Assessment and Development of Educational Resources for Hajdu-Cheney Syndrome

by

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B.S. Biology, University of Iowa, 2017

Submitted to the Graduate Faculty of the

School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2022

UNIVERSITY OF PITTSBURGH

SCHOOL OF PUBLIC HEALTH

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Hajdu-Cheney Syndrome (HCS) is a rare, hereditary connective tissue disorder which causes osteoporosis and acro-osteolysis, among other symptoms. As this condition affects fewer than 100 individuals, it is not well studied and has few available patient-centered educational resources. Most online educational materials about HCS use complex terminology and none consistently cover the same information about HCS.

This study aimed to create a comprehensive, understandable resource for patients and families impacted by HCS by assessing current resources and surveying an online patient support group. The first part of this study assessed five online HCS educational materials for readability and content. Evaluated resources were written at 9th grade to college graduate reading levels, above the nationally recommended 6-8th grade reading level. Additionally, the resources were reviewed for five content areas. Resources varied widely in areas of content covered and most resources did not contain all areas that were assessed. Further, only two resources provided links for patient support.

Next, individuals and their family members were surveyed to elicit their experiences learning about HCS and their preferences regarding format and content for a HCS specific educational resource. The survey was distributed through a private HCS Facebook support group and a total of 29 individuals responded to the survey. All respondents reported using the internet to find information about HCS at some point. Eleven participants continue to look online for information about HCS at least once a month. Participants also reported relying on geneticists,

genetic counselors, other healthcare professionals, scientific articles, and other affected individuals to get information.

Based on survey responses, a fact sheet was drafted including information about the cause, inheritance, features, and management of HCS. This study is significant to public health because although rare diseases are individually rare, they cumulatively affect millions of individuals. The development of clear, readable educational resources can promote better understanding of a diagnosis, which can increase feelings of empowerment and inform health care decisions for these many individuals.

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1.0 Introduction

In the United States, a rare disease is a condition that affects fewer than 200,000 individuals (GARD, 2021). In the United States there are more than 7,000 unique rare diseases, which when combined, affect from 25 to 30 million Americans (NORD, 2019). Some rare conditions such as cystic fibrosis are well-described. However, many rare diseases have not been well-studied and patients may have difficulty finding detailed, understandable information about the condition. Individuals with a rare disease face challenges in being diagnosed accurately, finding experienced doctors, and accessing treatments when they exist (Stoller, 2018).

Hajdu-Cheney syndrome (HCS) is a rare, hereditary connective tissue disorder that affects fewer than 100 individuals worldwide (Canalis & Zanotti, 2014). Individuals with HCS typically develop osteoporosis (low bone density) and acro-osteolysis (resorption of bone at the ends of fingers and toes). Affected individuals can have additional skeletal manifestations, heart defects, polycystic kidneys, neurologic issues, and dental anomalies (Brennan & Pauli, 2001; Canalis & Zanotti, 2014). Symptoms may manifest soon after birth or not until later in adolescence (Jirečková et al., 2018). This condition is known to be caused by pathogenic variants in exon 34 of the *NOTCH2* gene, though the disease mechanism is not yet fully understood (Simpson et al., 2011).

After receiving a diagnosis of a genetic disorder such as HCS, individuals and their family members often try to gather more information about the condition. They may do this by speaking with various medical professionals and by looking online (Rocha et al., 2018). In fact many general practitioners encourage rare disease patients to research their condition for themselves (McMullan et al., 2021). However, online information about individual rare diseases can be scarce, low in quality, and written in highly technical language (Pauer et al., 2017).

The goal of this study was to assess the quality of educational resources and develop understandable, patient-centered educational material for HCS patients and their families. Currently available online HCS-specific educational resources were evaluated for readability and content. Additionally, patients and their family members were surveyed about their experiences learning about HCS at and after initial diagnosis as well as their needs regarding format and content to include in an educational resource. A fact sheet about HCS was drafted based on survey responses. Future plans include sharing this resource in the Facebook HCS support group.

1.1 Specific Aim 1

Evaluate currently available HCS patient resources by calculating their reading levels and assessing their content.

1.2 Specific Aim 2

Create and distribute an online survey to understand HCS patients' and family members' awareness of and experiences using currently available educational resources about HCS.

1.3 Specific Aim 3

Develop and distribute understandable and patient-centered educational materials for HCS patients and their families.

2.0 Literature Review

2.1 Connective Tissue Disorders

Connective tissue plays an essential role in the body by supporting, connecting, protecting, and giving structure to other tissues and organs (Kamrani et al., 2022). This tissue consists of glycoaminoglycans and extracellular fibers (collagenous, elastic, and reticular) with a variety of specialized cells like fibroblasts, adipose, and mast cells distributed throughout (Fawcett, 2020). These components are found at different proportions depending on location in the body (Fawcett, 2020). Connective tissue disorders (CTD) are a large group of conditions in which the structure and function of this connective tissue is altered. There are currently over 200 heritable CTDs that have been identified. This large, heterogeneous group of conditions often has overlapping features and affect multiple parts of the body including the heart, vascular system, bones, joints, skin, and eyes.

Many CTDs have known, underlying single-gene causes. For example, Marfan syndrome is caused by variants in the *FBN1* gene and Osteogenesis imperfecta is most often caused by changes in the *COL1A1* and *COL1A2* genes (Steiner & Basel, 2021; Dietz, 2022). These conditions have been well characterized and when individuals are diagnosed with these syndromes there is a wealth of information available to help them understand the condition in the form of websites, articles, support groups, and other resources. More recently identified or rarer CTDs have been less well studied. These conditions are much less likely to have easily accessible, syndrome-specific educational resources available. Hajdu-Cheney syndrome (HCS) is a CTD which is lacking in useful, easy-to-understand educational resources for patients and their families.

2.2 Hajdu Cheney Syndrome

HCS is a rare, hereditary CTD with large skeletal involvement. The condition was first described by Nicholas Hajdu and Ralph Kauntze as Cranio-skeletal dysplasia in 1948 when they encountered a 37-year-old male patient with severe osteoporosis, acro-osteolysis of distal phalanges, and basilar impression (Hajdu & Kauntze, 1948). In 1965 WD Cheney added to the initial description and reported the disease as the Acro-osteolysis syndrome after identifying a mother and her four children who had acro-osteolysis, multiple wormian bones (small bones that occur within skull sutures), osteoporosis, and basilar impression (Cheney, 1965; Kamath et al., 2005). The condition goes by other names including Cheney syndrome, arthro-dento-osteodysplasia, hereditary osteodysplasia, and acro-osteolysis dominant type (Jimenez et al., 2021; Brennan & Pauli, 2001).

While HCS follows autosomal dominant inheritance, there are more sporadic cases than familial cases reported (Brennan & Pauli, 2001). Fewer than 100 individuals worldwide have been documented in medical literature as being diagnosed with HCS, but the exact prevalence of the condition is not known (Canalis & Zanotti, 2014). The condition is likely underdiagnosed as it is possible that some individuals with severe idiopathic osteoporosis actually have HCS (Canalis & Zanotti, 2014).

2.2.1 Features of HCS

Age of symptom onset for HCS is variable, with some individuals showing manifestations as early as infancy while others start showing signs later in adolescence (Jirečková et al., 2018). There is significant clinical variability among those diagnosed with this syndrome, but key

characteristic features are severe osteoporosis and acro-osteolysis of distal phalanges (Hajdu & Kauntze, 1948; Cheney, 1965). Acro-osteolysis can present with inflammation, neovascularization, swelling, and pain (Nunziata et al., 1990; Zanotti & Canalis, 2020). Other common findings involving the skeletal system include wormian bones, open skull sutures, bathrocephaly, hypermobility, and short stature (Canalis & Zanotti, 2014). The spine can be affected with vertebral compression fractures, scoliosis, and kyphosis. Platybasia and basilar invagination (top of the spine pushes up into the base of the skull) are caused by the bone weakness at the craniovertebral junction and can lead to severe neurological problems such as hydrocephalus, syringomyelia (fluid filled cysts within the spinal cord), and central respiratory arrest (Canalis & Zanotti, 2014; Nishimura et al., 1996).

The kidneys can also be affected in HCS. Approximately 10-18% cases of HCS are estimated to have renal abnormalities (Kaplan et al., 1995; Brennan & Pauli, 2001). This takes the form of renal hypoplasia, multiple renal cysts with concomitant hypertension, vesicoureteral reflux, and glomerulonephritis (Brennan & Pauli, 2001; Rosenmann et al., 1977). Individuals with skeletal findings characteristic of HCS plus bilateral polycystic kidneys and elongated serpentine fibulae used to be considered as having a condition called Serpentine fibula polycystic kidney syndrome (SFPKS). SFPKS is now thought to be a manifestation of HCS rather than a separate condition as affected individuals have been found to have genetic changes in the same *NOTCH2* location (Gray et al., 2012). Few cases of progression to end stage renal disease (ESRD) in HCS have been published. Most currently described cases of ESRD are in the adult population, but at least one infant has been reported to be born with dysplastic kidneys and multiple parenchymal cysts resulting in ESRD requiring dialysis and renal transplantation at age 2 (Battelino et al., 2016).

Cardiovascular defects are seen in some people with HCS. Heart issues that have been documented include patent ductus arteriosus, atrial septal defects, aortic valve stenosis, and aortic insufficiency (Regev et al., 2018; Kaler & Geggel, 1990). Sargin et al. also reported a patient with ventricular septal defect (Sargin et al., 2013).

Individuals with HCS display craniofacial dysmorphism. While many have normal facial appearance at birth, characteristic features are likely to become coarser and more apparent with age (Brennan & Pauli, 2001). These features can include low set ears, thick and coarse hair, thick eyebrows, synophrys, hypertelorism with telecanthus, long eyelashes, elongated philtrum, flat/broad nasal base, micrognathia, and midfacial flattening (Cortes-Martin et al., 2020; Canalis & Zanotti, 2014). Dental abnormalities observed in HCS include a delayed tooth eruption, premature tooth loss from aveolar bone resorption, and dental malocclusion. Some individuals also have a high arched palate and/or cleft palate (Lee et al., 2018, Antoniades et al., 2003).

2.2.2 Genetic Etiology of HCS

HCS is caused by changes in exon 34 of the *NOTCH2* gene, located at chromosome 1p12 (Simpson et al., 2011). This gene encodes for Notch2, one of four Notch single pass transmembrane receptors. Notch2 receptor activity has been shown to be important in mediating cell signaling (Canalis, 2018). Notch signaling also plays a role in the cell fate decisions through differentiation of skeletal cells, osteoblasts and osteoclasts, thereby affecting skeletal development and bone homeostasis (Palav et al., 2014).

Typically, the Notch2 receptor's extracellular domain interacts with membrane-bound ligands in neighboring cells, including those in the Jagged and Delta transmembrane protein families (Kopan & Ilagan, 2009). Interaction with these ligands results in the cleavage of the

intracellular domain of Notch2 (NICD), which then travels to the nucleus to form a complex with various transcription factors and regulates transcription of downstream target genes (Koval, 2008; Kopan & Ilagan, 2009).

Missense changes that result in an early termination of the Notch2 protein are reported in individuals with HCS. Specifically, these variants disrupt or cause complete absence of the proline-glutamate-serine-threonine-rich proteolytic recognition sequence (PEST sequence) at the C-terminus (Simpson et al., 2011). The PEST domain is needed for the *NOTCH2* NICD to be ubiquitinated and degraded. When Notch2 does not have a functional PEST sequence, the transcript is able to avoid ubiquitination, resulting in a stable protein with sustained signaling activity (Fukushima et al., 2017).

Exactly how gain-of-function *NOTCH2* pathogenic variants lead to the various clinical features of HCS is still unknown. Mouse models have been used to help uncover the processes leading to bone loss. Mice with heterozygous *NOTCH2* pathogenic variants developed cancellous and cortical bone osteopenia. Bone samples from these mice showed this was due to increased osteoclastogenesis and bone resorption without corresponding increases in the amount of osteoblasts or in new bone formation (Canalis et al., 2016). Osteoclastogenesis was enhanced due to Notch2 interactions with nuclear factors in cells of the osteoclast lineage as well as enhanced *RANKL* gene expression in cells of the osteoblast lineage. (Canalis et al., 2016; Fukushima et al., 2008). These findings do not however provide a possible explanation for other features commonly experienced in HCS, such as acro-osteolysis. Further, it should not be assumed that this mechanism leading to osteoporosis in HCS mouse models is the same in humans with HCS.

2.2.3 HCS Diagnosis

HCS can be diagnosed through examination of radiologic findings, and molecular genetic testing. While there are no formal criteria for a clinical diagnosis of HCS, imaging of the skeletal system can help to guide diagnosis. Multiple fractures may be seen throughout the spine and body. X-ray of the skull can show characteristic findings of HCS including open sutures and platybasia while imaging of hands and feet can demonstrate acro-osteolysis. DEXA scans can be used to identify osteoporosis. However, observation of one of these features alone are not enough for a diagnosis of HCS, as they are also seen in individuals with other conditions such as osteogenesis imperfecta and pycnodysostosis (skeletal disorders with fragile bones) (Jirečková et al., 2018). Genetic testing for HCS involves sequencing of exon 34 of *NOTCH2*, which may be analyzed through a single-gene test or as part of a multigene panel including the *NOTCH2* gene. A finding of a heterozygous truncating pathogenic variant in this gene is consistent with a diagnosis of HCS (Isidor et al. 2011).

2.2.4 Treatment of HCS

Currently there are no established guidelines for treatment in HCS. Medical management is based on treating individual symptoms and improving quality of life (Cortes-Martin et al., 2020). Surgeries may be required to treat congenital heart defects and renal issues (Canalis, 2018). Surgery is also frequently used to treat the spine and/or cranium deformities that develop. However, these surgeries can be complicated by abnormal craniospinal anatomy, severe osteoporosis, and osteolysis (Falls et al., 2021). Complications include fusion failure or cranial

suture diastasis, requiring additional surgeries (Murtagh-Schaffer & Moquin, 2008; Woon & Mardjetko, 2018).

Various medications have been used to treat osteoporosis in individuals with HCS, although there is not clear evidence that these treatments are effective and no controlled clinical trials have been completed within the HCS population (Canalis, 2018). Bisphosphonates are medications that work to increase bone density by inhibiting osteoclast activity, decreasing osteoclast progenitor development, and promoting osteoclast apoptosis (Rodan & Fleisch, 1996; Hughes et al., 1995). Since mouse models showed increased osteoclastogenesis as a mechanism for osteoporosis in HCS, bisphosphonates may be beneficial (Canalis et al., 2016). In a review of 15 published cases of individuals with HCS who underwent bisphosphonate treatment due to recurrent fractures and declining bone mineral density (BMD), overall spinal BMD z-scores increased during bisphosphonate use. The amount of increase varied by individual and was seemingly greater for younger patients. Acro-osteolysis was not improved in any of these individuals for whom data were recorded (Pittaway et al., 2018).

Another medication considered for HCS patients is denosumab. Denosumab is a monoclonal antibody that specifically inhibits the cytokine RANKL, thereby blocking osteoclast maturation and function (Hanley et al., 2012). Mice with *NOTCH2* pathogenic variants had increased RANKL expression in osteoblasts, so blocking RANKL may be particularly useful in treating osteoporosis in HCS. A published case of an individual with HCS using denosumab showed increased BMD and no new fractures while on the medication, though acro-osteolysis still progressed (Adami et al., 2016).

A third approach to increasing bone density in HCS is use of teriparatides. Teriparatide is a recombinant form of parathyroid hormone which works to improve bone density through

increasing new bone formation (Rosen & Bilezikian, 2001). There are fewer reports of individuals with HCS utilizing teriparatides rather than bisphosphonates, but in those that have been published lumbar spine BMD did increase over the course of treatment. Again there was no evidence that acro-osteolysis was prevented (Descartes et al., 2014; McKiernan ,2008; Terroso et al., 2013).

2.2.5 Psychosocial Concerns

A medical diagnosis can have a significant impact on one's life. The psychosocial aspects of living with some conditions that affect the skeletal system have been studied and reported in literature (Dogba et al., 2013; Hill et al., 2013; Hill et al., 2022). This is less often the case in rare conditions such as HCS (Von der Lippe et al., 2017). Examination of the experiences of individuals who have disorders that are also rare and/or have phenotypic overlap with HCS can help understand psychosocial issues those with HCS may encounter.

Due to the small population of affected individuals, a rare condition may not be well understood and have limited evidence-based information available to guide medical management (Baumbusch et al., 2018). Patients with rare diseases can struggle to find medical providers knowledgeable about the condition (Stoller, 2018; Groft et al., 2021) For some rare disorders, centers in which clinicians have developed deeper experience with the condition do exist. However, these centers are usually few and widely dispersed, requiring patients to travel long distances (Stoller, 2018). Lack of guidance following diagnosis can lead to a delay in treatment or in accessing community-based supports (Baumbusch et al., 2018). As HCS is a condition currently known to affect under 100 individuals it is possible that after diagnosis individuals with HCS experience similar difficulties in finding experienced practitioners to provide guidance on appropriate care and treatment (Canalis & Zanotti, 2014).

One of the fundamental symptoms of HCS is osteoporosis, which is often severe. Current treatments for bone density have not been proven to be significantly effective for people with HCS. Consequently, affected individuals live with an increased risk for bone breaks and fractures. Psychosocial research in osteogenesis imperfecta (OI), a condition also characterized by low bone density, has examined how this risk affects patients and their family members. Studies found that parents of children with OI had constant fear of fractures and concern for safety. This concern affected aspects of life including house layout and school choice for their child. It also caused some to restrict their child's participation in outdoor and social activities (Dogba et al., 2013). When older children with OI were interviewed about their quality of life, they reported similar fears regarding risk of injury. These individuals indicated they were wary of participating in activities that had previously caused fractures (Hill et al., 2014). As with those affected by OI, people diagnosed with HCS and their family members may have worries about injury and change their behaviors to minimize risk.

Studies have shown that children with OI experience feeling different and isolated from their peers. They feel left out due to the limitations put on activities they are allowed to do for safety reasons as well as from not being able to physically keep up with others when they do participate (Hill et al., 2014). Some individuals reported absences from school or work due to fractures increased feelings of loneliness and being withdrawn (Hill et al., 2022). Differences in physical appearance such as dental anomalies, contractures, and bone deformities can also contribute to feelings of isolation (Guillot, 2022). Individuals with HCS may struggle with similar feelings as they can face similar restrictions to activities and commonly have distinct physical appearances. Additional psychosocial support may be useful for these individuals and

modifications to some activities could increase affected individuals' access to more opportunities (Hill et al., 2014).

2.3 Current HCS Resources

2.3.1 Patient Support Resources

After receiving a new diagnosis, many individuals turn to the internet to learn more about the condition and to connect with others who are affected. Support groups provide a place where individuals may learn about the disorder and share personal experiences with aspects such as treatments. They can reduce anxiety and provide emotional support, encouragement, and empowerment (Rocha et al., 2017; Hu, 2017). Online support groups can be especially helpful in reducing feelings of isolation among those with rare disorders as the small number of affected individuals may be spread over a wide area and otherwise be unable to connect (Hoy, 2021). Benefits of online groups include that they are available 24 hours a day, are accessible to those whose condition may prevent travel, and may provide more anonymity (van Uden-Kraan et al., 2008; Delise et al., 2017; Hu, 2017).

Support groups for individuals with HCS are limited. In fact, the only current support group specifically intended for those affected by HCS is a private Facebook support group for individuals with HCS and their family members around the world (https://www.facebook.com/groups/1012807442094960). Other, more general support groups can be found online that individuals with HCS may utilize. For example, American Bone Health offers education about

bone health and a support network for patients with osteoporosis, their caregivers, and health advocates to connect online (americanbonehealth.org).

2.3.2 Scientific Research Articles

Peer reviewed research articles about HCS can be found through online databases such as PubMed and ScienceDirect. While using these resources to identify articles is free to the general population, the full articles themselves often exist behind a paywall. An individual can pay to view a single article or access them through an institution's journal subscription. Further, there are fewer papers published that mention HCS as compared to other more common conditions. For example a PubMed search for "Hajdu Cheney" brings up 206 results whereas a search for "osteogenesis imperfecta" brings up 6,243 results. In addition to these resources being fewer in number and more challenging to obtain, they are typically written using technical language that is difficult for those without medical or science education to understand.

2.3.3 Educational Resources

Outside of scientific papers and support groups, most online information available to HCS patients and their family can be found through the National Institute of Health's (NIH) MedlinePlus, the NIH's Genetic and Rare Disease Information Center (GARD), the National Organization for Rare Disorders (NORD), Orpha.net, and the Online Mendelian Inheritance in Man (OMIM).

MedlinePlus is a resource whose goal is to present high quality relevant health and wellness information to the public (MedlinePlus: Learn about MedlinePlus). It gives information about

general genetics as well as more detailed information for over a thousand different genetic conditions, including HCS (MedlinePlus: Genetics). The site gives a detailed description of symptoms seen in individuals with HCS. It also includes information about the genetic etiology and frequency of the condition. However, this resource does not provide information about condition management, detailed inheritance information, or links to support organizations. Additionally, the HCS page in MedlinePlus notes it was last updated in February of 2015. This means it is not the most up-to-date resource to learn about HCS and it may be missing more recently reported details about the condition.

The GARD website was created to provide reliable and easy-to-understand information to people living with rare disease and their families (About GARD). The GARD HCS page displays a list of possible syndrome features, including definitions of each medical term and the frequency with which the feature has been reported in medical literature about HCS (Acroosteolysis Dominant Type: GARD). Also included is a discussion of risks associated with autosomal dominant inheritance, condition frequency, and stage of life symptoms may start. Further, GARD provides general tips about next steps for individuals trying to find a diagnosis for their symptoms. Although the page does give much valuable information, it does not include more detailed information about the specific genetic variants that cause the condition or mention medical management.

NORD's Rare Disease Database acts as a resource for patients and caregivers to get an introduction to specific rare diseases. Pages for each disorder are developed by medical experts and patient organization representatives (NORD Rare Disease Database). The page about HCS was developed with assistance from Dr. Ernesto Canalis, a professor of orthopedic surgery and medicine who has published much research on HCS. The NORD page includes detailed

information about the signs and symptoms seen in HCS, the genetic cause, inheritance, prevalence, and related disorders. It also mentions treatments and provides links to multiple support organizations including the HCS-specific Facebook support group (NORD Hajdu Cheney Syndrome).

Orpha.net is a resource that gathers and publishes high quality knowledge about rare diseases and orphan drugs to help improve the care of patients (About Orpha.net). The site is available to patients, providers, and other rare disease stakeholders. It presents data about HCS including a clinical description of the disease, prevalence, genetic cause, diagnostic methods, inheritance, prognosis, and management but does not offer links to support groups (Orphanet: Hajdu-Cheney Syndrome).

Finally, OMIM is a collection of detailed information about human genes and genetic phenotypes. This site is primarily intended for use by genetic specialists, physicians, and other medical professionals (About Omim). The HCS page of OMIM includes a brief syndrome overview as well as material about clinical features and molecular genetics of the condition. Links to the source of each piece of information is included. Discussion of inheritance is limited and medical management of the condition is not reviewed. Links to support organizations are not provided (OMIM Entry - #102500).

These five websites are the main online resources, outside of scientific articles and support groups, available to individuals who want to learn about HCS. Most lack detailed, comprehensive information about at least one aspect of the condition that patients and their family members may be looking for.

3.0 Manuscript

3.1 Background

Hajdu-Cheney Syndrome (HCS) is a rare, hereditary connective tissue disorder. Currently less than 100 individuals worldwide have been documented in the medical literature as having this syndrome. However, the exact prevalence is unknown (Canalis & Zanotti, 2014). Key symptoms experienced by individuals with HCS are osteoporosis and acro-osteolysis. Other skeletal features such as Wormian bones, vertebral compression fractures, scoliosis, and short stature can also be seen (Zanotti & Canalis, 2020). Affected individuals may also develop basilar invagination due to weakness at the craniovertebral junction, which can then lead to severe neurological problems (Canalis & Zanotti, 2014). Additional body systems may be affected, causing features such as hearing loss, polycystic kidneys, cardiovascular defects, and dental abnormalities (Brennan & Pauli, 2001; Regev et al., 2018; Lee et al., 2018). Characteristic facial features of individuals with this condition include low set ears, hypertelorism, broad nasal base, and midfacial flattening (Cortes-Martin et al., 2020). The age of symptom onset for HCS is variable. Some individuals show manifestations as early as infancy while others do not show signs until later in adolescence (Jirečková et al., 2018). HCS can be diagnosed through radiologic findings such as multiple fractures, open skull sutures, basilar invagination, osteoporosis, and acro-osteolysis. Since any one of these features can be seen in a number of other medical conditions, observation of one feature alone is not enough for a diagnosis of HCS (Jirečková et al., 2018). Alternately, genetic testing identifying a pathogenic variant in exon 34 of *NOTCH2* is consistent with a diagnosis of HCS

(Isidor et al., 2011). These variants are inherited in an autosomal dominant manner or they may be de novo (Brennan & Pauli, 2001).

Pathogenic variants in exon 34 of the *NOTCH2* gene are known to cause HCS though the exact disease mechanism is not yet understood (Simpson et al., 2011). The Notch2 transmembrane receptor is important in mediating cell signaling. It also has a role in the differentiation of osteoblasts and osteoclasts, thereby affecting skeletal development as well as bone homeostasis throughout life (Palav et al., 2014). Pathogenic variants associated with HCS cause an early termination of the receptor, which leads to a stable protein that can sustain signaling for a longer period of time than typical (Fukushima et al., 2017). Mouse models suggest increased osteoclastogenesis may be a mechanism for the osteoporosis seen in this syndrome (Canalis et al., 2016).

Presently there are no formal guidelines for treatment of this syndrome. Medical management is based on treating an individual's symptoms (Cortes-Martin et al., 2020). Surgery may be used to manage some skeletal, cardiac, and renal manifestations. These surgeries can be difficult as poor bone density and abnormal anatomy typical in HCS may cause complications (Falls et al., 2021). Medications including bisphosphonates, teriparatides, and denosumab have been used to treat osteoporosis. However, none have been proven effective for HCS patients and none stopped progression of acro-osteolysis (Canalis, 2018).

Individuals with rare conditions and their family members are increasingly using the internet and social media to find support and information about their diagnosis (Nicholl et al., 2017; Morgan et al., 2014). There are currently a small number of resources available to individuals with HCS and their family members who want to learn more about their condition as compared to other more common syndromes. Those with the HCS may turn to support groups,

though today the only syndrome-specific support group is a private Facebook group. Additionally, there are a number of scientific articles about HCS. These can be difficult to access and are typically written in highly technical language which individuals without a background in science or medicine likely have difficulty understanding. Finally, there are some online educational resources that give information about HCS. These include the NIH's MedlinePlus, the NIH's Genetic and Rare Disease Information Center (GARD), the National Organization for Rare Disorders (NORD), Orpha.net, and the Online Mendelian Inheritance in Man (OMIM). These resources are available to the public free of charge, however even MedlinePlus, GARD, and NORD, which are intended for patient audiences, can be challenging for the average person to understand.

The goal of this study was to develop an easily understandable educational resources for HCS patients and their families. The first aim was to evaluate current patient resources by calculating reading levels and assessing content. The next aim was to construct and distribute a survey to understand HCS patients' and family members' experience finding information about the condition through these resources and through various medical providers. Finally, the survey results were used to develop an educational material that HCS patients and their families can use to learn about the syndrome.

3.2 Methods

This study and the survey used were approved by the University of Pittsburgh Institutional Review Board as exempt research (STUDY21120110) (Appendix D).

3.2.1 HCS Educational Material Selection

A web search for "Hajdu Cheney Syndrome" was completed in March 2022 to identify online HCS-specific educational materials. Websites returned were available to anyone with access to the internet, including individuals with medical training as well as patients and their families. The HCS pages from the National Institute of Health's (NIH) MedlinePlus (Hajdu-Cheney syndrome: MedlinePlus Genetics), the NIH's Genetic and Rare Disease Information Center (Acroosteolysis Dominant Type: GARD), the National Organization for Rare Disorder's (NORD) Rare Disease Database (NORD Hajdu Cheney Syndrome), Orpha.net (Orphanet: Hajdu-Cheney Syndrome), and the Online Mendelian Inheritance in Man (OMIM Entry - #102500) were assessed in the current study. This study did not evaluate readability for online peer-reviewed journal articles as these are typically written for an audience of scientists, researchers, and other professionals in the field rather than patients. This study also did not evaluate the Facebook HCS support group. This source is not directly intended to act as a primary source for information about HCS. Further, evaluation would be challenging as there are many posts and comments, some of which don't directly provide educational information.

3.2.2 Readability

Once the above educational resources were identified, the online Automatic Readability Checker (https://readabilityformulas.com/free-readability-formula-tests.php) analyzed their readability. This tool evaluates a sample of writing for its readability through multiple tests. The first test utilized in this study is the Flesch Reading Ease formula. This formula gives text a reading ease score from 1 to 100, with higher scores indicating easier reading. For example, scores of 90-

100 mean the writing is very easy to read. Scores of 0-29 indicate writing that is highly confusing. Average sentence length (number of words divided by number of sentences) and average number of syllables per word determine the reading ease score. The second method of evaluation is the Flesch-Kincaid Grade Level. This modifies the Reading Ease formula to provide a U.S. school grade-level score indicating the approximate grade level in which a student should be able to read and comprehend the text. Finally, the Automated Readability Index was applied. This index is different from the Flesch-Kincaid Grade Level because it provides a grade level based on word difficulty (letters per word) and sentence difficulty (words per sentence).

3.2.3 Population Assessment

In order to collect anonymous data on patient and family member experiences, a survey was created using Qualtrics software provided through the University of Pittsburgh (Appendix B and C). A master certified health education specialist with extensive evaluation experience and two genetic counselors reviewed the survey questions. Four genetic counseling students and one of the genetic counselors who was involved in the review of the survey piloted the survey. The survey was updated based on consecutive rounds of feedback prior to opening the survey to responses.

The final survey consisted of a total of 29 questions. Five questions elicited participants' satisfaction with medical information provided at initial diagnosis. Six questions ascertained participants' experiences with accessing and understanding educational resources, both online and from various medical providers. Finally, the survey asked three questions about the type of educational resource participants would find most useful and what information they would like included in that resource. Relevant areas of information about HCS were listed for individuals to

choose from and there was an option write in additional categories. The remaining questions inquired about patient demographic information. Twenty-four questions were multiple choice. Others were constructed as a Likert scale or as an open-ended question where participants could write in their own unique answers. Participants were able to leave questions unanswered if desired, although they were prompted for a response before moving on to the next question (Appendix C).

3.2.4 Participant Selection

In order to be eligible to take the survey, individuals needed to be at least 18 years old so they could provide informed consent. They also had to speak English as translated copies of the survey were unavailable. Finally, only people diagnosed with HCS or with a family member diagnosed with HCS were allowed to take the survey. People without a personal diagnosis but with a family member with HCS were invited to participate in the survey as they likely have experience trying to find information about the condition. This is especially true in cases where the affected individual is an infant or child and the unaffected parents are the ones trying to understand the syndrome. There was no restriction on how closely related an unaffected family member had to be to the affected individual to take the survey. However, unaffected respondents were likely 1st or 2nd degree relatives of an individual with HCS as this is the relationship of most members of the support group the survey was posted in. It is also possible that more than one relative of a single affected individual may have responded to the survey, but there is no way for us to determine this due to the anonymous nature of the survey.

The survey link was shared in a private Facebook HCS support group along with an approved invitation script (Appendix A). The survey was posted on this Facebook page since, with 140 members, it was the largest group of people affected by HCS. The survey was shared again

along with a reminder two weeks after the initial Facebook posting (Appendix A.1). The survey remained open to responses for approximately one month total, from March 22, 2022 through April 19, 2022.

3.2.5 Analysis

Complete, anonymous survey responses were analyzed. Partial responses in which the respondent answered more than the first question regarding age were also included in analysis. Respondents were not required to answer every question. This allowed them to participate in important research without being forced to respond to questions they felt uncomfortable answering. It also let people who did not have time available to answer every question contribute. Including these responses can be helpful since they increase sample size for questions completed.

Microsoft Excel performed descriptive statistics including counts, means, median, standard deviations, and percentages. Microsoft Excel created tables and graphs of results. Additionally, perceived helpfulness of each non-online resource to provide information about HCS were entered into Stata to perform a Kruskal-Wallis test. Kruskal-Wallis tests are used to determine if there are statistically significant differences on an ordinal dependent variable by a categorical independent variable with two or more groups. Unlike a one-way ANOVA test, the dependent variable does not need to be normally distributed to use this test. In this study, the Kruskal-Wallis test determined if there was a non-online resource with a statistically significant difference in helpfulness. Kruskal-Wallis tests do not tell exactly which of the resources is significantly different, so Stata also performed a Dunn’s test with Holm Sidak adjustment. Dunn’s test compared helpfulness ratings of each individual resource with the each of the others to determine which specific resources had significantly different helpfulness from each other.

3.2.6 Creation of Educational Material

Microsoft Word was used to draft an HCS-specific educational resource based on the results of the Qualtrics survey. This took the form of a fact sheet that contained information regarding cause, inheritance, features, and management of HCS as these were indicated as information survey respondents would like (Appendix G). At this time the fact sheet has not been piloted or shared with the patient population.

3.3 Results

3.3.1 Readability Analysis

The Flesch Reading Ease formula, Flesch-Kincaid Grade Level, and Automated Readability Index evaluated each online educational resource. Flesch Reading Ease scores ranged from 8.9 to 45.8, Flesch-Kincaid Grade Levels ranged from 10.5 to 15.8, and Automated Readability Index scores ranged from 9.7 to 15.2 (Table 1).

Table 1. Online HCS Educational Material Readability Scores

Online Resource	Flesch Reading Ease	Flesch-Kincaid Grade Level	Automated Readability Index
Medline Plus	40.7	12.6	13.2
GARD	45.8	10.5	9.7
NORD	36.6	12.5	12.7
Orpha.net	8.9	15.8	15.2
OMIM	35.5	12	10.9

3.3.2 Content Analysis

Online educational resources were also evaluated based on the types of information about HCS that they provided. As shown in Table 2, all websites included information about the features typically seen in individuals who have HCS, including key features such as osteoporosis and acro-osteolysis. All resources mentioned variants in *NOTCH2* as causative of HCS, although the GARD website did not specify changes are gain-of-function variants causing prolonged activation. This extra detail was sought out since it differentiates HCS-causing *NOTCH2* variants from other *NOTCH2* variants that cause a reduced function and Alagille syndrome (Kamath et al., 2012). Each resource mentioned autosomal dominant inheritance, but only GARD, NORD, and Orpha.net went into detail and provided actual risk figures for children of individuals with HCS. Both NORD and Orpha.net addressed some aspects of management, namely treatment is symptomatic and medications like bisphosphonates have been used to treat osteoporosis. Finally, the resources were checked for their provision of links to support organizations. NORD and GARD gave links to groups like Gene Alliance and the European Skeletal Dysplasia Network. Notably only NORD supplied information about the Facebook HCS-specific support group.

Table 2. Online HCS Educational Material Content Analysis

Online Resource	Syndrome Features	Genetic Etiology	In Depth Inheritance Information	Management	Links to Support Orgs
Medline Plus	Yes	Yes	No	No	No
GARD	Yes	No	Yes	No	Yes
NORD	Yes	Yes	Yes	Yes	Yes
Orpha.net	Yes	Yes	Yes	Yes	No
OMIM	Yes	Yes	No	No	No

3.3.3 Demographic Information

A total of 29 individuals participated in the survey. The Facebook support group contained 140 members at the time the survey was open to responses. Therefore, the estimated survey response rate is 20.71%. Responses from the 29 participants were analyzed and the data are displayed in Table 3. A majority of the respondents (19/29) had a diagnosis of HCS. All individuals who did not have a personal diagnosis of HCS were family members of an individual with HCS. It is possible that a respondent had more than one individual with a diagnosis of HCS in their family. Ages of respondents varied, with the greatest percentage in the range of 35 to 44 years old (8/29, 27.59%). Additionally, 75% of participants identify as women (18/24) with 75% having female as sex recorded at birth (18/24). Most individuals reported race as White (23/26) and 86.96% reported ethnicity as non-Hispanic or Latino (20/23). The highest education level reported was a graduate or professional degree, seen in 16.67% of individuals (4/24). The most common education level was a Bachelor's degree (8/24), followed by High School/GED (7/24). Most had at least 1 child (13/24, 54.17%) with 11 individuals having one child with a diagnosis of HCS (11/13, 84.62%). Finally, most live in urban regions (10/24).

Table 3. Respondent Demographics

		N	Percentage
Diagnosed with HCS (N = 29)	Yes: Genetic Testing	7	24.14%
	Yes: Clinical Exam	5	17.24%
	Yes: Genetic Testing & Clinical Exam	7	24.14%
	No	10	34.48%
	18-24 Years	4	13.79%

Age (N = 29)	25-34 Years	6	20.69%
	35-44 Years	8	27.59%
	45-54 Years	7	24.14%
	55-64 Years	2	6.90%
	Over 65 Years	2	6.90%
Gender (N = 24)	Woman	18	75%
	Man	6	25%
Sex Recorded at Birth (N = 24)	Female	18	75%
	Male	6	25%
Race (N = 26)	White	23	88.46%
	Black or African American	1	3.85%
	American Indian or Alaska Native	1	3.85%
	Self Describe	1	3.85%
Hispanic or Latino (N = 23)	Yes	2	8.70%
	No	20	86.96%
	Prefer Not to Answer	1	4.35%
Education Level (N = 24)	Grade School	1	4.17%
	High School/GED	7	29.17%
	Associate Degree	3	12.50%
	Bachelor's Degree	8	33.33%
	Graduate or Professional Degree	4	16.67%
	Prefer Not to Answer	1	4.17%
Number of Children (N = 24)	0	11	45.83%
	1	1	4.17%
	2	3	12.50%
	3	6	25%
	4 or More	3	12.50%
Children with HCS (N = 13)	0	2	15.38%
	1	11	84.62%
Community Type (N = 24)	Urban	10	41.67%
	Suburban	6	25%
	Rural	8	33.33%

3.3.4 Age of Diagnosis

The survey asked participants if they have or their family member has a diagnosis of HCS and the age of diagnosis. Out of the 19 individuals who reported having a personal diagnosis of HCS, a diagnosis between the ages of 0 and 5 (9/19) was most common (Table 4).

Table 4. Age at HCS Diagnosis – Respondent

Age	N (N = 19)	Percentage
0-5 Years	9	47.37%
6-10 Years	4	21.05%
11-15 Years	1	5.26%
16-20 Years	0	0%
21-25 Years	3	15.79%
26-30 Years	1	5.26%
Over 30 Years	1	5.26%

Table 5 provides the age ranges of family member diagnosis. For those 17 individuals who had a family member diagnosed with HCS, the greatest number of people had family members diagnosed between ages of 0 and 5 (7/17), with some being diagnosed as old as ages 26 to 30 (1/17). Seven respondents had a personal diagnosis of HCS as well as a family member with a diagnosis of HCS and therefore answered both questions about their own age of diagnosis and their family member's age.

Table 5. Age at HCS Diagnosis – Family Member

Age	N (N = 17)	Percentage
0-5 Years	7	41.18%
6-10 Years	4	23.53%
11-15 Years	1	5.88%
16-20 Years	2	11.76%
21-25 Years	1	5.88%
26-30 Years	1	5.88%
Over 30 Years	0	0%
Unsure	1	5.88%

3.3.5 Diagnosing Provider and Satisfaction

The next section of the survey elicited information about the affected individuals' diagnosing provider and the respondent's satisfaction with that provider's initial explanation of HCS (Table 6). Most individuals reported a geneticist provided their diagnosis (17/28). The rest received the diagnosis from an orthopedist (4/28), primary care physician (2/28), or genetic counselor (1/28). Two individuals indicated a provider not listed in the survey and were given the option to write in their own answer. One indicated they received diagnosis from a neurologist while the other chose not to indicate the provider. Two individuals said they were unsure who the diagnosing provider was.

Table 6. HCS Diagnosing Provider

Diagnosing Provider	N (N = 28)	Percentage
Primary Care Physician	2	7.14%
Orthopedist	4	14.29%
Genetic Counselor	1	3.57%
Geneticist	17	60.71%
Other (write in)	2	7.14%
Unsure	2	7.14%

Table 7 provides satisfaction levels. A majority of individuals indicated they were satisfied or highly satisfied with the diagnosing provider's initial explanation of HCS (15/27). Some individuals reported being unsatisfied with the description (3/27) and others felt neutral (8/27). One individual was unsure of how they felt at that time.

Table 7. Satisfaction with Initial Explanation

Satisfaction Level	N (N = 27)	Percentage
Highly Satisfied	6	22.22%
Satisfied	9	33.33%
Neutral	8	29.63%
Unsatisfied	3	11.11%
Highly Unsatisfied	0	0%
Unsure	1	3.70%

The survey asked all individuals who indicated they were unsatisfied or unsure to explain what lead to this assessment (Table 8). This question was multiple choice with the option to write in additional reasons. Half felt the provider used language that was too complex and confusing (2/4). One person reported dissatisfaction due to the provider not being able to answer their

questions about the condition. Finally, an individual noted there were additional reasons for their dissatisfaction but did not explain further.

Table 8. Reasons for HCS Explanation Dissatisfaction

Reasons Unsatisfied	N (N = 4)	Percentage
Complex Language	2	50%
Couldn't Answer Questions	1	25%
Additional Reasons	1	25%

Table 9 shows reasons for satisfaction with the initial description of HCS. This was a multiple choice question with the option to write in additional reasons for satisfaction. Most participants reported the provider used understandable language (11/23) while some felt the provider was able to adequately answer their questions regarding HCS (9/23). A few individuals noted additional reasons for their answer (3/23). Their written in responses included that their provider gave them copies of medical research articles on HCS, their provider hadn’t heard of the condition but did a lot of research to explain it to them, and their provider always answered their questions or would consult with other doctors more familiar with the condition if he did not know an answer.

Table 9. Reasons for HCS Explanation Satisfaction

Reasons Satisfied	N (N = 23)	Percentage
Understandable Language	11	47.83%
Could Answer Questions	9	39.13%
Additional Reasons	3	13.04%

Respondents who stated feeling neutral towards the initial description were asked what would have made them more satisfied. They were given space to write in an answer and seven chose to do so. Most responses revolved around physician knowledge of the condition (5/7). They felt that if the provider had heard of HCS before, had known the range of issues associated with a specific pathogenic variant, or had been able to give more information in general they would have been more satisfied. One person mentioned they would have been happier if they had been offered genetic counseling and provided a comprehensive care plan to make sure aspects of the condition were monitored adequately. One respondent was unsure of what would have improved their experience.

3.3.6 Online Materials and Timing

The survey asked participants if they had ever looked online to find information about HCS. Responses are provided in Table 10. All individuals who answered this question indicated they have looked online at some point (27/27).

Table 10. Respondents' Use of the Web

Looked Online for Info	N (N = 27)	Percentage
Yes	27	100%
No	0	0%

These individuals were asked how long it took to find the online information they were seeking about HCS (Table 11). Approximately 1/3 of individuals reported it took less than 30 minutes to find the needed information (9/27). However, almost 1/3 looked more than 2 hours (8/27) and some were unable to find the information they were seeking (3/27).

These respondents were also asked how often they currently go online to find information about HCS. Nearly 45% reported they do this less than once a month (12/27). Around 40% look online once a month or more frequently (11/27). Approximately 15% do not look online currently (4/27).

Table 11. Ability to Find HCS Information Online

		N (N = 27)	Percentage
Time to Find Information Initially	Less Than 30 Minutes	9	33.33%
	1 Hour	4	14.81%
	2 Hours	0	0%
	More Than 2 Hours	8	29.63%
	Could Not Find Information	3	11.11%
	Did Not Look Online Initially	3	11.11%
Current Frequency	Daily	0	0%
	Once a Week	1	3.70%
	Twice a Week	1	3.70%
	Once a Month	9	33.33%
	Less Than Once a Month	12	44.44%
	Do Not Look Online Currently	4	14.81%

Individuals who reported having gone online were given a list of online resources about HCS and asked to select the ones they found helpful. They could choose multiple options. Twenty-six individuals responded to this question, with some selecting more than one resource. As shown in Table 12, the most respondents indicated that the NORD webpage for HCS (16) and online community support groups (11) were helpful. The resource that was least helpful was OMIM (1). Participants could write in a helpful resource if it was not listed. Those who chose to do this stated PubMed, Google, and looking at articles from medical journals online were useful.

Table 12. Most Helpful Online Resources

Resource*	N
NORD	16
Online Support Groups	11
Medline Plus	7
GARD	6
Other (Write In)	6
None	3
OMIM	1
* Respondents were able to select multiple options	

3.3.7 Other Educational Resources

After the questions exploring online resource use, participants were asked what other resources they use to learn about HCS (Table 13). Twenty-four individuals responded to this question and each individual could select multiple resources. Speaking with a geneticist (12) and reading scientific articles (10) were the most common non-online methods individuals have used to learn more about HCS. Others reported genetic counselors (6), other physicians (7), and other healthcare professionals (3) improved their understanding. Participants who wrote in their own answers included family members and communication with other individuals/families with HCS as being sources of information.

Table 13. Respondents' Sources of Information Other Than Online

Resource*	N
Geneticist	12
Scientific Articles	10
Other Physician	7
Genetic Counselor	6
Other (Write In)	5
Other Healthcare Professional	3
Books	0
*Respondents were able to select multiple options	

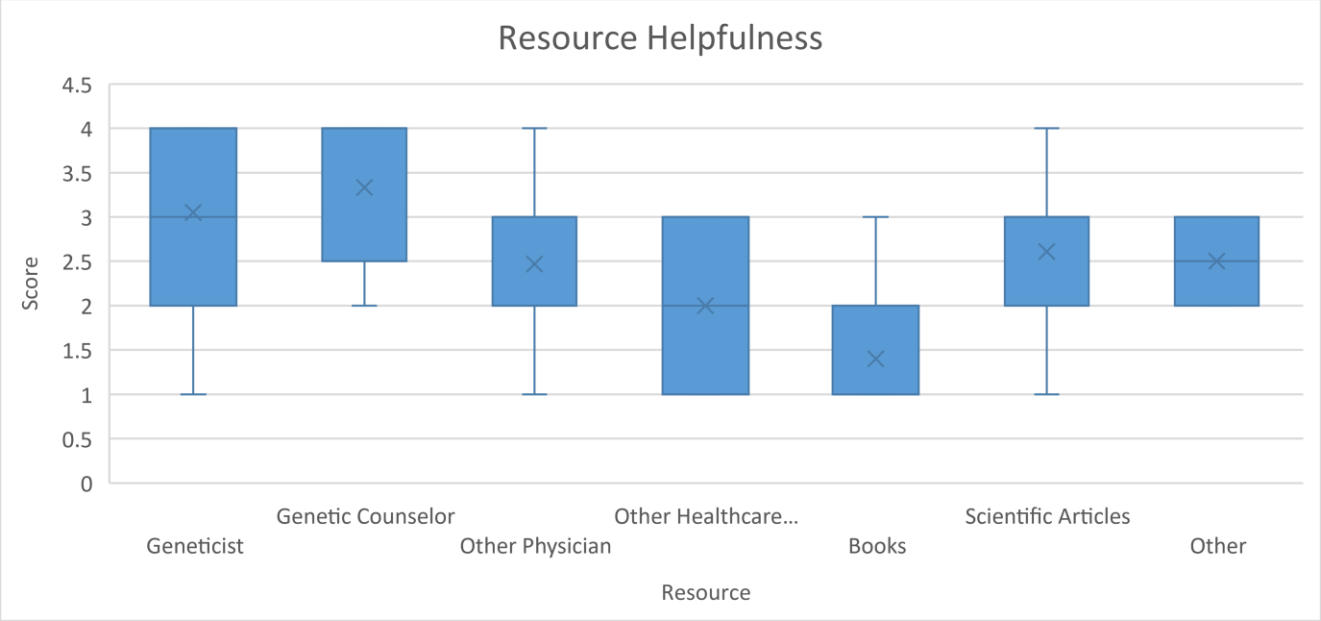
Participants ranked each of these offline resources on a Likert scale based on how helpful they were in providing information about HCS. Online resources were not listed here for rating as previous questions focused in on use of the internet to find information about HCS. Answers of 'not at all helpful' were given a score of 1, 'slightly helpful' a score of 2, 'moderately helpful' a score of 3, and 'very helpful' a score of 4. Participants could also select N/A if they had not used a particular resource. Table 14 provides these ratings. Median scores of each resource are compared in Figure 1. Overall, geneticists and genetic counselors were rated as being the most helpful sources based on average of ratings. The sources with the lowest average helpfulness ratings were books and other healthcare professionals. A Kruskal-Wallis test was performed, which resulted in a p value of 0.0002 (Appendix E). This indicates that at least one resource has a median helpfulness rating that is significantly different from another source. A Dunn's pairwise comparison test was then performed to identify which sources had significantly different median helpfulness ratings (Appendix F). Significant differences were found between books and

geneticists (p=0.0005), books and genetic counselors (p=0.0006), books and scientific articles (p=0.0173), and genetic counselors and other healthcare professionals (p=0.0214).

Table 14. Participants' Rating of Sources' Helpfulness

Source	Count (N)	Mean	Standard Deviation	Median
Geneticist	20	3.05	0.92	3
Genetic Counselor	9	3.33	0.82	4
Other Physician	17	2.47	0.85	2
Other Healthcare Professional	13	2	0.78	2
Books	10	1.4	0.66	1
Scientific Articles	23	2.61	1.05	3
Other	2	2.5	0.5	2.5

Figure 1. Box and Whisker Plot Comparing Helpfulness Scores of Resources



3.3.8 Material Development

Participants were asked what their preferred format would be for an educational resource (Table 15). The question instructed them to choose their top two options, with the goal being that one of the most chosen formats be drafted as part of this study. The resource would likely be shared online in order to be available to the most individuals. The formats chosen most were a fact sheet (19) or video (11). Least preferred formats were pamphlets (8) and infographics (10). One individual wrote in a preference for using in-depth scientific articles to learn about HCS.

Table 15. Participants' Preference for Resource Format

Preferred Source*	N
Fact Sheet	19
Video	11
Infographic	10
Pamphlet	8
Other (Write In)	2
* Respondents were able to select multiple options	

In order to make sure the educational material created would be most useful, the survey asked what information respondents would like included. Participants could select all applicable options out of a list of subjects. These subjects aligned with the content areas current online educational resources were assessed for. Table 16 summarizes the responses. Management of the condition was the aspect most people wanted included in the resource (21). Cause (17), inheritance (14), and features (11) of HCS were also indicated as topics respondents would like covered. The question included the option to write in an answer as well. Entries included life expectations, long

term effects, median life expectancy, access to list of expertise, treatments that have not worked for certain medical issues, and regular updates on treatments and remedial surgeries that can be done.

Table 16. Information to Include in HCS Educational Material

Subject*	N
Condition Management	21
Cause of HCS	17
Inheritance/Risk to Family	14
Features of HCS	11
Other (Write In)	7
* Respondents were able to select multiple options	

Finally, participants were asked what information about HCS they feel they still do not understand as these may be helpful to include in an educational resource. This was an open-ended question allowing for each respondent to write in their own answer. Some respondents indicated they don't understand information within the subjects to be included in a resource in the previous question. These included HCS genetics and how the gene mutation occurs, likely progression of the condition, and long term health prognosis/life expectations. Multiple individuals feel they don't understand medical management. The responses they wrote said they do not understand current worldwide best practices to remediate teeth and bone loss, effectiveness of cervical fusion, preventative treatments, when to start treatment for osteoporosis, and if there is gene therapy or other 'cures'. Further, participants indicated they do not fully understand availability of IVF, lifespan, and main causes of death. One individual wrote in that since it such a rare disease, it feels

like you never know enough about it. Another wrote in that while new things they don't know do pop up, they have had the diagnosis for so long they feel they end up educating others.

3.4 Discussion

HCS is a rare connective tissue disorder. While case reports and research articles about HCS exist in scientific journals, there are few easily understandable educational resources available for patients and their families. This study evaluated the readability and content of existing online HCS-specific resources to determine the current availability of comprehensive, patient-friendly materials. Additionally, the study obtained patient and family members' experiences using online and other resources to find information about HCS in order to better understand their needs. The survey also elicited the format of educational material about HCS participants would prefer be created and what areas of information they would like included in that resource.

3.4.1 HCS Online Educational Resource Evaluation

This study evaluated online educational materials about HCS for readability and content provided. Reviewing readability ensures patients are able to understand and apply the information presented. As stated previously, standardized evaluation of HCS resources showed all to be at least difficult to read and well above the 6-8 grade reading level recommended by the National Institute of Health (Weiss, 2003; Rooney et al., 2021; Eltorai et al., 2014). Possible reasons for the low reading ease scores and high reading grade levels are that resources such as OMIM and Orpha.net are intended for medical provider use. GARD's HCS page received the highest Reading Ease score

and lowest reading grade level. This supports their stated aim of providing easy to understand information about genetic and rare diseases (About GARD).

The online educational materials were also evaluated for content. Each contained information in multiple areas assessed for, but a majority did not encompass all areas. It is possible that in some cases this is due to the intended audience of the resource. As mentioned above, OMIM and Orpha.net are primarily intended for medical providers, which may be why they do not focus on patient support resources. On the other hand, GARD did not meet our standard for genetic etiology information. It is possible that GARD assumes patients' top priority is not to understand in depth information about the specific type of *NOTCH2* variants that cause HCS. Only the NORD website contained all the areas of information looked for. Together, this means if an individual wants to learn about HCS they may need to look at multiple resources to have full knowledge of the condition. Needing to look at many sources could cause a delay in patient understanding. Additionally, if an individual happens upon a complicated resource first, they may become frustrated and give up on their research without getting complete information about HCS.

3.4.2 Demographics

A majority of respondents had a personal diagnosis of HCS (19/29). The remaining participants were family members of someone with HCS. The most common age at diagnosis was between 0 and 5 years of age. This is consistent with the fact that signs of the condition can be seen as early as infancy and early childhood (Jirečková et al., 2018; Brennan & Pauli, 2001). Furthermore, the availability of genetic testing since *NOTCH2* was reported to be the cause of HCS in 2011 means patients may be diagnosed more quickly at these young ages rather than waiting years or decades to find a diagnosis.

The most common education level among participants was a bachelor's degree (8/24) and the highest level reported was a graduate or professional degree (4/24). In 2021, 23.5% of the United States population over age 25 held a bachelor's degree as their highest education level. 14.4% achieved a more advanced degree as their highest degree (Census.gov, 2022). This means a greater proportion of the individuals that took this survey had at least an undergraduate degree than in the general US population. This also puts these individuals at the education level the readability measures predict is needed to read the materials assessed in this study. However, college education does not guarantee sufficient health literacy or genetic literacy needed to fully comprehend HCS educational materials. In fact, the National Assessment of Adult Literacy found that approximately 36% of adults have basic and below basic health literacy. Only around 12% are estimated to have proficient health literacy (NAAL, 2006). Individuals who have lower levels of health literacy may struggle to find, understand, and use health information.

3.4.3 Diagnosis Satisfaction

Around 60% (17/28) of individuals with HCS represented in survey responses received their diagnosis from a geneticist. Others were diagnosed by primary care physicians (7.14%), orthopedists (14.29%), neurologists (3.57%), and genetic counselors (3.57%). Most participants were satisfied or highly satisfied with the provider's explanation of HCS. These satisfied individuals felt the provider used understandable language (47.83%) and was able to answer their questions (39.13%). It is possible that the overall higher education levels demonstrated in this survey's participants also contributed to the number of individuals reporting satisfaction. These individuals are more likely to be able to understand the concepts and language used by medical providers. This result may therefore not be representative of how easily many individuals in the

general population would understand the information and come away from the meeting satisfied. Another factor that increased satisfaction was when providers who were unfamiliar with the condition put in effort to do extra research before explaining to the patients and their family members. This could increase patient confidence in their physician's competency, thereby contributing to patient satisfaction with the provided information.

Some individuals were unsatisfied with the initial explanation (11.11%). They felt unsatisfied due to provider use of too complex language and not being able to answer questions about the condition. Most of those who had a neutral response (29.63%) to the provider's description of HCS felt that more physician knowledge about the condition would have made them more satisfied. This suggests more physician education about rare diseases in training or through continuing education could improve the diagnosis experiences of individuals with rare diseases. Another possibility is physicians may need more support in providing condition information in an accessible way.

3.4.4 Online Materials

All respondents went online to find information about HCS. For rare conditions like HCS, the amount of syndrome-specific information on the web can be limited. This can make it difficult for patients and their family members to find needed information. Around one third of study participants took more than two hours to get an answer to their questions about HCS while a few could not find the material they were looking for. This could indicate they had a hard time finding a website with the information they wanted or that they found educational materials, but they were difficult to understand. Resources available online for those were diagnosed many years ago may have been different than those that are available now. It is possible that there were not as many

websites with pages describing HCS at that time, meaning time to find desired information about HCS online would likely have been longer for these individuals. Even for individuals diagnosed more recently online resources may have changed since their diagnosis. For example, in recent months the GARD website has reconfigured the way they report information about genetic conditions. Newer layouts may be easier to use than they were when first visited.

The most individuals found the NORD page for HCS to be helpful. This is understandable since NORD's Rare Disease Database is meant to be a resource for rare disease patients and caregivers, providing unbiased and complete information about many rare diseases. While this study found readability for the NORD page as difficult to read and above the recommended reading grade levels, its readability score was higher and its reading grade level lower than some of the other resources examined. Respondents may have felt this source was helpful since NORD's webpage includes all topics we evaluated for in this study, with different areas of information clearly separated by bolded headings. It was also the only online resource that gave information about the patient support group, something that is likely very important to newly diagnosed patients as support groups can change perceptions about a diagnosis and reduce feelings of isolation (Garabedian et al., 2020; Simmons, M.) . Online support groups were the second most popular online resource selected. This is in line with findings that family members of rare disease patients use social media to find support and information on their child's condition (Nicholl et al., 2017). Only one participant chose OMIM as being helpful. This result is not surprising since OMIM contains detailed information about clinical features and the genetic basis of HCS and is primarily tailored towards health care providers. Three individuals said they found no online resources to be helpful. This suggests that currently available online resources for HCS are not sufficient.

3.4.5 Other Resources Ability to Provide Information

Many individuals in the world do not have internet access or may not be tech savvy. Therefore, exploring experiences gathering information from other sources was of interest. A box and whisker plot compared the perceived helpfulness of the different non-online resources in providing information about HCS. Geneticists and genetic counselors had the highest average helpfulness ratings (3.05 and 3.33). This speaks to their ability to effectively provide information about rare genetic conditions like HCS. Therefore, speaking with these genetic specialists could be beneficial for individuals who still have questions about HCS. The source with the lowest median helpfulness ratings was books, which no one found to be more than moderately helpful. This could indicate a lack of available books with information about HCS or that books with information about HCS reviewed by survey participants were too difficult to understand. Scientific articles received a higher average helpfulness rating (2.61) than non-genetics healthcare professionals. This may be due in part to 50% (12/24) of participants holding a bachelor's degree or higher, therefore being more likely to read and understand these articles.

A Kruskal-Wallis test was also performed to compare the median helpfulness scores of each resource. This statistical test found a significant difference in median scores across some of the sources ($p<0.05$). A follow-up Dunn's test with Holm Sidak adjustment found a difference in median helpfulness scores between books and geneticists, books and genetic counselors, and books and scientific articles. These results show that participants found geneticist, genetic counselors, and scientific articles to be significantly more helpful than books in learning about HCS. A significant difference in helpfulness medians was also found between genetic counselors and other healthcare professionals. This indicates participants favored genetic counselors over other healthcare professionals. It is however difficult to fully interpret the results of these tests. The

number of individuals who provided ratings for each resource does not match the number of individuals who indicated they had used that resource in the previous question. For example, in the first question, no individuals selected they had used books to learn about HCS. In the section to rate each resource, 10 individuals provided a rating. Additionally, only 7 individuals reported they had used 'other physicians' to gather more information, but 17 individuals gave a rating to 'other physicians'. This makes it difficult to say if there was truly a significant difference in median scores between books and the other sources or between genetic counselors and 'other physicians'. It is possible the discrepancy in response counts is due to some individuals choosing to not answer the question about which sources they have used as responses to all questions were not required. Another possibility is individuals may have misunderstood the question asking them to select all of the sources they have ever used to learn about HCS and only picked the most helpful or most recently used resources.

3.4.6 Informational Needs

Survey participants were asked what aspects of HCS they would most like to find in an educational resource. They were able to indicate multiple areas of information about HCS. Participants were also asked what information about HCS they still do not understand, as these topics would also be beneficial to cover. 17 respondents wanted information about the cause of HCS to be included in a resource. One individual specified that they do not understand how the gene mutation itself occurs. It is possible that they are concerned they did something to cause themselves or their family member to have the syndrome (Gomez-Zuniga et al., 2019). Pathogenic variants in *NOTCH2* occur spontaneously by chance or they can be inherited from an affected parent. 14 survey respondents desired information about this inheritance. Availability of IVF was

an area that was mentioned as not being understood. These individuals may be worried about passing the condition on to children in the future and believe this information could be useful for family planning. When pathogenetic variants are passed down, they are inherited in an autosomal dominant pattern. This means risk to children of an individual with HCS is 50%. Preimplantation genetic testing for monogenic disorders (PGT-M) should be possible to check for familial HCS variants in embryos during in vitro fertilization (IVF). To date, no cases of PGT-M being used for HCS have been published. The Human Fertilisation and Embryology Authority recently reviewed and approved this method for use in the UK (HFEA, 2022).

Finally, information about condition management was requested by 21 participants. This sentiment was also expressed in statements about what respondents felt they still don't understand. Individuals mentioned not knowing best ways to be proactive to minimize medical issues, if there is gene therapy available, and what the ideal treatment for improving bone mineral density. This shows that a challenge in this community is figuring out how to take care of themselves or affected family members after the diagnosis. Unfortunately, at this time there are not any official management guidelines for people who have HCS. There are no gene therapies or clinical research trials for medications available. Management is symptomatic. Medications like bisphosphonates and teriparatides have been used to improve osteoporosis. Surgeries have been used for other complications that may arise, with varying degrees of success (Murtagh-Schaffer et al., 2008; Sakka et al., 2017; Canalis, 2018). Participants indicating they would want information about medical management included may therefore mean that patients are searching for answers to their problems that do not currently exist rather than that current educational resources with that piece of information are hard to find or understand.

Some individuals mentioned they do not understand long term prognosis and expected lifespan. Due to the limited number of individuals with the syndrome reported in medical literature it is difficult to determine if these are reduced, though it is reasonable to predict they would be in those with neurological complications (Canalis & Zanotti, 2014). Management of individual symptoms as they arise may improve these aspects.

3.4.7 Preferred Resource Format

The survey asked respondents to choose their top two educational material formats for learning about HCS from a list. The least preferred formats were pamphlets and (8) and infographics (10). One individual wrote in a preference for using in-depth scientific articles to understand the condition. The formats chosen most were fact sheets (19) and videos (11).

Fact sheets are short documents that provide basic, relevant information about a subject in the least amount of space. Their goal is to present facts and key points in a clear, easy to understand manner (Cubon-Bell, 2019). This format has often been used to communicate health information in a way that patients, family members, and caregivers can use. Videos about HCS were the second most requested option. Multiple studies found video education about medical conditions or treatments improved patient-reported knowledge, satisfaction, and confidence (Kumar et al., 2020; Jamshidi et al., 2013; Navarro et al., 2021). Videos are particularly useful for conveying information to those with low health literacy as they often do not require the individual to read written word. Another potential reason for selecting the video option is that group members likely have different learning styles. Videos appeal to auditory as well as visual learners. A drawback to use of videos is the potential for technological issues as well as possible increased cost to produce.

3.4.8 Developing Educational Materials

Creating easily understandable educational materials intended for general population use can be a challenge. Medical information can be even harder to convey at high readability levels. Language used to describe aspects of a condition such as genetics, inheritance patterns, and treatment options is often complex. More words may be needed to explain these concepts and medical words often require many characters and syllables. Despite this difficulty, it is important to make patient educational materials that meet the national recommendations of writing below 6th – 8th grade levels as an estimated 80% of adults who use the internet have used it to find health information (Amante et al., 2015). Materials written at lower reading levels are accessible to a broader range of individuals, allowing them to increase knowledge and make more informed medical decisions.

Authors of patient education materials make resources more readable by using shorter sentences as well as more common words in their writing as much as possible. Including definitions for the necessary complex words can also be helpful. The fact sheet drafted in this study included a definition section on the first page to explain more complex words used in the sheet in simple terms. Additionally, the layout of the resource impacts the readability. Using distinct headings, bullet points, graphics, and leaving white space are all recommended ways to make a fact sheet clear and help readers find information they are looking for easily (Plain Language at NIH; CHCS, 2013). Some sections in the HCS fact sheet were written using bulleted lists in order to avoid large, overwhelming blocks of text. Pictures were also used to break up writing and to help explain inheritance patterns in a more visual way.

The fact sheet prepared in this project is intended to be used by individuals who have a recent diagnosis of HCS or have a newly diagnosed family member. Therefore, working with

current patients benefitted material development. Survey responses from HCS patients and family members prior to creating the drafted educational resource ensured the most needed information was included in the resource such as common symptoms, genetic cause, and inheritance patterns. These individuals can also review the resource once drafted and give detailed feedback as to its readability and areas to improve.

Readability formulas were applied to the draft HCS fact sheet which was created based on survey responses. Prior to running these formulas, the written-out name of the syndrome was removed from the document, as the name being repeated throughout increases grade scores without actually making the text more difficult to understand. Additionally, periods were inserted after each bulleted item so they would not be interpreted as one continuous sentence. The Flesch Reading Ease score was 64.4 (standard ease), the Flesch Kinkaid Grade Level was 6.9 (7th grade), and the Automated Readability Index was 6.4 (10-11 year olds, 5th and 6th graders).

3.4.9 Limitations

This study has several limitations. First, the number of survey responses received was small, which can limit the generalizability of survey data. This was expected given that the rarity of the condition limits the pool of potential respondents. This pool was further reduced since only those who were over the age of 18 and who spoke English were eligible to take the survey. The survey was only posted in the Facebook group, meaning individuals with HCS who are not members of the Facebook group would not know about the study unless a current member shared the link with them.

The overall survey response rate is 20.71%. However, it is possible that the true response rate is different. If group members shared the survey link with family who are not in the Facebook

group themselves, the real response rate would be smaller. Another possibility is that not everyone in the group actually saw the survey posting. Per Facebook, 105 members saw the initial survey posting and 104 members saw the reminder post. It is unknown if these view counts are only from the time the survey was open or if some reported views are from after the survey closed.

There was potential for volunteer bias in the study. Filling out the survey was completely voluntary, with no compensation for taking it. It is possible that the people that chose to participate did so because they had an especially difficult time finding or using educational resources about HCS.

Another limitation is some individuals who completed the survey were diagnosed or had a family member diagnosed with HCS a long time ago. Since these participants self-reported about their experiences years after diagnosis there could be recall bias. These individuals may not accurately remember details such as how long it took them to find needed information about HCS online initially after the diagnosis. They may also not fully remember their provider's explanation of the condition or their satisfaction level.

A further limitation of this study is that the HCS Facebook support group was not evaluated for readability or content. While the group is not meant to be used as a primary source of information about HCS, it is a place where information about the condition is shared. A study exploring social media use among patients with rare or newly-described genetic conditions found that 83% of participants used social media to look for information about their diagnosis or test results (Rocha et al., 2017). Evaluating the Facebook page would have been difficult due to the large number of posts and comments as well as the fact that they are not all written in English and need to be translated. Plus, not all posts and comments written are intended to educate about the condition.

The tools used to evaluate readability of sources also have limitations. The three formulas used in this study give readability scores and grades based on words per sentence, syllables per word, and letters per word. The fact that the syndrome name contains a hyphen may have affected scores by increasing characters and syllables per word as defined by the program. The name of the syndrome was then repeated many times within the resource. Also, having the name of the syndrome written out does not make the resource more complex for readers since the patients are familiar with the name of the syndrome.

These formulas don't consider the way different online educational resources display information. The layout impacts how easily individuals are able to find desired information. The material may use pictures and tables to break up the text and make the amount of information less overwhelming, increasing individuals' satisfaction with the resource. Furthermore, some resources provide definitions for more complex words. Having a section with definitions makes the resource more easy for people to understand, despite those same words driving up the reading difficulty levels as determined by the readability formulas.

3.4.10 Study Strengths

As mentioned above, the number of survey responses could be considered a limitation. Typically, larger amounts of data are more useful to draw reliable, meaningful conclusions in a research study. However, there are fewer than 100 individuals reported as having HCS in the current medical literature. Given the rarity of the condition, receiving survey responses from 29 individuals is a fairly substantial part of the HCS patient population.

Another strength of this study is it is the first study to directly survey this patient population. Current scientific literature about the condition mainly consists of patient case reports,

determining the genetic cause of HCS, and research to figure out how the *NOTCH2* variants lead to clinical features. Patients' personal experiences living with the condition have not been explored. This study gave a valuable introductory look into patients' experience with the diagnosis and HCS informational needs.

3.4.11 Future Research

In the future, the educational material created in this study should be piloted. This involves affected individuals and their family members reviewing the resource and providing feedback prior to the final version being released for public use. While readability formulas provide some assessment, this additional step would help to ensure the resource is written and designed in a way patients truly find understandable by having actual patients read them.

Assessment of existing educational resources and determining the HCS population's educational needs were aims completed in this study. A third aim was to develop and distribute an educational material. We created a draft HCS fact sheet containing information about HCS based on survey responses, but a final copy has not yet been distributed. In the future the finalized fact sheet can actually be made available to HCS patients and their family members. This resource would be shared online in the HCS Facebook support group. Individuals often come to the Facebook group after a new diagnosis, making it a good place to access an educational fact sheet with basic information about the syndrome. The fact sheet could also be shared with the couple medical providers who follow multiple patients with HCS. They could share the resource with current and future HCS patients and family members.

Future research could work to increase the number of responses to a similar survey in the future. This could be done by keeping the survey open for a longer amount of time and by including

more reminders to potential participants. Asking medical providers to share the survey with patients who have HCS could allow affected individuals outside the Facebook support group to participate. More participants could ensure that received survey responses are fully representative of the HCS population and would increase the study's statistical power.

The survey asked only a couple of questions that were open-ended. In a future study more of these types of questions could be asked or qualitative interviews could be incorporated. These adjustments would allow participants to explain in more detail what they liked or disliked about each resource. Knowing what elements led respondents to indicate particular online sources as being most helpful would help investigators to create or refine additional educational materials in the future based on latest research findings.

The survey asked participants to rate how helpful different non-online resources were in providing information about HCS. While it also asked many questions about use of online HCS resources, it did not ask to rate helpfulness of the web resources in the same way. In the future, a survey could ask respondents to rate the helpfulness of online resources on a Likert scale in addition to non-online resources in order to more directly compare them.

Lastly, a video resource is another educational material that could be created. This could be considered since a video was the second most popular resource format among participants. As discussed previously, videos can be useful tools for increasing patient knowledge. Some individuals may learn better through videos than written word, and no videos were available on the online resources evaluated in this study.

3.5 Conclusion

This study found that few educational materials about HCS are available online. The resources that are currently available are written in complex, difficult to understand language. Resources examined in this study were all evaluated to be written above an 8th grade reading level. The resources also often did not contain information on all aspects of the condition or links to support for patients and their families.

Study participants all indicated they have looked online to learn about the condition. Some of these individuals took hours to find the information they were looking for and some were not able to find the needed information at all. People also utilized sources that are not online to find out more about HCS. Overall, geneticists and genetic counselors had the highest average helpfulness ratings for non-web-based sources of information.

Participants indicated a preference for a fact sheet to be developed. Desired content for this fact sheet included information about the cause of HCS, risks to family, possible features, and condition management. Based on this information, a fact sheet called All About Hajdu-Cheney Syndrome was created. Future plans are to share a completed fact sheet with individuals diagnosed with HCS in the online HCS Facebook support group.

4.0 Significance to Genetic Counseling and Public Health

4.1 Genetic Counseling

Genetic counselors are medical professionals who help those who have or are at risk for genetic disorders and their families understand their genetic health. Part of this process can include providing individuals with educational materials and support resources. In determining which materials are best to provide, counselors may consider many factors including the material's relevance, accuracy, and recency. As genetic counselors meet with patients who have varying levels of education and health literacy, they also need to be cognizant of the readability of the resources they supply.

As this and other studies show, individuals affected by rare conditions, including HCS, look for information about their diagnosis online (Rocha et al., 2018). They utilize online educational materials and/or support groups to find needed knowledge but are not always able to locate the information they are looking for. This is in part due to many current online materials not meeting the NIH and AMA's recommendations of writing below a 6th to 8th grade reading level (Weiss, 2003; Rooney et al., 2021; Eltorai et al., 2014). More complex writing makes it difficult for a large portion of the population to read and understand the resource. Additionally, some current websites do not contain information on all aspects of a condition, requiring individuals to visit multiple locations to get complete information. These are factors counselors need to be aware of when identifying online information to share with patients.

In some cases, no easily understandable and accessible educational materials are available for a specific condition. Since genetic counselors are trained to explain genetic and health

information in a way that individuals with different backgrounds can understand, they have the skills to create clear, usable educational materials. When producing these materials, genetic counselors should take into account the patient population's preferred format and content in order to maximize patient learning.

The results of this study showed current online educational resources for HCS have readability levels above what a large portion of the population can understand. Further they do not all contain information about relevant aspects of the condition. Some participants ranked current resources as not being very helpful. These indicate a continued need for genetic counselors to actively participate in the creation of relevant, clear, and up-to-date patient educational materials in order to enhance patient understanding.

4.2 Public Health

The goal of public health is to protect and improve the health of people and their communities (CDC Foundation, 2022). These communities are often thought of as including entire cities or countries. However, a community may also be defined as the individuals impacted by a rare disease. In the United State each rare disease affects fewer than 200,000 individuals (GARD, 2021). Although a relatively small number of people may have a particular rare disease, when those with any of the over 7,000 different rare disorders are taken together, 1 in every 10 people have a rare condition (NORD, 2019). With millions affected in the US alone, improving the health of people with rare diseases is certainly a public health concern.

A core function of public health is to communicate effectively to inform and educate people about health, factors that influence it, and how to improve it (CDC, 2021). In order to improve

public health, genetic counselors can identify and create comprehensible educational materials for patients to increase their knowledge about the condition and inform their decision making. This role is especially needed in cases of rare diseases, where individuals may have a harder time finding readable information about their diagnosis. Making educational materials useful for everyone can be difficult to do since the average American is estimated to read at the 8th grade level (Cotugna et al., 2005). A goal of larger public health initiatives such as Healthy People 2030 is to increase health literacy of the population (Health.gov).

Another core function is to support and mobilize communities and partnerships to improve health (CDC, 2021). This involves authentically engaging with community members and organizations to develop public health solutions. One way to do this is to collaborate with the patient population when creating educational materials. Gathering input prior to developing the materials and using patient feedback to make updates ensures the materials made are in the format and include the right content to satisfy the target audience's needs. This is the first known study to directly survey individuals with HCS and their family members about their informational needs. The HCS population's responses informed the format of the educational resource drafted in this study along with the types of information about HCS it included.

Appendix A HCS Facebook Group Post

Greetings,

As you may know, I am currently in graduate school and working towards a degree in Genetic Counseling at the University of Pittsburgh. Part of the program involves completing a research project. My project is focusing on educational resources about Hajdu-Cheney syndrome (HCS).

I have created an online survey to help understand your (individuals with HCS and their family members) experiences with using these resources. The survey is anonymous and your responses will not be identifiable. The survey should take around 15 minutes to complete. In addition to either having HCS or having a family member with HCS, you must be 18 years or older and speak English to participate in the survey.

You can complete the survey by using the below link. Ultimately, the goal of this research is to create needed educational resources for the HCS community.

Please let me know if you have any questions.

Survey link: https://pitt.co1.qualtrics.com/jfe/form/SV_0DuUmvse1gL06Eu

Thank you for considering taking this survey.

Sincerely,

Liz Bombal

Appendix A.1 HCS Facebook Group Reminder Post

Anyone who has not taken the below survey already about HCS resources, please consider completing it! The survey will close on April 19!

Greetings,

As you may know, I am currently in graduate school and working towards a degree in Genetic Counseling at the University of Pittsburgh. Part of the program involves completing a research project. My project is focusing on educational resources about Hajdu-Cheney syndrome (HCS).

I have created an online survey to help understand your (individuals with HCS and their family members) experiences with using these resources. The survey is anonymous and your responses will not be identifiable. The survey should take around 15 minutes to complete. In addition to either having HCS or having a family member with HCS, you must be 18 years or older and speak English to participate in the survey.

You can complete the survey by using the below link. Ultimately, the goal of this research is to create needed educational resources for the HCS community.

Please let me know if you have any questions.

Survey link: https://pitt.co1.qualtrics.com/jfe/form/SV_0DuUmvse1gL06Eu

Thank you for considering taking this survey.

Sincerely,

Liz Bombal

Appendix B Survey Introduction

Hello,

My name is Liz Bombal and I am a student in the Genetic Counseling Program at the University of Pittsburgh. I am conducting a research study to understand the perspectives of individuals with Hajdu-Cheney syndrome (HCS) and their family members regarding HCS-specific educational materials. For this reason, I am asking individuals who have HCS as well as family members of individuals who have HCS to complete a survey. I hope the results of this study will lead to the development of needed educational resources for the HCS community.

Individuals completing the survey online through Qualtrics must be age 18 years or older and speak English. The survey should take approximately 15 minutes to complete. There are minimal risks associated with completing the survey, including but not limited to the infrequent risk of a breach of confidentiality. There are also no direct benefits/compensation for completing the survey. All responses will be anonymous, so your responses are confidential. You can withdraw from the study any time prior to survey submission, but once answers are submitted they can not be removed from analysis due to the anonymous nature of the survey.

Should you have any questions, please do not hesitate to email me at: elb173@pitt.edu. Thank you for considering participating. I appreciate your assistance in developing educational materials for HCS.

Appendix C HCS Survey

Q1 What is your age?

- ○ Under 18 years
- ○ 18 – 24 years
- ○ 25 – 34 years
- ○ 35 – 44 years
- ○ 45 – 54 years
- ○ 55 – 64 years
- ○ Over 65 years
- ○ Prefer not to answer

Q2 Have you been diagnosed with Hajdu Cheney Syndrome (HCS)?

- ○ Yes, from genetic testing which found a change in the Notch2 gene (the gene involved in HCS)
- ○ Yes, by clinical exam only

- ○ Yes, by both clinical exam and genetic testing
- ○ No

Q3 At what age were you diagnosed with HCS?

- ○ 0 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ 16 – 20 years
- ○ 21 – 25 years
- ○ 26 – 30 years
- ○ Over 30 years
- ○ Do not know / Not sure

Q4 Do you have a family member who has been diagnosed with HCS?

- ○ Yes
- ○ No

Q5 At what age was your affected relative diagnosed with HCS?

- ○ 0 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ 16 – 20 years
- ○ 21 – 25 years
- ○ 26 – 30 years
- ○ Over 30 years
- ○ Do not know / Not sure

Q6 From what type of provider did you (or your family member) receive the diagnosis of HCS? Please answer for the individual who was diagnosed with HCS first.

- ○ Primary care physician
- ○ Orthopedist – a doctor who specializes in treating conditions of the bones, joints, and muscles
- ○ Genetic counselor – a medical professional who provides information and support to people who have or are at risk for genetic disorders

○ Geneticist – a doctor who specializes in genetics

○ Do not know / Not sure

○ Other _____

Q7 Thinking of that provider, how satisfied were you with their initial explanation of HCS?

- ○ Highly satisfied
- ○ Satisfied
- ○ Neutral (neither satisfied or unsatisfied)
- ○ Unsatisfied
- ○ Highly unsatisfied
- ○ Do not know / Not sure

Q8 Why were you unsatisfied with their explanation? (select all that apply)

- ☐ Used too complex or confusing language
- ☐ Unable to answer your questions about the condition
- ☐ Additional _____

Q9 What would have made you more satisfied with the explanation?

_____

Q10 What did you feel they did well in their initial explanation? (select all that apply)

- ☐ Used understandable language
- ☐ Were able to answer your questions about the condition
- ☐ Additional

_____

Q11 Have you looked for information about HCS online?

- ○ Yes
- ○ No

Q12 How long did it take to find the information you were looking for about HCS online after your (or your family member's) **initial diagnosis**?

- ○ Less than 30 minutes
- ○ 1 hour
- ○ 2 hours
- ○ More than 2 hours
- ○ Could not find the information I was looking for about HCS online

○ Did not look online initially

Q13 How often do you currently go online for information about HCS?

○ Daily

○ Once a week

○ Twice a week

○ Once a month

○ Less than once a month

○ I do not currently look online

Q14 What online resources did you find to be most helpful? (select all that apply)

☐ Online Mendelian Inheritance in Man (OMIM)

☐ National Organization for Rare Disorders (NORD)

☐ Medline Plus (previously NIH Genetics Home Reference)

☐ Genetic and Rare Diseases Information Center (GARD)

☐ Online community support groups

☐ Other _____

☐ None

Q15 People get health information from different sources. What resources (other than online) did you use to improve your understanding of HCS? (select all that apply)

☐ Geneticist

☐ Genetic counselor

☐ Other physician

☐ Other healthcare professional (e.g. nurse, physician's assistant, nurse practitioner)

☐ Books

☐ Scientific articles

☐ Other _____

Q16 Rate how helpful above resources were

	Not at all helpful	Slightly helpful	Moderately helpful	Very helpful	N/A
Geneticist (1)	○	○	○	○	○
Genetic Counselor (2)	○	○	○	○	○
Other Physician (3)	○	○	○	○	○
Other Healthcare Professional (4)	○	○	○	○	○
Books (5)	○	○	○	○	○
Scientific Articles (6)	○	○	○	○	○
Other (7)	○	○	○	○	○

Q17 What information about HCS do you feel you still do not understand?

_____

Q18 What information/aspects of HCS would you like to find in an educational resource? (select all that apply)

- ☐ Cause of HCS
- ☐ Inheritance/risk to family members
- ☐ Features of the condition
- ☐ Management of the condition
- ☐ Other _____

Q19 How do you prefer to learn about HCS? (choose your top **two** sources)

- ☐ Fact sheet
- ☐ Infographic
- ☐ Video
- ☐ Pamphlet
- ☐ Other _____

Q20 What is your gender?

- ○ Woman
- ○ Man
- ○ Trans women/transfeminine
- ○ Trans man/transmasculine
- ○ Nonbinary/genderqueer
- ○ Not listed
- ○ Prefer not to answer

Q21 What was the sex recorded on your original birth certificate?

- ○ Female
- ○ Male
- ○ Intersex
- ○ Prefer not to say

Q22 What is your race? (select all that apply)

- ☐ White
- ☐ Black or African American
- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Native Hawaiian or Pacific Islander

☐ My race is not represented, please self-describe

_____

☐ Prefer not to answer

Q23 Are you Hispanic or Latino?

○ Yes

○ No

○ Prefer not to answer

Q24 What is your highest education level or highest degree you have received?

- ○ Grade school
- ○ High school/GED
- ○ Associate degree – a degree given after a 2-year course of study, often by a community or junior college
- ○ Bachelor's degree– a degree given by a college or university, usually after 4 years of undergraduate study
- ○ Graduate or professional degree
- ○ Prefer not to answer

Q25 How many children do you have?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4 or more
- ○ Prefer not to answer

Q26 How many of your children have HCS?

- ○ 0
- ○ 1
- ○ 2
- ○ 3

○ 4 or more

○ Prefer not to answer

Q27 What country do you reside in?

_____

Q28 Which of the following best describes the general area where you live?

○ Urban – A densely populated, well-developed area in a city or town with a population of at least 50,000 people.

○ Suburban – Areas that surround cities and are usually less densely populated with less than 50,000 people. A majority of buildings are residential.

○ Rural – An area with a small, spread-out population and large amounts of undeveloped land.

○ Prefer not to answer

Appendix D IRB Exemption Letter

University of Pittsburgh | Institutional Review Board
Office of Research Protections

EXEMPT DETERMINATION

Date:	March 22, 2022
IRB:	STUDY21120110
PI:	Elizabeth Bombal
Title:	Assessment and Development of Educational Resources for Hajdu-Cheney Syndrome

The Institutional Review Board reviewed and determined the above referenced study meets the regulatory requirements for exempt research under 45 CFR 46.104.

Determination Documentation

Determination Date:	3/22/2022
Exempt Category:	(2)(i) Tests, surveys, interviews, or observation (non-identifiable)

Approved Documents:	• Survey Introductory Script V2.docx, Category: Waiver Script; • HCS Qualtrics Survey 3_8_22.docx, Category: Data Collection; • FB Invitation Script V3.docx, Category: Recruitment Materials; • IRB Exemption Form.docx, Category: IRB Protocol;

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Ali Arak.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

Human Research Protection Office 3500 Fifth Avenue, Suite 106 Pittsburgh, PA 15213 www.hrpo.pitt.edu

Appendix E Kruskal-Wallis Result - STATA

```
Kruskal-Wallis equality-of-populations rank test
```

group	Obs	Rank Sum
1	20	1181.00
2	9	593.50
3	17	760.00
4	13	434.00
5	10	192.50
6	23	1117.00

```
chi-squared =    22.956 with 5 d.f.
probability =     0.0003

chi-squared with ties =    24.610 with 5 d.f.
probability =     0.0002
```

Appendix F Dunn's Pairwise Comparison – STATA

```
. dunntest scores, by(group) nokwallis ma(hs)

Warning: by() values are unlabeled, option nolabel implicit
```

Dunn's Pairwise Comparison of scores by group
(Holm-Sidák)

Col Mean- Row Mean	1	2	3	4	5
2	-0.666046 0.4415				
3	1.686087 0.2456	1.997799 0.1880			
4	2.793477 0.0283	2.911598 0.0214	1.191511 0.3109		
5	3.984787 0.0005	3.940736 0.0006	2.476842 0.0643	1.303045 0.3330	
6	1.329755 0.3821	1.713990 0.2980	-0.467884 0.3199	-1.696450 0.2750	-3.001012 0.0173

1=geneticist

2=genetic counselor

3=other physician

4=other healthcare professional

5=books

6=scientific articles

Appendix G HCS Fact Sheet

All About Hajdu-Cheney Syndrome

Hajdu-Cheney Syndrome (HCS) is a rare **connective tissue disorder** caused by harmful changes in the *NOTCH2* **gene**. This gene is involved in the development of many tissues in the body. It also has a role in normal bone formation and breakdown.

Who Does HCS Affect?

Fewer than 100 people are reported as having HCS in medical literature. However, the exact number of affected individuals in the general population is unknown. Men and women get HCS equally.

What are Symptoms of HCS?

The symptoms and severity of HCS vary from person to person. Most people with HCS have low bone density (osteoporosis) and breakdown of bone in the fingers and toes (acro-osteolysis).

People with HCS can also have other features listed below. Each individual may not experience all features listed:

- Extremely flexible joints
- Bones that fracture or break more easily
- Curved long bones in the arms and legs (serpentine fibulae)

- A build-up of fluid on the brain (hydrocephalus)
- Bones of the spine pushing up into the skull and brain (basilar invagination)
- Brain tissue extending into the spinal canal due to defects at the base of the skull (chiari malformation)

- Heart defects present at birth, such as a hole in the heart

Key Terms

Connective Tissue Disorder: A medical condition which affects the tissues needed for binding and connecting various parts of the body and giving them shape.
DNA: The genetic information that is passed on from parent to child. It provides instructions for our bodies on how to grow and develop.
Embryo: A fertilized egg that has begun dividing and is in the early stages of growth in pregnancy.
Genes: The physical units of information found in DNA. They provide the instructions to make proteins.
Genetic: Used to describe something as being related to or determined by DNA and genes.
Inherit: Genes are inherited, meaning they are passed down from a parent to their child. This is why certain traits and disorders appear to 'run in a family'.

- A curved spine (scoliosis, kyphosis)
- Fractures in the bones that make up the spine (vertebrae)
- Short stature

- Multiple sacs of fluid (cysts) in the kidneys

- Early loss of adult teeth
- An opening in the roof of the mouth (cleft palate)
- Under bite or overbite

- Differences in skull shape
- Skull bones that do not fuse or close after birth (open skull sutures)
- Coarse facial features

What is the Treatment for HCS?

Currently there are no agreed-upon treatments or guidelines for treating HCS. Instead, doctors focus on managing each patient's symptoms. Individuals may need surgeries to treat complications of HCS. The most common surgeries involve the heart, spine, skull, and/or kidneys.

Medications like bisphosphonates may help lower the chance of bone breaks and fractures. In general, these medications are used to increase bone density in groups such as women who have gone through menopause. These medications have increased bone density for some people with HCS. There is not clear evidence that a particular bone treatment is effective in people with HCS. No clinical trials have been done to test these medications in HCS patients.

What Causes HCS?

Our bodies are made up of millions of cells, each of which contain our **DNA**. DNA is the **genetic** material that provides instructions for our bodies on how to grow and develop.

DNA contains thousands of different genes. These genes have the information needed to make the various proteins our bodies need. Every individual typically has two copies of each gene, receiving one copy from each parent.

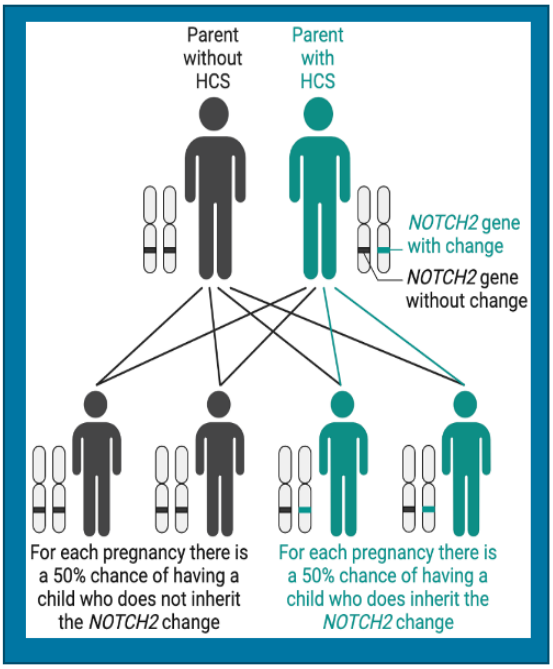
Changes in the DNA near the end of the *NOTCH2* gene cause HCS. These changes cause the protein made from the *NOTCH2* gene to be shorter and active longer than usual. We don't fully understand exactly how this leads to all the symptoms of HCS.

Changes in *NOTCH2* can be **inherited** from an affected parent. In other cases it is a new, random change found only in the individual with HCS. There is nothing a person did to cause themselves or their child to have an HCS-causing *NOTCH2* change.

How is HCS Inherited?

HCS is inherited in an autosomal dominant manner. This means:

- You only need one copy of the *NOTCH2* gene with a change to show signs and symptoms of HCS.
- If a parent has HCS, each child they have has a 50% chance to inherit the copy of *NOTCH2* that has a change and be diagnosed with HCS.
- Each child also has a 50% chance to *not* inherit the copy of *NOTCH2* with a change. In other words, they have a 50-50 chance of inheriting the gene change.
- Both male and female individuals can inherit and pass down *NOTCH2* changes that cause HCS.



Adapted from "Autosomal Dominant VS Recessive Inheritance", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates

- Individuals who have HCS and want to have children without the condition can use a method called preimplantation genetic testing (PGT). This involves testing **embryos** for changes in *NOTCH2* before they are transferred into the uterus (womb) using in vitro fertilization (IVF) procedures. Genetic counselors are a good source of information about PGT.

Additional Resources

You can find more information at the following resources:

https://rarediseases.info.nih.gov/diseases/508/acroosteolysis-dominant-type

https://rarediseases.org/rare-diseases/hajdu-cheney-syndrome/

An HCS-specific support group is on Facebook. Individuals who have a diagnosis of HCS and their family members can join this group. You can find this group by searching Hajdu-Cheney Syndrome on Facebook or by following this link:

https://www.facebook.com/groups/1012807442094960

Future Research

Clinical trials are research studies that test if a medical approach is safe and effective. Currently there are not any clinical trials available for HCS. This could change in the future. Clinicaltrials.gov can be used to identify clinical trials should they become available.

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