Pre-Processing

The file type for editing a part in Inventor is known as an .ipt file. After the .ipt file had been modified, the file was saved as a .stl file, which is also known as a stereolithography file format. A .stl file type is the industry standard for fabrication. Next, the .stl files were processed using the slicer program known as Simplify 3D. The slicer file produces g-code that includes the geographic coordinates and parameters of how and where to place the PLA filament. This information is used by the printer to fabricate the part. The g-code is saved to a Secure Digital (SD) card for transfer.

Printing

Once the g-code was put onto the memory card, the memory card was placed into the 3D printer. The infill of all of the parts printed for the knee brace was 75%. The temperature of the extruder was set between 211 to 215 °F. The parts were printed onto a hot print bed at a temperature of 64 °F.

Post-Processing

The cooling protocol was to allow the print bed to cool down to a temperature of at least 40 °F before removing the parts from the print bed surface. This was done to avoid deforming the parts, and allowed them to maintain their rigid shape. After removing the parts from the print bed, any support material was removed from the parts. The parts were then sanded down for patient safety.

Methods of Testing

Through a series of tests, the effectiveness of the knee brace was determined. Testing was broken up into two major focus areas consisting of qualitative and quantitative testing. First, the qualitative assessment of the patient consisted of two main parts. The first part of the qualitative assessment was through the form of observation. Each Tuesday, the patient was observed and video was taken at his weekly physical therapy sessions at Kids Therapy Spot in Starkville, MS. For consistency, each week the same four activities were observed. The patient was monitored while going up and down stairs, and while doing his step up and step down exercises on a step platform. These exercises were chosen to observe for hyperextension. The patient was also observed playing the game Red Light, Green Light, as well as riding an adaptive bicycle. Red Light, Green Light allowed us to qualitatively observe the patient's balance, control, gait, and knee hyperextension. By riding the adaptive bicycle, the functionality and range of motion of the brace could be assessed. For the first month of observation, the patient was observed without wearing his new knee brace. Then, the following month, the knee brace was put on the patient during the four activities and observed for improvement in the hyperextension of his knee and overall gait.

The second method of qualitative assessment was in the form of a survey. The survey was administered two times throughout the semester to the patient's parents, physical therapist at Kids Therapy Spot, teacher, and inclusion teacher. A simplified assessment was given to the patient himself. The qualitative assessment consisted of various questions evaluating the patient's gait and overall knee and muscle function with and without the knee brace. The assessments were delivered prior to the addition of the knee brace, and at the end of our testing period with the new knee brace. The answers were collected and evaluated to qualitatively assess the effectiveness of the brace.

The final method of testing conducted was quantitative assessment of the patient using force plate technology and 2D MaxTRAQ video analysis software. Quantitative testing was performed on January 31, 2019, February 28, 2019 and finally on March 28, 2019. During the January testing period, the patient was tested without wearing any assistive device. For the February and March testing periods, the patient was tested wearing both his AFOs and the new knee brace. A picture of the force plate walking surface is shown below.

The force plates were used to measure the ground reaction forces during a series of activities. The patient completed approximately three trials of walking across the force plates, running across the force plates, jumping from one force plate to the other, jumping from an elevated surface onto the force plates, walking down stairs using the force plates and walking upstairs using the force plates. Markers were placed on the patient prior to testing at his hip, knee, ankle, and foot as shown below, to measure his joint angles.

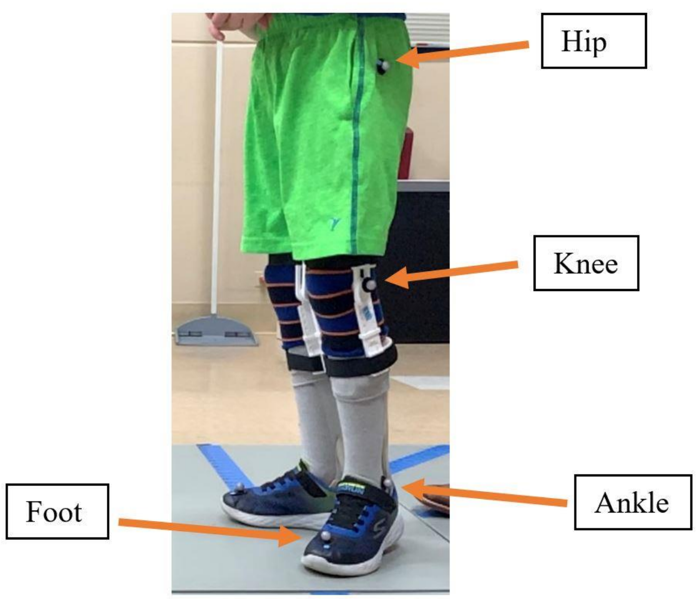

Figure 9: Cameron with the markers on his legs.

Each trial was videoed and analyzed using MaxTRAQ motion analysis software. Using this software, gait was analyzed to measure the angle at the knee in the sagittal plane. Using the angles, the degree of hyperextension, occurring in a single frame, was determined. The data from the force plates was recorded using NetForce software and analyzed using Bioanalysis. The data was then exported into Microsoft Excel to make comparisons between the testing sessions.

Figure 10: Force Plate Walking Surface

RESULTS

The 3D-Printed Knee Brace

In fitting sessions, parts of the brace did break and redesigns were produced. The evolution of the brace can be seen in Figure 11 below. The first design was multiple parts that were to be cemented together. Next, brace elements were combined to produce a more cohesive design. The Velcro attachment was also introduced. Lastly, from iteration two to three, the “U-bend” portion was made thicker and various edges were filleted to make the brace smoother and stronger.

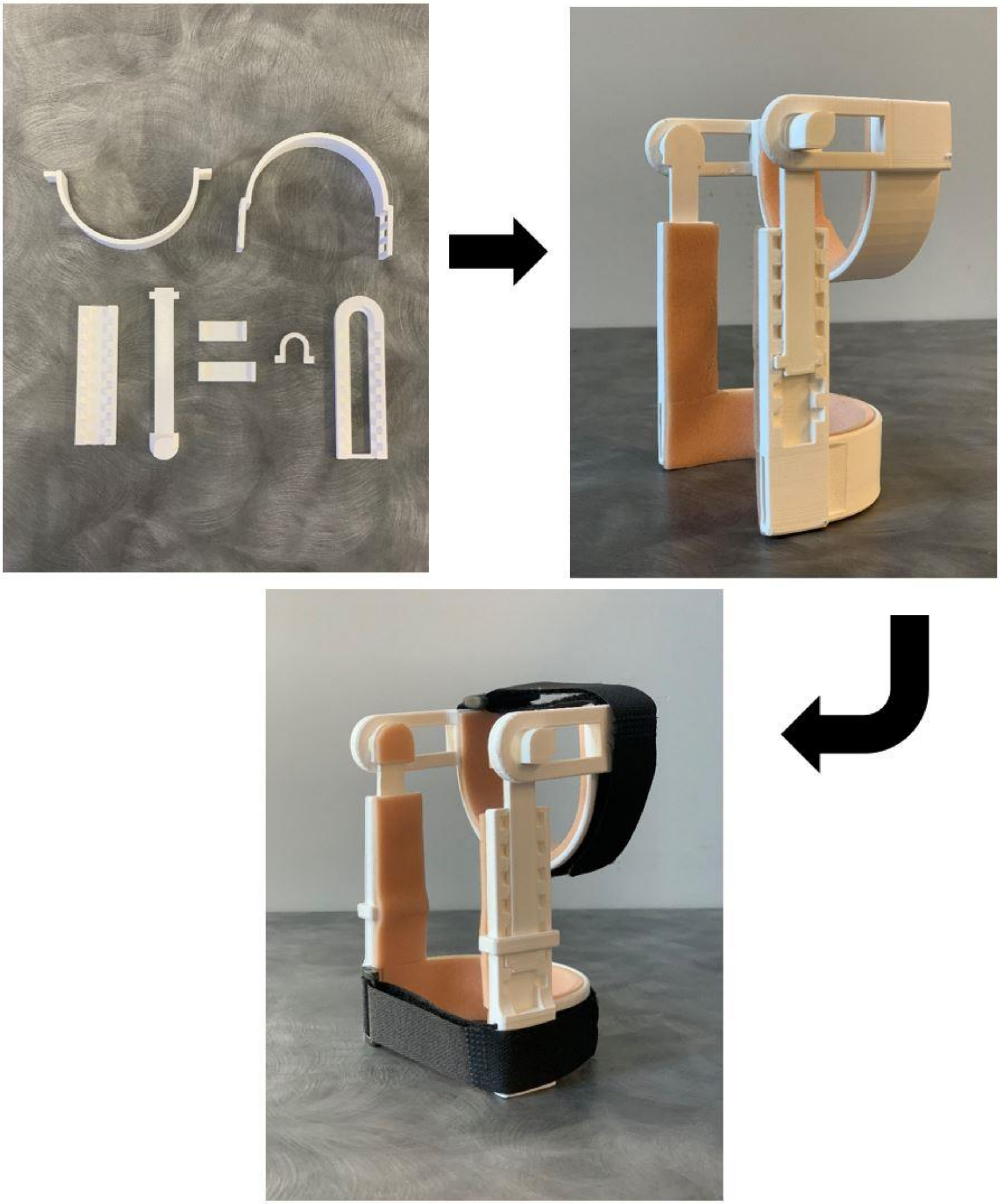

Figure 11: Evolution of Knee Brace

Qualitative Results

Qualitative tests were performed in two ways. The first was weekly observations at the patient's physical therapy sessions at Kids Therapy Spot. From the weekly visits to the clinic, the patient was monitored with and without the new knee brace. Without the knee brace, the patient's gait appeared abnormal. He also was prone to hyperextending his knees on his step up and step down exercises. With the addition of the brace over the last month, qualitative improvements were seen. This improvement was also noticed by the patient's physical therapist. The brace was also shown to one pediatric rheumatologist and two pediatric neurologists and they all noted the potential effectiveness of the brace. A final assessment interview was also conducted with the patient's physical therapist, Catherine Fandel. In this interview, Mrs. Fandel was asked how she would describe Cameron's improvement when completing the following exercises with one being no improvement and five being extremely significant improvement. The effectiveness of the brace in this chart was based solely on how effective the brace was at improving the hyperextension the patient experienced during each activity. The rating of improvement is shown for each exercise by the maroon box.

	1	**2**	**3**	**4**	**5**
Step Ups					
Step Downs					
Going Up Stairs					
Going Down Stairs					
Red Light, Green Light					

Figure 12: Final interview results from Cameron's physical therapist

The second way the brace was qualitatively assessed was through surveys. The patient himself was given a simplified survey to fill out. The patient's parents, teacher, inclusion teacher, and physical therapist all completed a Google survey prior to the new hyperextension knee brace and after the new hyperextension knee brace. The patient's parents observed him in the brace at home and on a family cruise over Spring Break. The patient's teacher and inclusion teacher observed the patient in the brace in the classroom and at recess. The patient's physical therapist was able to see him perform his therapy exercises in the knee brace weekly for a month.

Figure 13 below shows the patient's first qualitative assessment. As seen in the image, the red circle indicates feeling very weak and the green circle indicates feeling very strong. This assessment was given prior to the new knee brace. The second assessment shown in Figure 14 was given to the patient after the addition of the knee brace and asked similar questions as the first assessment. From these two surveys, the patient showed improvement in how strong his legs feel from wearing no assistive device at all, to just wearing his AFOs, to finally wearing his AFOs and his new knee brace. Our patient also highly rated the knee brace in helping him walk and in the overall comfort of the knee brace.

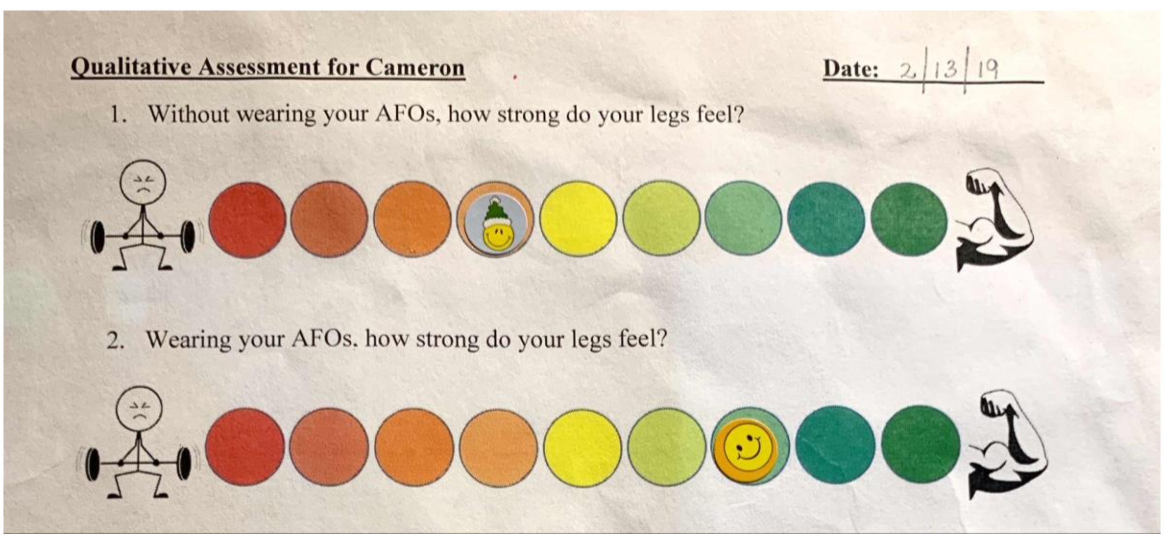

Figure 13: The first qualitative assessment given to our patient on February 13, 2019.

Figure 14: The second qualitative assessment given to our patient on April 1, 2019.

The patient's parents, teacher, inclusion teacher, and physical therapist all completed a Google survey to rate the overall success of the brace from a qualitative perspective. They were asked questions regarding Cameron's gait, balance, and overall hyperextension of his knee in three different situations. In Situation A, Cameron was wearing no assistive device. In Situations B and C, our patient was wearing his AFOs and his AFOs with his new knee brace, respectively. A free response section was also provided to allow the participant to give feedback regarding the overall quality of life of our patient with the addition of the new knee brace. The five participants were also asked to rank various activities as either being negatively, neutrally, or positively impacted by the knee brace. In Figure 15 below, each of the answers given in the Google Survey in regards to gait, balance and hyperextension were averaged. The answers from Situation B were averaged and are shown in the grey columns. The average answers from Situation C are shown in the maroon columns. Based off Figure 15, the patient's gait and balance were improved and the patient's hyperextension was significantly reduced, resulting in a better performance score in overall hyperextension.

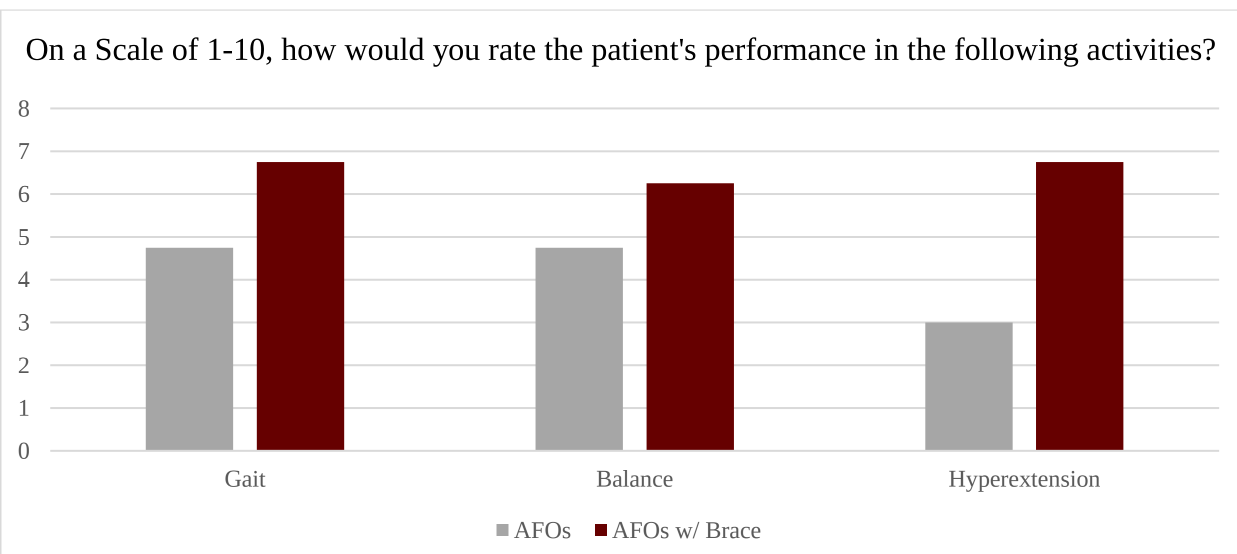

Figure 15: A bar graph comparing the patient's gait, balance, and hyperextension with the AFOs and while wearing his AFOs along with the knee brace

The patient's parents, physical therapist, teacher, and inclusion teacher were asked to assess Cameron in the new knee brace in his day-to-day activities. These results are shown in Figure 16. The participants in the survey were asked to assess the patient while walking, running, jumping, going up and down stairs, and climbing or playing. The results shown in the figure are optimistic. From a qualitative stand point numerous people have seen the brace positively impact the patient's day-to-day life.

For the following activities, please rate whether the patient is negatively impacted, neutrally impacted, or positively impacted regarding situation C.

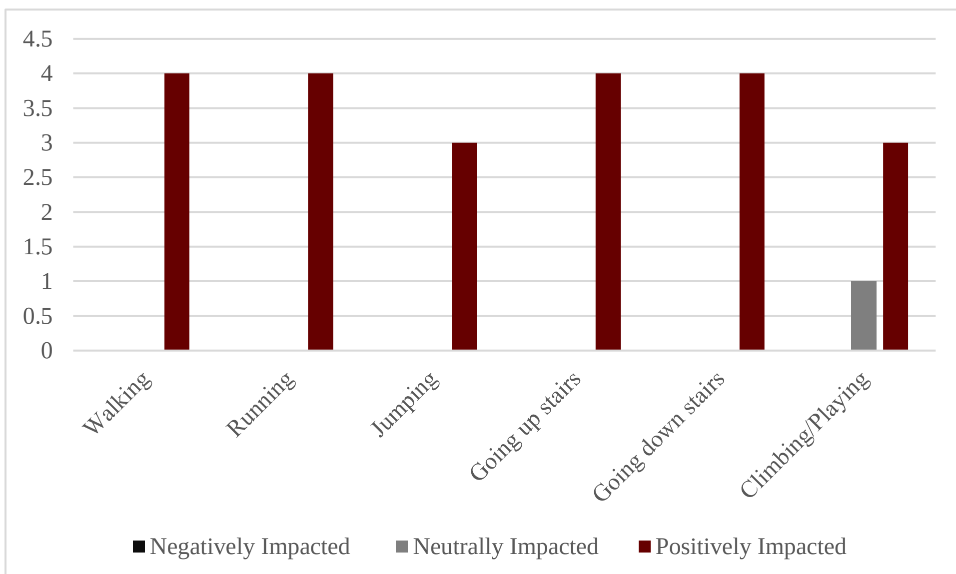

Figure 16: A chart qualitatively assessing the effectiveness of the brace in the patient's day-to-day activities.

Overall, the majority of the qualitative feedback received has been very optimistic. The adult survey participants saw the brace as adding both stability and mobility for the patient. The patient appeared more confident and in control of his gait. The brace was not cumbersome or bulky, and the brace is easy to use. It is our hope that the brace will help with the patient's energy conservation throughout the day and allow his legs to feel stronger.

Quantitative Results

Quantitatively, the patient was assessed once a month on the last Thursday of January, February, and March. With the patient's movements being highly variable due to his muscle weakness, ataxia, and genetic disorder, finding trends in the data was challenging. Figure 17 below shows an image of the patient during the first testing session. The patient is jumping from one force plate to the other, and as the picture shows, severe hyperextension was seen (approximately 22° of hyperextension). The knee angle was significantly decreased with the addition of the new knee brace as seen in Figure 18 below (40° reduction). These angles were measured using the MaxTRAQ software.

Figure 17: Knee angle without brace (202.5)

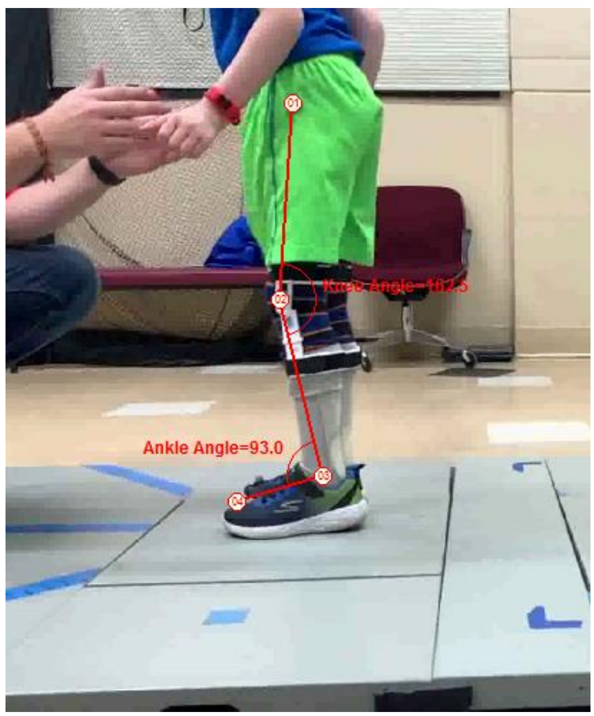

Figure 18: Knee angle with brace (162.5°)

When examining the ground reactions forces from this same jumping task, the patient was able to increase the amount of force during the propulsive phase of the jump across the three testing sessions, which would allow him to jump further, and he was able to reduce the amount of force upon landing from the jump, which would reduce the stress placed on his lower extremities. These results can be seen in the following two figures, Figures 19 and 20. Figure 19 shows the increase in the propulsive force created by the patient after the addition of the brace. Figure 20 shows the decrease in the landing force in testing sessions two and three as compared to testing session one. The results here are worth noting in two ways. The first way has already been discussed. The propulsive force increased and the landing force decreased. With the propulsive force increasing it is expected that the landing force will also increase, because if one leaves with a greater force, one is likely to land with a greater force as well. However, since the patient left with a greater force and still landed with less force, he was likely able to increase the time over which the force was applied to his lower extremities when landing, due to the decrease in knee extension and an increase in knee flexion (Figures 17 and 18). These results are promising in terms of his overall control of his movements while wearing the brace.

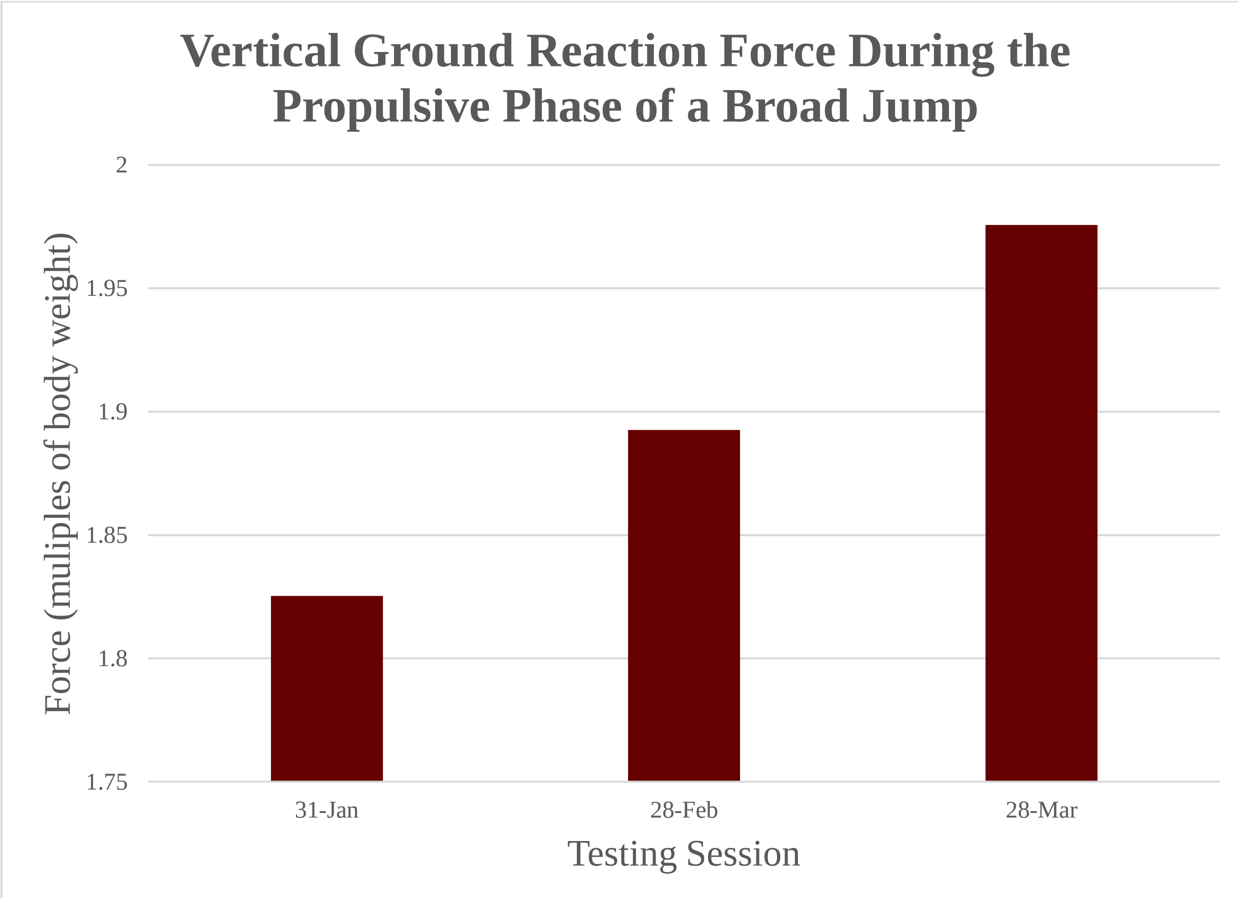

Figure 19: Displays the peak vertical component of the ground reaction force produced by the patient in multiples of his body weight (BW) during the propulsive phase of a broad jump

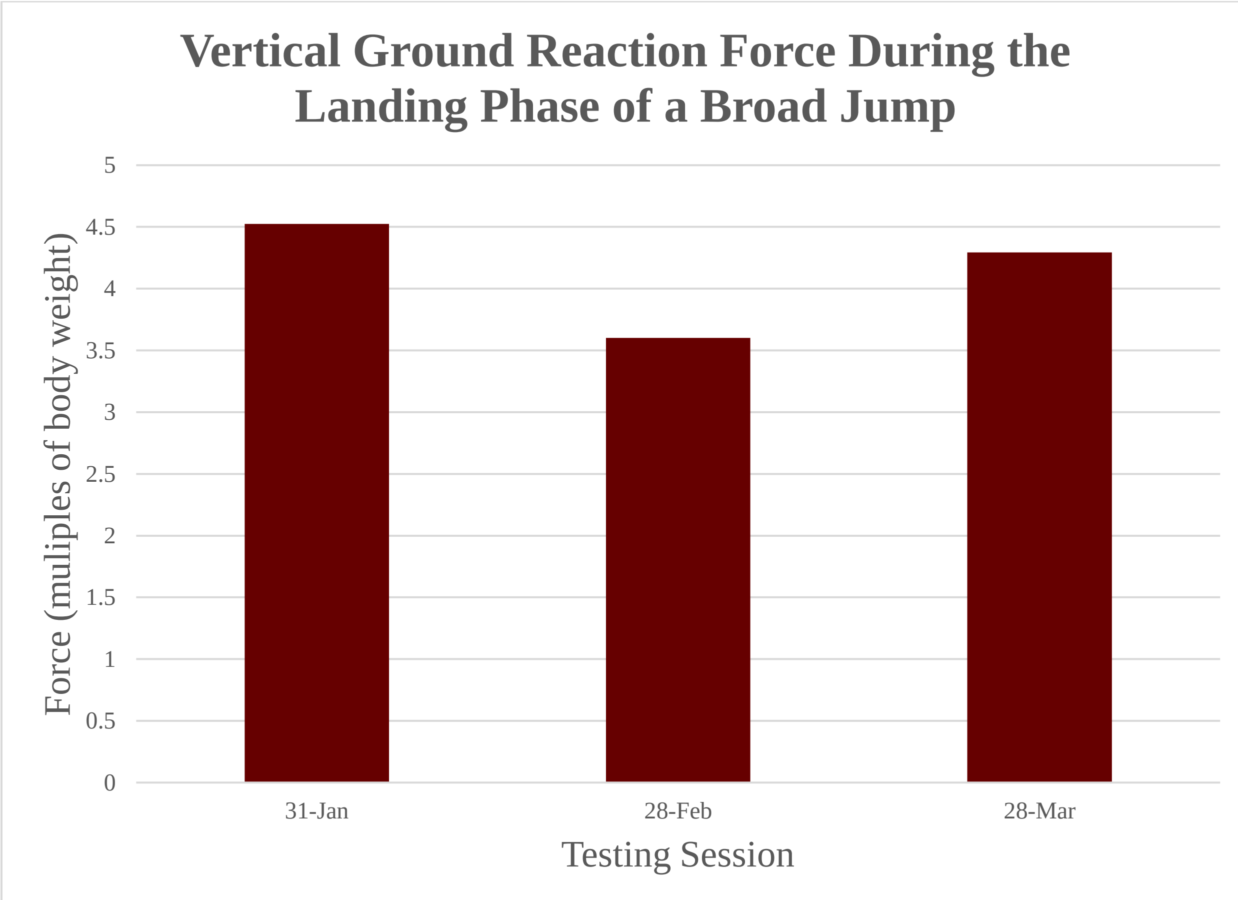

Figure 20: Displays the peak vertical component of the ground reaction force produced by the patient in multiples of his BW during the landing phase of a broad jump

The following three Figures (21, 22 and 23) display the average forces produced by the patient in the various activities described. While this data is not conclusive, it exhibits the asymmetry of the patient and the unpredictability of his movements. Ideally, one would like to observe lower and more equivalent force production when stepping up and down on the force plates when going up and down the stairs. In terms of walking and running, ideally, the braking and propulsive forces would be somewhat equivalent. Also, the vertical force created by both legs would be symmetrical.

Step Up			Step Down		
Testing Day	**Left Leg**	**Right Leg**	**Testing Day**	**Left Leg**	**Right Leg**
Jan 31	1.92	1.15	**Jan 31**	2.51	1.59
Feb 28	1.84	0.99	**Feb 28**	2.19	1.89
Mar 28	1.87	1.55	**Mar 28**	2.28	2.77

Figure 21: Displays the peak vertical component of the ground reaction force in multiples of the patient's BW as the patient walked up and down stairs on the force plates.

Walking						
Testing Day	**Left Braking**	**Left Propulsive**	**Right Braking**	**Right Propulsive**	**Left Vertical**	**Right Vertical**
Jan 31	13.95	6.95	14.54	14.17	74.16	66.11
Feb 28	19.82	12.51	11.37	11.96	91.24	80.98
Mar 28	10.60	10.93	11.02	13.82	76.17	70.77

Figure 22: Displays the peak component of the ground reaction force (in pounds) as the patient walked across the force plates. The three forces measured here are the braking, propulsive, and vertical components of the ground reaction force during the stance phase of walking.

Running						
Testing Day	**Left Braking**	**Left Propulsive**	**Right Braking**	**Right Propulsive**	**Left Vertical**	**Right Vertical**
Jan 31	12.40	10.75	12.66	14.14	111.39	95.48
Feb 28	14.11	18.08	19.26	10.55	103.30	117.40
Mar 28	8.36	14.12	22.13	11.01	123.47	123.50

Figure 23: Displays the peak component of the ground reaction force (in pounds) as the patient ran across the force plates. The three forces measured here are the braking, propulsive, and vertical components of the ground reaction force during the stance phase of running.

OVERARCHING EFFECTS OF THE PROJECT

Limitations

One limitation to our project was our material choice. Using the 3D printer in the Agricultural and Biological Engineering building, the material most closely representative to the patient's current brace that was available for use was the PLA. The PLA was an appropriate choice for our design because of its low cost, weight, and similarity in modulus to his current AFOs. One issue encountered while testing the prototype on the patient was its tendency to fracture. The redeeming factor was that the point of fracture was always at the same spot, thus by just redesigning one piece the brace could be fixed. The brace was modified by making that part thicker and filleting the edges for a smoother more cohesive appearance. If a new material was to be chosen, carbon fiber would likely be the material of choice because of its light weight and flexible nature while also providing strength.

Another limitation to the reproducibility of this design on a large scale is access to a 3D printer. The cost of the 3D printer used to print the brace was around $900, however once the initial investment is made producing the knee brace is relatively cost-effective. In the scope of the design for this project, access to the 3D printer was free to use. A larger 3D printer, with a greater print bed area, would allow for multiple knee braces to be produced at once. The overall material cost is relatively low and easily accessible.

A final limitation to this project is the patient availability. With only testing one patient, quantitative data was hard to compare and measure. Again, with only twelve confirmed cases in the world, the population with this mutation is exceptionally small. However, the amount of children and adults that could benefit from a brace like this is large. Many other diseases have the adverse effects of hypotonia causing the individuals to have an abnormal gait or increased muscle weakness. If this brace were to be tested again on numerous individuals, tests would be run to see if it does help reduce the rate of fatigue. The patients could be monitored by looking at the effect of wearing the brace while on the treadmill. By incorporating another type of test along with more patients, the effectiveness of the brace could better be determined.

Future Directions

If proven successful, the brace has the potential to be marketable. With its adjustability, cost effectiveness, and time efficient nature in comparison to what is currently available, it is possible that the market for such a brace is out there. While this study focused on improving the life of a child in the Mississippi State family, the number of children experiencing hypotonia with hypermobile joints is numerous. This brace could impact more than just children with a mutation of the BCL11A gene. With other individuals with diseases such as cerebral palsy, muscular dystrophy, Down syndrome, Tay-Sachs disease, and Multiple Sclerosis suffering from hypotonia to a certain degree, the number of people who could benefit from a brace such as this one grows. Thus, the market for a brace such as this is out there especially in the realm of pediatrics. It is my hope that this brace greatly benefits the Knight family and improves Cameron’s quality of life. If it is determined that this brace fits a niche that would improve the lives of others in a market that is currently untapped, steps to patent the design can be taken.

Conclusion

The goal of creating an adjustable cost-effective option for custom orthotics was met. The brace proved, especially qualitatively, to be effective. The brace mitigated the hyperextension tendencies of the patient in his day-to-day activities and improved his overall gait while walking and running. Cameron appeared more confident and more controlled with his steps. It is my hope that this brace will continue to serve Cameron and the Knight family well in the future.

References

Basak, A., Hancarova, M., Ulirsch, J. C., Balci, T. B., Trkova, M., Pelisek, M., . . . Sankaran, V. G. (2015). BCL11A deletions result in fetal hemoglobin persistence and neurodevelopmental alterations. Journal of Clinical Investigation, 125(6), 2363-2368. doi:10.1172/jci81163

Beighton, P. H., Grahame, R., & Bird, H. (2012). Hypermobility of Joints. London: Springer London.

Chanasit, P., Sa-Ngasoongsong, P., Chanplakorn, P., Jaovisidha, S., Suphachatwong, C., & Wajanavisit, W. (2013). Anteromedial marginal fracture of medial tibial plateau without significant knee ligamentous injury in hypermobility patient: A case report and review of literature. Orthopedic Reviews, 5(2), 12. doi:10.4081/or.2013.e12

Chen, C., Chern, S., Wu, P., Chen, S., Lai, S., Chuang, T., . . . Wang, W. (2018). Prenatal diagnosis of a 3.2-Mb 2p16.1-p15 duplication associated with familial intellectual disability. Taiwanese Journal of Obstetrics and Gynecology, 57(4), 578-582. doi:10.1016/j.tjog.2018.06.018

Dias, C., Estruch, S., Graham, S., Mcrae, J., Sawiak, S., Hurst, J., . . . Logan, D. (2016). BCL11A Haploinsufficiency Causes an Intellectual Disability Syndrome and Dysregulates Transcription. The American Journal of Human Genetics, 99(2), 253-274. doi:10.1016/j.ajhg.2016.05.030

Estruch, S. B. (2018). Characterization of transcription factors in monogenic disorders of speech and language. 143-170. Retrieved March 14, 2019.

Martin, K., Inman, J., Kirschner, A., Deming, K., Gumbel, R., & Voelker, L. (2005). Characteristics of Hypotonia in Children: A Consensus Opinion of Pediatric Occupational and Physical Therapists. Pediatric Physical Therapy, 17(4), 275-282. doi:10.1097/01.pep.0000186506.48500.7c

McDonald, K. (2018). Genetic Testing Report. GeneDx.

Payne, V.G. & Issacs, L.D. (2008). Voluntary Movements of Infancy. In *Human Motor Development* (pp. 257-274). New York, NY: McGraw-Hill.

Peter, B., Matsushita, M., Oda, K., & Raskind, W. (2014). De novo microdeletion of BCL11A is associated with severe speech sound disorder. American Journal of Medical Genetics Part A,164(8), 2091-2096. doi:10.1002/ajmg.a.36599

Ramesh, R., Arx, O. V., Azzopardi, T., & Schranz, P. J. (2005). The risk of anterior cruciate ligament rupture with generalised joint laxity. The Journal of Bone and Joint Surgery. British Volume, 87-B(6), 800-803. doi:10.1302/0301-620x.87b6.15833

Shimbo, H., Yokoi, T., Aida, N., Mizuno, S., Suzumura, H., Nagai, J., . . . Kurosawa, K. (2017). Haploinsufficiency of BCL11A associated with cerebellar abnormalities in 2p15p16.1 deletion syndrome. Molecular Genetics & Genomic Medicine, 5(4), 429-437. doi:10.1002/mgg3.289

Soblet, J., Dimov, I., Kalckreuth, C. G., Cano-Chervel, J., Baijot, S., Pelc, K., . . . Deconinck, N. (2017). BCL11A frameshift mutation associated with dyspraxia and hypotonia affecting the fine, gross, oral, and speech motor systems. American Journal of Medical Genetics Part A, 176(1), 201-208. doi:10.1002/ajmg.a.38479

Yoshida, M., Nakashima, M., Okanishi, T., Kanai, S., Fujimoto, A., Itomi, K., . . . Chiyonobu, T. (2017). Identification of novel BCL11A variants in patients with epileptic encephalopathy: Expanding the phenotypic spectrum. Clinical Genetics, 93(2), 368-373. doi:10.1111/cge.13067

APPENDIX

Apraxia: motor disorder causing increased difficulty in performing a simple task

Ataxia: impaired coordination

Dyspraxia: developmental coordination disorder

Fillet: an engineering tool to round off the corners of a part design

Ground Reaction Force: a force exerted by the ground on an object in contact with it

Haploinsufficiency: a condition in which having a single working copy of an allele is insufficient

Hematopoietic system: consists of the organs and tissues involved in the production of blood

Hyperextension: excessive extension of a joint where the angle formed is beyond the normal range of motion

Hypermobility: increased range of motion among the joints due to abnormal flexibility

Hypotonia: reduced muscle tone

Microcephaly: decreased circumference of the head