Creation of a Novel Framework Resource for the New Hereditary Hemorrhagic Telangiectasia Patient Journey

by

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Abstract

Background: Hereditary hemorrhagic telangiectasia (HHT) impacts one in every 5,000 individuals worldwide. HHT, also known as Osler-Weber-Rendu syndrome, affects both children and adults and is characterized by multiple arteriovenous malformations (AVMs) in various organ systems, mucous membranes, and on the skin. These AVMs in organs can lead to complications and mucocutaneous telangiectasias that can rupture spontaneously and cause recurrent bleeding. It can take over 25 years to be correctly diagnosed with HHT, which speaks to the public health significance of the condition. New HHT patients and providers without extensive knowledge need a framework resource to follow to ensure the correct steps are taking place to correctly diagnose and manage HHT patients. Moreover, it is important to recognize the difference in access to healthcare for people of lower socioeconomic status (SES). Managing a disease can be expensive and the framework resource will reduce the disparity in information accessible to those who cannot afford to visit an HHT Center of Excellence (COE).

Methods: A SurveyMonkey survey was created and distributed to 30 COEs in North America. Center directors, geneticists, genetic counselors, and other medical providers responded to the survey to provide insight on what steps should be included in a novel framework resource for HHT patients.

Results: Survey respondents ordered provided steps to determine what the typical HHT patient journey should look like. An adult framework resource was developed based on these

survey results and a pediatric framework resource was adapted from the adult resource to include pediatric specific recommendations from the published literature. Respondents also commented on the different payment methods used by COE patients, suggesting individuals of lower SES do not visit COEs as often as people of higher SES.

Conclusions: A novel framework resource was developed based on survey results to give HHT patients of all demographic groups the appropriate information to manage their condition.

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Preface

I am dedicating this essay to the worldwide community of HHT physicians, researchers, patients, and families – especially those who have yet to be diagnosed. I am also dedicating this essay to my mom and dad for their unwavering support and encouragement throughout my life.

I would like to thank the following people, without whom this essay would not be what it is today. Cody Autrey for his assistance and advice and my sisters for always being there when I need them. My mom for pushing me to be the best and my dad for always being the voice of reason. My essay readers, Dr. Beth Roman and Dr. Suneeta Madan-Khetarpal for their expertise and guidance and Cure HHT for allowing me to take part in this research. Lastly, I would like to thank the leadership, faculty, staff, and fellow students at the University of Pittsburgh School of Public Health, Human Genetics Department.

1.0 Introduction

Hereditary hemorrhagic telangiectasia (HHT) is a genetic disease that affects approximately one in every 5,000 individuals worldwide (Cure HHT, 2022b). Due to the variable way symptoms present and the general lack of awareness of the disease, the average delay in diagnosis of HHT is 27 years (Pierucci et al., 2012). Healthcare providers who are not HHT experts often do not tend to recognize the signs and symptoms of HHT and/or do not know how to manage diagnosed HHT patients. In fact, a widely accepted new patient framework does not currently exist for HHT. Therefore, a goal of this research is to develop a novel framework outlining the idealized journey for a new HHT patient to ensure they are receiving the highest level of care. This resource will be able to help healthcare providers understand what their patients need. Moreover, it will provide easily accessible information to patients so that they know what care they require and can advocate for proper disease management.

To develop this novel framework, the geneticists, genetic counselors, and directors of HHT Centers of Excellence (COEs) across North America were contacted via survey. Their knowledge and expertise helped to decide what to include in building a robust new patient framework. The framework makes a clear distinction between the journey of a child and of an adult because screening and treatment guidelines are different between these groups (Faughnan et al., 2020). The goal was to develop a protocol that successfully guides a new patient through the steps from the beginning of their HHT journey, to their screenings and initial appointments at a COE, past their genetic testing experience and result disclosure, and into their follow-up care. The framework will be accessible to patients who cannot visit a COE due to socioeconomic status to reduce healthcare inequities.

To reach patients and family members, the framework will be featured on the Cure HHT website, which is frequented by those who are looking for more information about HHT. The intent is to eventually publish the information in an academic journal to disseminate the work to others in the scientific community.

In summary, surveying HHT COEs throughout North America provided the necessary information to create a novel, robust framework for the new HHT patient journey. HHT is often misdiagnosed, which can lead to a delay in proper treatment. An easy-to-follow, step-by-step guide can perhaps help to speed diagnosis and treatment by empowering patients with information that will allow them to educate their physicians and help guide their own disease management.

1.1 Specific Aims

1. To develop a survey, collect responses from HHT Centers of Excellence, and analyze survey data regarding the typical new HHT patient journey. Data collected will help to create a standardized method for HHT patient diagnoses in the form of a novel framework resource for those who are both suspected to have and are diagnosed with HHT to adequately inform them on how to navigate their condition and manage follow-up care.
2. To highlight the inequities socioeconomic status creates for HHT patients when trying to obtain quality healthcare to understand and manage their condition.

2.0 Background

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, was first characterized as including epistaxis (nosebleeds) and malformations of the vascular system by Henry Sutton in 1864. One year later, Benjamin Babington noted that the epistaxis was hereditary (Gomez, 2015). Henri Rendu distinguished HHT from another disease known as hemophilia while working in France in 1896 (McDonald, Bayrak-Toydemir, & Pyeritz, 2011). In the United States in 1901, William Osler fully established HHT as an inherited disorder and noted the presence of arteriovenous malformations (AVMs) in affected patients. A few years later, in 1907 in the United Kingdom, Frederick Weber wrote the first case series on HHT (McDonald et al., 2011). The disease name Osler-Weber-Rendu came from these early scientific contributors, and the more practical name hereditary hemorrhagic telangiectasia was coined in 1909 and is still used today (Gomez, 2015). HHT has a recorded history that goes back over 150 years. Moving into the present day, the goal within the HHT community is to diagnose as many families as possible and to give those newly diagnosed patients the knowledge they need to manage their disease.

2.1 Genetic Characteristics

HHT has an estimated worldwide prevalence of 1 in every 5,000 people (Faughnan et al., 2020). HHT is an autosomal dominant genetic disease which, to date, is associated with multiple genetic mutations, also known as genetic variants, that can occur within at least three different

genes. Pathogenic (PV) and likely pathogenic (LPV) variants have strong evidence to support that the DNA change they create is disease causing (Richards et al., 2015). An individual's genetic variant influences their HHT subtype. An affected person with HHT may have HHT Type 1 (HHT1), HHT Type 2 (HHT2), or juvenile polyposis-HHT (JP-HHT). HHT1 is caused by a variant within the *ENG* gene locus at 9q34.11 (Marchuk, 1998). HHT2 is characterized by a variant within the *ALK1* gene (also known as *ACVRL1)* locus at 12q13.13 (Marchuk, 1998). Finally, JP-HHT is caused by a variant in the *SMAD4* gene locus at 18q21.1 (Gallione et al., 2004). Variants in *ALK1* and *ENG* together account for nearly 96% of HHT cases (McDonald et al., 2015).

It is difficult to determine which HHT type more commonly affects certain population subgroups because of the levels of misdiagnosis and missed diagnosis associated with this disease. However, it has been reported that HHT1 is more commonly found in North America and Europe while HHT2 predominates in South America and the Mediterranean (Marchuk, 1998). HHT does not affect one biologic sex more than the other (Cure HHT, 2022b).

2.2 A Clinical Picture: Symptoms of HHT

HHT shows the characteristics of a disease with complete penetrance and variable expressivity so clinical symptoms of the disease can vary, even among family members (Kritharis, Al-Samkari, & Kuter, 2018) also known as intrafamilial variability. The distinct HHT subtype may be associated with the inter-familial clinical manifestations. For example, those with HHT1 tend to have more pulmonary and brain AVMs while those with HHT2 have more liver and spinal AVMs (Kritharis et al., 2018).

2.2.1 Arteriovenous Malformations

An arteriovenous malformation (AVM) occurs when an artery and a vein are directly connected instead of being connected by a capillary bed. This type of blood vessel malformation leads to the shunting of blood from a high-pressure arterial system directly into a low-pressure venous system which can lead to many kinds of complications (Bernabeu, Bayrak-Toydemir, McDonald, & Letarte, 2020). Capillary beds are where normally arterial blood flows through and slows down before it enters the venous system. Capillaries are the site for gas and nutrient exchange between the blood and the tissues. When there is an AVM, these normal vital processes are impaired.

Pulmonary AVMs (PAVMs) occur in the lungs and are present in about half of all HHT patients. In fact, about 70% of all pulmonary AVMs are caused by the patient having HHT, so HHT diagnosis can come after a pulmonary AVM is identified (Kritharis et al., 2018). PAVMs can lead to migraine because of the relative excess of serotonin in the circulation due to the lack of gas exchange in the pulmonary capillaries (Thenganatt et al., 2006). Additionally, if bacteria enter the body via procedures such as dental exams, the pathogens can bypass capillary filtration due to PAVM formation and go directly to the brain causing abscess (Kritharis et al., 2018). For similar reasons, circulating emboli may lead to stroke (Sueda, Horiuchi, Funakoshi, & Hiraoka, 2020). Brain abscess and stroke can lead to a multitude of additional complications, which highlights how severe PAVMs can be for patients with HHT. Of note, PAVMs are more likely to rupture during late-stage pregnancy due to increased blood volume and cardiac output. Most HHT pregnancies continue without issue, but they are still considered high risk (Ference, Shannon, White, Zawin, & Burdge, 1994).

Liver AVMs are seen in about 70% of all HHT patients (Buonamico et al., 2008), but they do not always present with symptoms a patient will notice; only about 8% of HHT patients have symptomatic liver AVMs (Garcia-Tsao, 2007). For those who do experience symptoms, they can range in frequency and severity. For example, a liver AVM can cause fatigue and shortness of breath, but it can also cause high-output heart failure. With this type of heart failure, there is an increase in heart rate and cardiac output that is caused by low systemic vascular resistance due to large and/or numerous liver AVMs (Kritharis et al., 2018).

Brain AVMs occur in about 10% of all HHT patients, more commonly in those with HHT1, and can rupture without warning (Brinjikji, Iyer, Wood, & Lanzino, 2017). There is no difference in brain AVM prevalence when comparing adult and pediatric age groups, suggesting that brain AVM development occurs during childhood. Studies indicate that about 20% of HHT patients who have brain AVMs will experience a rupture and about 50% have seizures and headaches (Brinjikji et al., 2017).

Spinal AVMs are extremely rare and are seen in only about 1% of all HHT patients. Of those patients with spinal AVMs, most are found in children (Brinjikji, Nasr, Cloft, Iyer, & Lanzino, 2016). Due to their location in the central nervous system, these AVMs can cause loss of feeling in the extremities or back pain (Cure HHT, 2022b).

2.2.2 Telangiectasias and Bleeding

Telangiectasias are one of the hallmark symptoms of HHT and they can be seen on the hands, face, lips, inside the nose, or in the GI tract (Kritharis et al., 2018). Telangiectasias are small AVMs that appear as purple or red dots that are the size of a pinhead and tend to increase in number with age. They can rupture which can lead to bleeding (NORD, 2021).

Epistaxis is the formal term for nosebleed, which is the most common and earliest seen symptom in patients with HHT (Cure HHT, 2022b). Nosebleeds can range in frequency and severity, and they are relatively common in the general population, leading to years of missed diagnosis of HHT in many patients. Some individuals can bleed from their nose at such extreme rates that it can cause iron deficiency and anemia, sometimes requiring frequent blood transfusions (NORD, 2021).

Gastrointestinal bleeding affects about 20-30% of all HHT patients. This type of bleeding can lead to bloody stool as well as iron deficiency and anemia. Patients with the JP-HHT type, who are predisposed to development of GI polyps, are more likely to have GI bleeding than any other type of HHT (Kilian et al., 2020). Amongst JP-HHT type patients and families, the risk of developing GI cancer during their lifetime is estimated to be quite variable (Schwenter et al., 2012).

2.3 Molecular Mechanism

The molecular mechanism of all three HHT types involves deficits in transforming growth factor-β (TGF-β)/bone morphogenic protein (BMP) signaling, with ALK1 signaling specifically important in endothelial cells. Both ENG and ALK1 bind to circulating ligands, BMP9 and BMP10. ENG is a non-signaling receptor that likely transfers ligand to ALK1, allowing recruitment of a type II receptor such as BMPRII or ActRII (Roman & Hinck, 2017). Once this ligand/receptor complex is formed, the type II receptors phosphorylate ALK1, which can then phosphorylate SMAD proteins 1, 5, or 8. Phosphorylated SMADs then bind to Smad4 and function as a transcription factor (Roman & Hinck, 2017). Overall, AVMs and abnormal capillary beds are

the result of disrupted BMP signaling due to variants in the *ENG* and *ALK1* genes (Vorselaars et al., 2018).

2.4 Diagnostic Criteria

It is important to note that North America and Europe have their own guidelines for HHT, and both will be considered and commented on throughout this essay. HHT is diagnosed using a set of standards known as the clinical Curaçao criteria, which were developed in 2000 (Pahl et al., 2018). The Curaçao criteria can be summarized as follows (Shovlin et al., 2000):

1. *Spontaneous, recurrent epistaxis*
2. *Multiple telangiectasia on the lips, mouth, fingers or inside the nose*
3. *Visceral lesions such as gastrointestinal telangiectasia or lung, liver, brain or spinal AVMs*
4. *A family history of a first degree relative diagnosed with HHT using these same criteria*

To be diagnosed with definite HHT, at least three of the above criteria need to be met. Suspected or possible HHT is suggested if two criteria are met. Finally, HHT is unlikely if fewer than two of the criteria are present (Shovlin et al., 2000).

These criteria were created so there would be a consensus regarding who would be diagnosed with HHT and so there could be standardization moving forward in research of the disease. The criteria still allow some subjectivity in diagnosis, however. For example, there is no set number of nosebleeds someone needs to have per day to qualify as an HHT patient; nosebleeds simply must be “spontaneous and recurrent” (Shovlin et al., 2000).

It is important to note that children with a family history of HHT may not meet three of the above criteria necessary to be diagnosed with HHT. The Curaçao criteria have low sensitivity for

children younger than 15 years of age because often their only symptom would be family history (Pahl et al., 2018). On the other hand, the criteria have high specificity across all age groups because there are very low false positive rates. It is suggested that individuals younger than 21 years of age who only meet one or two of the Curacao criteria, usually including family history, complete genetic testing to confirm their HHT diagnosis. In those younger than 21 years who already meet three or four of the criteria, genetic testing is not deemed necessary for diagnostic purposes (Pahl et al., 2018) but is still recommended for medical management (Shovlin, 2021).

2.5 Lack of Diagnosis

Rare diseases are often difficult to diagnose in a timely manner due to healthcare providers not having adequate knowledge of the disease or families not being aware that a certain disease runs in their family. HHT manifests differently in every patient, even among members of the same family. HHT symptoms can also present in an atypical manner, which can lead to a lack or delay of diagnosis. For example, it has been found that chronic anemia observed in patients as a primary symptom can lead to a delay in HHT diagnosis (Qin, Yin, & Xie, 2019).

An Italian study looked at the diagnostic delay—the elapsed time between disease onset to the first correct HHT diagnosis—in HHT patients and determined that the average time lag was about 25.7 years (Pierucci et al., 2012). Of note, affected family members did not have quite as long of a diagnostic delay as the index patient, and low patient education level was also seen to be associated with an increased time lag. These results highlight the importance of a novel patient framework because patients will be able to self-advocate and bring up important questions to their physicians regardless of education status.

While lack of provider knowledge is a large part of the overall lack of diagnosis of HHT, the patients themselves can also be reluctant to accept their doctor's advice regarding screening options. A case study in Hungary mentions a 19-year-old male who had multisystemic symptoms but did not comply with medical advice, leading to a delay in his HHT diagnosis. Because different specialists may identify different symptoms of HHT, a patient will not necessarily receive a diagnosis of HHT because of a lack of communication among these specialists (Major et al., 2020). Also, because HHT patients typically present with additional or more severe symptoms as they age, those who are young and who have few or no symptoms may be non-compliant when it comes to screening guidelines (Major et al., 2020).

2.6 Screening Guidelines

Screening tests should be performed on anyone who is known or suspected to have HHT to identify an abnormality before it starts to cause a catastrophic problem.

2.6.1 Adult Screening

Adults with possible or definite HHT should be screened for pulmonary AVMs (Faughnan et al., 2020). All adults over the age of 16 who suspect they have HHT should be screened for pulmonary AVMs via CT scan or bubble echocardiography, depending on the expertise of the physician performing the screening (Shovlin, 2021). If an adult screens negative for pulmonary AVMs, they should have a repeat screen in five years or if new symptoms arise, whichever comes first (Shovlin, 2021).

Adults with possible or definite HHT should also be screened for brain AVMs (Faughnan et al., 2020). Magnetic resonance imaging (MRI) with contrast is the preferred screening method for cerebral AVMs because it is more sensitive than a CT scan and does not expose the patient to radiation. The needed frequency of screening for cerebral AVMs is debated because the risk of developing a cerebral AVM after having a negative screen is still unclear (Shovlin, 2021). Patients with known HHT1 or a *SMAD4* genetic variant are at higher risk of having a cerebral AVM and should be considered when deciding whether screening is needed.

All adult HHT patients should be screened annually for iron deficiency and anemia (Cure HHT, 2022b). Additionally, all suspected and definite HHT patients should be screened for liver AVMs via Doppler ultrasound (Faughnan et al., 2020), especially those with known HHT2 (Shovlin, 2021). Further study is needed to develop more specific screening guidelines for liver AVMs. There is currently no consensus on how often an HHT patient should be screened for them (Shovlin, 2021).

Adult patients who are suspected to have HHT-related gastrointestinal (GI) bleeding should undergo esophagogastroduodenoscopy (EGD), and if they have the *SMAD4* genetic variant, they should also receive a colonoscopy starting at age 15. If polyps are found, both EGD and colonoscopy should be repeated every year. If no polyps are found, colonoscopy alone can be repeated every three years (Faughnan et al., 2020).

Pregnant individuals with HHT should be screened for brain AVMs if they are having symptoms. Pulmonary AVMs should be screened for in all pregnant individuals with HHT, if they have not been recently screened, regardless of symptoms, due to the increased risk of pulmonary AVM rupture during pregnancy, as mentioned previously (Shovlin et al., 2008). If the patient is found to have a symptomatic pulmonary AVM, they should have an immediate embolization at

any point during the pregnancy (Faughnan et al., 2020). If the pulmonary AVM found is not causing symptoms, the risks of the treatment on the fetus should be considered against the risks of not treating the AVM for the pregnant individual (Faughnan et al., 2020).

2.6.2 Pediatric Screening

All HHT pediatric patients who have recurrent bleeding and symptoms of anemia should be screened yearly for iron deficiency and anemia (Cure HHT, 2022b). In addition, all children who have a parent who has HHT should be offered genetic testing for the familial variant even if the child is asymptomatic. All children who have been diagnosed with HHT or are at risk of having HHT due to a parent having it, should be screened for pulmonary AVMs, even if they are asymptomatic, every five years until adulthood (Faughnan et al., 2020). If an asymptomatic child screens negative, they should have a repeat pulmonary AVM screen when they reach adulthood (Shovlin, 2021) and then follow the screening protocols for adults. Other sources claim that in clinical practice pulmonary AVM screening can wait until adulthood in asymptomatic children without major risk because of the general lack of complication they cause in these patients (Shovlin, 2021). Moreover, they should also be screened for brain AVMs via MRI (Faughnan et al., 2020) because their lifelong risk of cerebral AVM rupture is higher than an adult patient (Shovlin, 2021). A child with possible or definite HHT should be screened for cerebral AVMs in infancy or at the time of their diagnosis, even if they are asymptomatic (Shovlin, 2021). It has been observed that congenital AVMs can be the first presenting sign of HHT in children (Mei-Zahav et al., 2006).

2.7 Treatment

The various symptoms associated with HHT all have different treatment recommendations that were developed by an expert panel. Nosebleeds should be treated by using the following strategies in this order from the least to most drastic: moisturizing topical therapy, antifibrinolytics (e.g. oral tranexamic acid), ablative therapies, systemic antiangiogenic agents (e.g. bevacizumab), septodermoplasty, and nasal closure surgery (Faughnan et al., 2020). In regard to GI AVMs, the expert panel decided that mild bleeding should be treated with oral antifibrinolytics and moderate to severe bleeding should be treated with bevacizumab (Faughnan et al., 2020).

Iron deficiency and anemia impact many HHT patients, and treatment should begin with oral iron replacement, followed by intravenous iron replacement if needed. Red blood cell transfusions might be necessary in certain patients with low hemoglobin levels (Faughnan et al., 2020). Additionally, liver AVMs should only be treated if they are symptomatic. Bevacizumab and liver transplantation are treatment options that can be considered, though the transplanted liver can also begin to develop AVMs and lifelong follow-up is required (Dumortier et al., 2019). Of note, it is not recommended for any HHT patient to have a liver biopsy for any reason (Faughnan et al., 2020).

The expert panel decided that HHT patients with brain bleeding due to a cerebral AVM should be treated. However, if a pregnant HHT patient is discovered to have a brain AVM, it is recommended that treatment is put off until after delivery (Faughnan et al., 2020). Moreover, pulmonary AVMs with a feeding artery that is three millimeters or greater should be treated with transcatheter embolotherapy (McWilliams, 2016). It is important for HHT patients with pulmonary AVMs to know that they need antibiotics before any dental work or procedures that can introduce bacteria into the bloodstream, and SCUBA diving should also be avoided (Faughnan et al., 2020).

For children, it is recommended that any pulmonary or high-risk/ruptured cerebral AVMs found should be treated (Faughnan et al., 2020). However, pulmonary AVMs can wait to be treated until the patient is 18 years old (McWilliams, 2016). Current literature suggests that unruptured cerebral AVMs should be left untreated in pediatric and adult HHT patients (Cenzato et al., 2017).

2.8 Genetic Testing

When a person is genetically tested for HHT, the underlying goal is to determine if they possess one of the pathogenic variants currently known to cause the condition. Genetic testing can be helpful to identify an index patient whose results can be used to test family members. Multigene panels are typically used to genetically test for HHT in potential index patients (Lam, Guthrie, Latif, & Weiss, 2021). These panels should include the well-known *ACVRL1, ENG* (including the 5' untranslated region), and *SMAD4* genes (McDonald et al., 2015). Newer research has revealed that the *GDF2, RASA1* (McDonald et al., 2015), and *EPHB4* (Wooderchak-Donahue et al., 2019) genes have been implicated in suspected HHT cases. These genes are involved in HHT-like conditions that can be difficult to distinguish for a non-expert physician (McDonald et al., 2015). Furthermore, the idea that non-coding regions of the *ENG, ACVRL1,* and *SMAD4* genes play a role in HHT development sparked research concluding that *ACVRL1* intron 9 is involved in some cases of HHT and would be useful to include in genetic testing panels for the condition (Wooderchak-Donahue et al., 2019).

As an example, the genetic testing laboratory Blueprint Genetics offers an HHT multi-gene panel that includes the following genes: *ACVRL1, ENG, EPHB4, GDF2, RASA1,* and *SMAD4.* The

panel also includes non-coding disease causing variants located in both *ACVRL1* and *ENG* (Blueprint Genetics, 2022).

If a family variant is discovered in an index patient, genetic testing can be pivotal in diagnosing a family member before symptoms begin. Single-gene tests, as opposed to multi-gene panels, are usually performed on family members when the variant of interest is already known and can be performed easily by using a DNA sample (Lam et al., 2021).

It is recommended that all adults who meet the Curaçao Criteria for at least probable HHT be genetically tested. If the person tests positive for HHT, genetic testing should be offered to all at-risk family members (Lam et al., 2021). If a person has no symptoms of HHT, but is known to be at-risk, genetic testing should be offered in lieu of clinical screening options to save money on medical spending. It is important to remember that not all pathogenic variants of HHT have been discovered, so if someone tests negative for HHT but is still symptomatic, they should not be completely ruled out as an HHT patient. If a family member tests negative for a family variant, however, then that family member can definitively say they do not have HHT (Lam et al., 2021).

As previously mentioned, it is important that all children of a parent with HHT be genetically tested for their family variant due to the autosomal dominant nature of the condition. HHT symptoms do not always fully present in childhood, so diagnosing a child is difficult without an adult family member index patient (Lam et al., 2021). If a child tests negative for a known family-causing variant of HHT, it can be safely said that the child does not have HHT. However, if the family variant is not known, a negative genetic test does not rule out HHT in that child (Shovlin, 2021).

Preimplantation genetic diagnosis is an option for parents who have a known HHT variant. Essentially, *in vitro*-fertilized embryos are tested for the known parental HHT pathogenic variant,

and embryos without the variant are implanted. The ethics of preimplantation genetic diagnosis in the case of HHT is still debated because of the unpredictable phenotype of HHT patients (Lam et al., 2021).

2.9 Public Health Significance

The proposed novel patient framework will have a significant impact on the current state of public health. Education is an important part of management for HHT patients (Shovlin, 2021) so the novel framework will give patients the ability to be advocates in their own healthcare, which is a power that not every patient feels they have. Moreover, it is important to understand what is going on with one's health, no matter your education level or socioeconomic status. To better reach every type of audience, the novel framework will be written at a reading level that the average American can easily understand. It is imperative that individuals who face barriers to healthcare and who cannot meet with HHT experts can easily access helpful information on how to manage their suspected condition. This novel framework will be available to the public online and will have references for how to apply for government-assisted medical insurance, which oftentimes covers medically necessary genetic testing.

Some patients may deeply believe they have HHT but need a physician to believe it, too. With this novel framework, patients will be able to provide their physicians with a resource that details what HHT is, what the recommended screening guidelines are, and where they can order necessary genetic testing. In the end, this framework will not only educate potential HHT patients and their families, but also their physicians who may not be experts on the condition.

This framework will ultimately lead to enhanced and more accurate diagnosis of HHT patients and families, initiate earlier prevention and treatment strategies, and lead to a healthier overall population.

2.10 Health Equity and Hereditary Hemorrhagic Telangiectasia

As previously discussed, HHT is both misdiagnosed and underdiagnosed worldwide (Cure HHT, 2022b). It is important to consider the social inequities that play a role in these phenomena when developing the novel framework resources deliverables of this research essay.

A 2010 study from the United Kingdom concluded that the prevalence rate ratio of HHT was statistically significantly higher ($p<0.0001$) in those who were part of the least deprived socioeconomic group than those who were part of the most deprived group (Donaldson, McKeever, Hall, Hubbard, & Fogarty, 2014). This conclusion does not come as a great shock because it is well known that the less affluent have poorer access to reliable healthcare services, tend to have more distrust in medical professionals, and downplay symptoms when compared to the more affluent (Donaldson et al., 2014).

Additionally, a 2021 United States study looked at about 4,000 HHT patients and matched them 1:1 with controls. The study showed that both commercially insured and Medicare advantage insured HHT patients had statistically significantly higher ($p<0.001$) median overall healthcare costs than their matched controls. Spending was highest one year after diagnosis (Hasan Albitar et al., 2021). This is due to an increased number of outpatient office visits (e.g., primary care, hematology, pulmonology), hospitalizations, emergency room visits, imaging studies (e.g., MRI, CT, ultrasound), and invasive procedures (e.g., endoscopy, embolization, blood transfusions)

(Hasan Albitar et al., 2021). The results of this study show that receiving an HHT diagnosis leads to substantial medical costs. Individuals of low socioeconomic status do not always have funds available to cover extra medical bills, and they certainly do not have the money or flexibility to travel to a far-away HHT Center of Excellence (COE).

This same study noted that the vast majority of HHT cases in their cohort were managed by primary care physicians, not specialty providers (Hasan Albitar et al., 2021). This implies that many current HHT patients do not seek out the care of specialty providers at COEs, instead relying on local, non-expert physicians. These findings highlight the importance of the novel patient framework resource that will be available online to anyone, regardless of socioeconomic status. It will help to remove the HHT educational barrier and reduce the need to visit a COE for quality care, which is especially important because it seems many HHT patients already do not visit COEs. Any suspected HHT patient will be able to access the resource and share it with a medical provider they trust and have access to, minimizing the inequities currently seen in HHT diagnosis and disease management.

3.0 Methods

3.1 Data Collection

The data collection for this project was exclusively done via survey collection methods. The Cure HHT SurveyMonkey account was used to develop and disseminate the "Patient Journey at HHT Centers of Excellence" survey (Appendix B). The survey took, on average, ten minutes to complete and contained 21 questions that were a mixture of multiple choice, select all that apply, open ended, and ranking style questions. Some of the questions had "skip logic" where if they were answered a certain way, they would be directed to certain follow up questions. Drafted survey questions were sent to two genetic counselors who work at HHT COEs for feedback. After making suggested edits to the survey questions, they were imported into SurveyMonkey. The survey was tested by the two genetic counselors and Cure HHT staff to ensure it worked before it was sent out to intended survey respondents.

Cure HHT provided the e-mail contact information for 60 different geneticists, genetic counselors, center directors, and other medical providers from the 30 COEs currently established in North America. On August 4th, 2021, an e-mail was sent to each contact that described the purpose of the survey, the survey link, and a QR code that also linked to the survey. A reminder e-mail was sent on August 14, 2021, and by August 20, 2021, 34 responses were collected from 25 distinct North American COEs.

3.2 Study Population

The survey respondents were all either center directors, geneticists, genetic counselors, or other medical providers who work for one of the 30 COEs in North America. They were specifically selected because their job descriptions qualify them to possess the knowledge required to answer the survey questions. Center coordinators, for example, were not asked to participate because the survey questions were outside the scope of what they would be expected to know.

3.3 Data Analysis

The survey data were visualized in tables and graphs as percentages and proportions. The data collected are entirely descriptive and statistical hypothesis testing is neither required nor appropriate.

3.4 IRB Approval

The University of Pittsburgh Institutional Review Board concluded that this project did not include human subjects research and, therefore, determined an IRB application was not required (Appendix A).

4.0 Results

Of the 34 survey respondents, 23 identified as directors (67.6%), three were geneticists (8.82%), five were genetic counselors (14.7%), and three were some sort of other medical provider (8.82%). Twenty-five distinct COE's replied to the survey, with some centers having more than one person reply (Table 1). Of the 34 surveys that were started, 27 were finished through the final question.

Table 1 Demographic Characteristics of Survey Respondents

Demographic Characteristics					
Center of Excellence					
	State	**Director**	**Geneticist**	**Genetic Counselor**	**Other Medical Provider**
UAMS	Arkansas	1			
Barrow	Arizona	1			
UCSF	California	1	1		
Stanford	California	1	*		
UCLA	California	1			
University of Colorado	Colorado	1	1		
Yale	Connecticut			1	
Augusta University	Georgia	1			
University of Chicago	Illinois	1			
Massachusetts General Hospital	Massachusetts	1			1
Johns Hopkins	Maryland			1	
Washington University - St. Louis	Missouri	1			
UNC Chapel Hill	North Carolina	1			
Cleveland Clinic	Ohio	2			
Cincinnati	Ohio	1		1	
OHSU	Oregon	1			
University of Pennsylvania	Pennsylvania	1	1		
University of Pittsburgh	Pennsylvania	1			
UT Southwestern	Texas	1			
Wisconsin	Wisconsin	1			
Vancouver	Canada				1
Edmonton	Canada	3		1	
Alberta	Canada			1	
Cranbrook	Canada				1
Toronto	Canada	1			
Total		23	3	5	3

*One person self-identified as two roles, but will only be counted as having one role

A specific area of interest for the survey was whether the COEs who responded to the survey employed genetic counselors or not. Genetic counselors often bring a certain expertise that is desired when it comes to diagnosing a genetic condition like HHT. Having genetic counselors is also thought by Cure HHT leadership to lead a more organized and structured Center. The survey results for this question can shed some light on how Centers may become more well-rounded. About 82% (n = 34) of respondents claim their COE employs genetic counselors. Of note, the only Centers who claimed not to employ genetic counselors were UCSF, UAMS, Augusta, Washington University - St. Louis, Alberta, Vancouver, and Cranbrook.

Each respondent (n = 34) was also asked if the COE they work at offers any sort of advice or resources to patients who call the Center but are not currently Center patients. The respondent could choose either yes or no. About 85% (n = 29) of respondents reported that their COE provides resources to non-HHT Center patients.

Skip logic allowed only those who responded "yes" (n = 26) to move onto the next question which asked what specifically was discussed with non-Center patients. Twenty respondents said they discuss what genetic counseling is, 19 discuss details about HHT genetic testing, 21 discuss HHT screening guidelines, 12 discuss how to find a non-Center geneticist, 22 discuss the Cure HHT website, and six mentioned "other" topics. "Other" topics included: "precautions for those with AVMs; how to get extended family interested in the possibility of having HHT; telemedicine options; insurance coverage; and logistics of scheduling future appointments with a COE."

Similarly, respondents (n = 26) were asked specifically what information they provide non-Center patients about genetic testing. They provided open-ended responses such as: "recommend they come to the COE to determine if genetic testing is appropriate; let them know how to get tested by a local provider; provide them with contact information for a genetic testing laboratory;

and email them a handout with frequently asked questions." Respondents who continued with the survey (n = 25) were asked what information they would give to Center patients who wish to get genetic testing outside of the COE. Open-ended responses included: "would be more active in finding outside genetic professionals; discuss telemedicine options to continue testing at COE; provide them with all necessary medical records from the COE so they can go elsewhere; arrange for a DNA kit to be mailed to them from the COE lab that is used; outside testing is not facilitated."

Skip logic returned all respondents to the following question (n = 30) who were asked to order a list of eight given steps in the patient journey, from first to last, to reflect what typically happens at their COE. A score of zero given to a step indicated the person either skipped the question or claimed the step does not occur at their COE at all (Figure 1). Respondents were given a chance to add any steps they felt were left out of the ranking question, but these suggested steps were not able to be included in the data analysis because the suggestions could not be ordered by each respondent. It was mentioned by a survey respondent that screening for iron deficiency was left out of the given steps to order.

The survey question (Appendix B) had eight separate steps listed in the order that was deemed the most likely to be accurate by Cure HHT leadership and genetic counselors who screened the survey questions before they were sent out. Having the steps in the same rational order for each survey respondent may have introduced bias into this survey question by limiting the critical thinking necessary to complete it. To determine a consensus on the typical order the steps are performed at COEs, first the number of times someone voted for a step to be in a certain spot were tallied. Next, spots one through eight were assigned a weight (spot one was worth one, spot two was worth two, and so on). The tallied number of times a step was assigned a spot was then multiplied by the weight given to that spot. This was repeated for each step given in the survey

question and resulted in a weighted total number of points given to each given step. The weighted totals were arranged in ascending order to determine the order of occurrence of the given steps at a COE with a patient. In the end, steps one, two, seven and eight were confidently assigned their slot, whereas steps three through six were more fluid.

The same respondents (n = 30) were asked how the steps would change if a person was not a COE patient. Most respondents were not aware of how the steps work for a patient who is not able to visit a COE. Some mentioned how they do not offer anything other than basic information to non-Center patients. One respondent said, “if the person is a family member of a COE patient genetic counseling is done by phone and they are mailed a genetic testing DNA kit.”

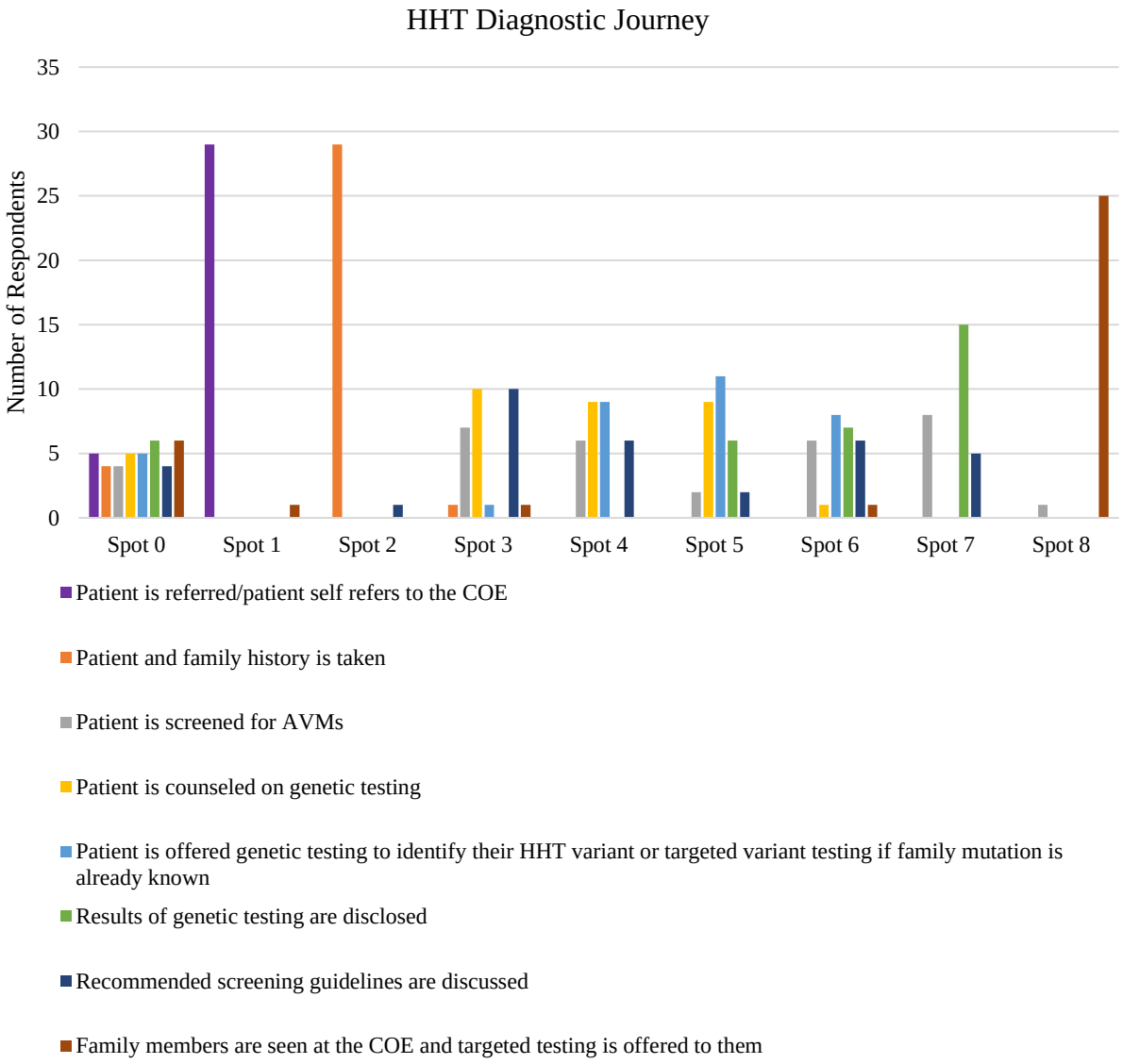

Figure 1 Genetic Diagnostic Journey Rankings

Respondents who got to the following question (n = 30) were asked approximately what percentage of their patients only have a clinical diagnosis of HHT, meaning they have never had confirmatory genetic testing (Table 2). This percentage was relatively low for most COEs, ranging from 1-40%.

Table 2 Percent of Patients Who Only Have a Clinical Diagnosis of HHT

%	0	1-20	21-40	41-60	61-80	81-99	100
Respondents	0	12	11	3	2	2	0

The same respondents (n = 30) were asked what is done at the COE to determine a clinical diagnosis of HHT. All respondents chose lung AVM screening, family history, and physical exam. Twenty-nine chose that they obtain a personal health history and 28 chose brain AVM screening. Eight chose "other" which included: "liver AVM screening; ENT evaluation; and familial genetic testing results if applicable."

Respondents (n = 30) were also asked about the reasons why genetic testing would not follow a clinical diagnosis. Twenty-three people chose family members were not interested in testing, 18 chose concerns about cost/insurance coverage, 17 chose that it would not change medical management, and eight selected "other." "Other" included "anxiety about genetic test results; long waitlists to see a doctor who can prescribe genetic testing; and clinical diagnosis is all that is needed if parent has a known mutation and child is symptomatic."

Respondents (n = 30) were also asked approximately what percentage of their patients complete genetic testing through their COE (Table 3).

Table 3 Percentage of Patients Who Complete Genetic Testing at COEs

%	0-20	21-40	41-60	61-80	81-100
Respondents	2	3	8	10	7

Respondents (n = 30) were asked approximately what percentage of their patients use various payment methods when genetic testing is coordinated through their COE. Answers needed to add up to 100% and could be split between the following options: institutional (corporate

account), private insurance, Medicaid, Medicare, self-pay or other. Overall, for the genetic testing ordered by respondents, about 2% is paid for using institutional billing, 37% by private insurance, 14% by Medicaid, 16% by Medicare, 8% by self-pay, and 23% by some other form of payment method, which respondents were unfortunately not able to expand upon (Table 4).

Table 4 Genetic Testing Payment Methods

Center of Excellence	Role	Insurance Type Used (%)					
		Institutional	Private Insurance	Medicaid	Medicare	Self-Pay	Other
UAMS	Director	0	60	0	40	0	0
Barrow	Director	0	30	30	30	10	0
UCSF	Geneticist	0	30	20	50	0	0
UCSF	Director	10	50	10	20	10	0
Stanford	Director	0	50	40	5	5	0
UCLA	Director	10	50	20	20	0	0
University of Colorado	Director	0	0	0	0	100	0
Yale	Genetic Counselor	0	85	5	0	10	0
Augusta	Director	0	0	0	0	0	100
University of Chicago	Director	20	20	50	10	0	0
MGH	Geneticist	0	40	30	30	0	0
Johns Hopkins	Genetic Counselor	0	60	20	20	0	0
Washington University - St. Louis	Director	0	60	10	25	5	0
UNC	Director	0	60	10	30	0	0
Cleveland Clinic	Director	0	100	0	0	0	0
Cleveland Clinic	Director	20	20	20	20	20	0
Cincinnati	Genetic Counselor	0	25	55	5	15	0
Cincinnati	Director	0	60	30	0	10	0
OHSU	Director	0	70	0	20	10	0
UPenn	Geneticist	0	35	15	20	30	0
UPenn	Director	0	0	0	0	0	100
Pittsburgh	Director	0	55	15	30	0	0
UT Southwestern	Director	0	80	0	12	8	0
Wisconsin	Director	0	70	30	0	0	0
Vancouver	Other	0	0	0	0	0	100
Edmonton	Director	0	0	0	0	0	100
Edmonton	Director	0	0	0	0	0	100
Edmonton	Director	0	0	0	0	0	100
Cranbrook	Other	0	0	0	0	0	100
Toronto	Director	0	0	0	100	0	0

Respondents who got to the following question (n = 30) were asked why they would order genetic testing for a patient who already has a clinical diagnosis of HHT (Figure 2), and results were compared to published data in the discussion section. The "select all that apply" answer choices given were: to determine a family genetic mutation to better screen at risk family members, to determine medical management, to receive a genetic diagnosis for someone determined to have "possible HHT" by the Curaçao criteria, and other. Overall, there was not a standard answer distribution for this survey question. The respondents who chose "other" said "genetic testing results could be used in future research and clinical trials, to reclassify a previous misdiagnosis, and as information when considering reproductive options such as preimplantation genetic diagnosis."

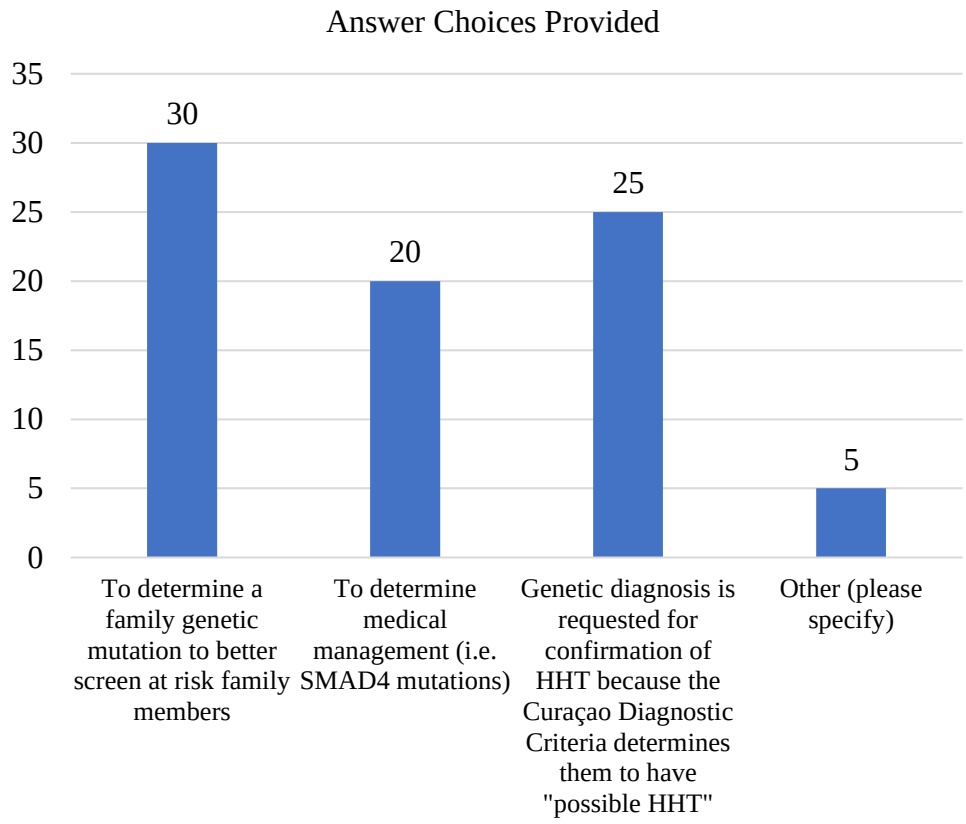

Figure 2 Genetic Testing for Those Already Clinically Diagnosed

When respondents (n = 30) were asked if a patient referred by a local physician should receive genetic testing before visiting a COE for clinical diagnosis and screening, none of them said yes, 20 said no and ten said maybe. Those who said maybe explained, "if another family member has a known pathogenic mutation and the patient is currently asymptomatic, they can get tested before if their local physician knows the right test to order." The same respondents (n = 30) were asked if patients typically have genetic testing done before traveling to the COE and one said yes, 15 said no, and 14 said sometimes. Those who said sometimes responded with ranges between 10-50% of patients already having a genetic test result before going to the COE.

Skip logic determined who was eligible to answer the following question (n = 14) about the different ways patients obtain genetic testing before traveling to a COE. Overall, it was a nearly even split between patients being referred to a local physician by the COE, local physicians ordering genetic testing or referring them to a geneticist, specialty providers ordering genetic testing or referring them to a geneticist, and patients self-referring to a genetic counselor.

Finally, all respondents who completed the entire survey (n = 28) were asked which COE employees typically perform various steps when ordering genetic testing through the COE (Figure 3). Results indicated that genetic counselors typically provide genetic counseling, obtain informed consent, coordinate genetic testing, and discuss testing costs most often. Center directors were also substantially reported to provide genetic counseling and pre- and post-test counseling. It can be speculated that geneticists and other medical providers leave the genetic testing coordination to the COE genetic counselors.

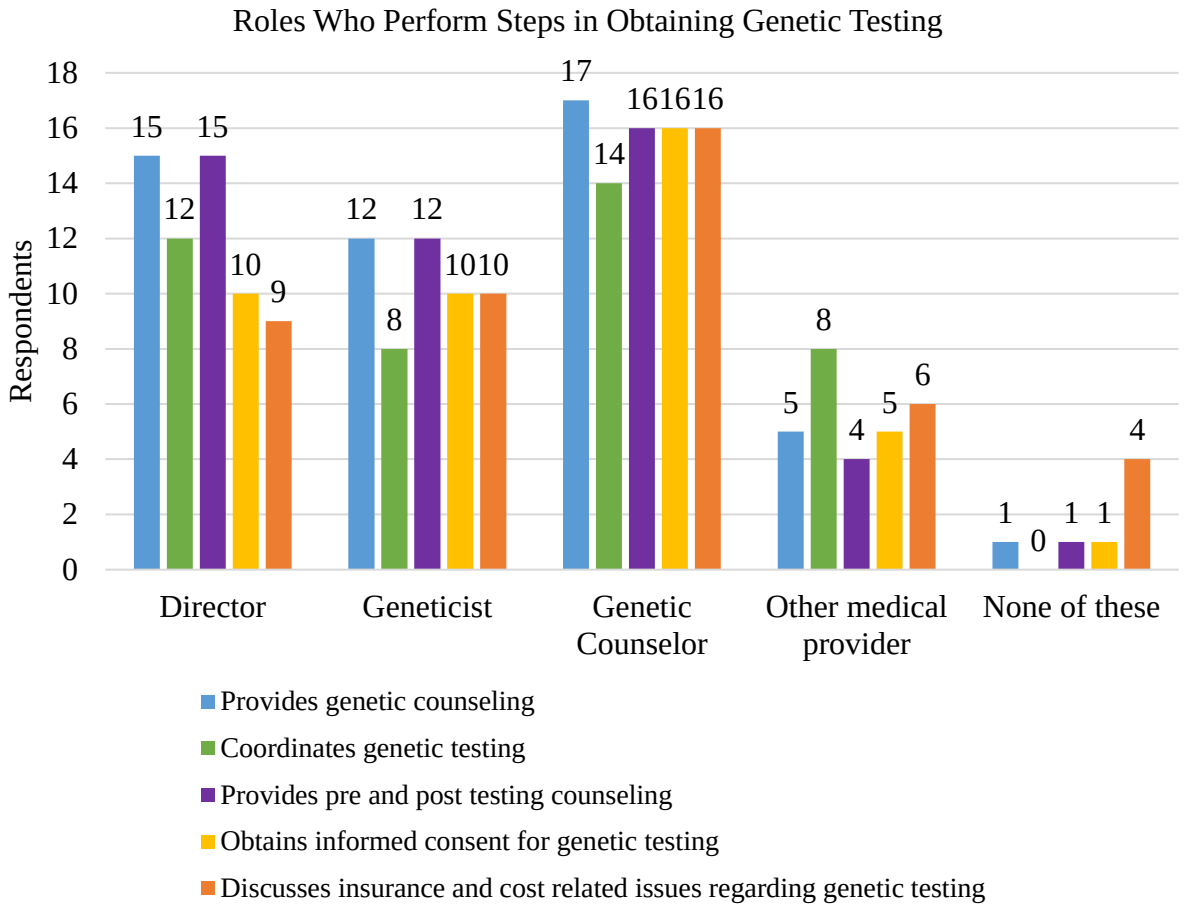

Figure 3 Roles Who Perform Steps in Obtaining Genetic Testing

5.0 Discussion

The primary goal of this research project was to create a standardized method for HHT patient diagnoses in the form of a novel framework resource for those who are both suspected to have and are diagnosed with HHT to adequately inform them on how to navigate their condition and manage follow-up care. This was adequately achieved after a survey collection method was used to determine what order the appropriate steps are in the HHT genetic diagnosis journey. As was seen in Figure 1, survey respondents dictated which steps occur in which order, for the typical patient they see in their COE. Based on the survey results and data analysis, the following is the stepwise journey a patient should take once they suspect they have HHT.

1. Patient is referred/self-referred to a COE
2. A patient and family history are collected
3. The patient is counseled on genetic testing
4. Recommended screening guidelines are discussed
5. Genetic testing is offered to identify the HHT family variant
6. The patient is screened for AVMs
7. Results of genetic testing are disclosed
8. Family members are seen, and targeted testing is offered

A few key pieces of information gleaned from the survey must accompany this stepwise journey. First, it is important to remember that steps three through six can happen in any number of different orders depending on the level of suspicion of HHT in the specific patient (Figures 4 and 5). For example, if suspicion for HHT is low in someone, genetic testing is recommended to happen before AVM screening. This type of flexibility in the framework has also been discussed

in the literature (Lam et al., 2021); the genetic diagnostic journey will not be exactly the same for every patient. It is also important to remember that not everyone is able to visit a COE immediately after thinking they may have HHT. Some of the steps in the journey can be completed by an outside physician, but this further shows the importance of the creation of the novel framework resource. If a patient can bring the resource to their outside doctor, it will be more likely that non-HHT Center patients have a similar experience before they are able to visit a COE. This is further highlighted by the fact that some survey respondents mentioned that they do not offer more than basic information over the phone to someone who is not a Center patient. The framework resource can provide a supplement to the limited information these HHT patients are able to get from COEs.

One survey respondent mentioned that screening for iron deficiency was left out of the given steps to order. Screening for iron deficiency has been deemed crucial for all adults and certain children with HHT (Faughnan et al., 2020), so this should indeed be considered one of the steps in the patient journey.

The survey administered did not address the differences between the adult and pediatric HHT patient journey. The pediatric framework was created by adapting the adult framework based on the international guidelines set forth for HHT diagnosis and management in children (Faughnan et al., 2020).

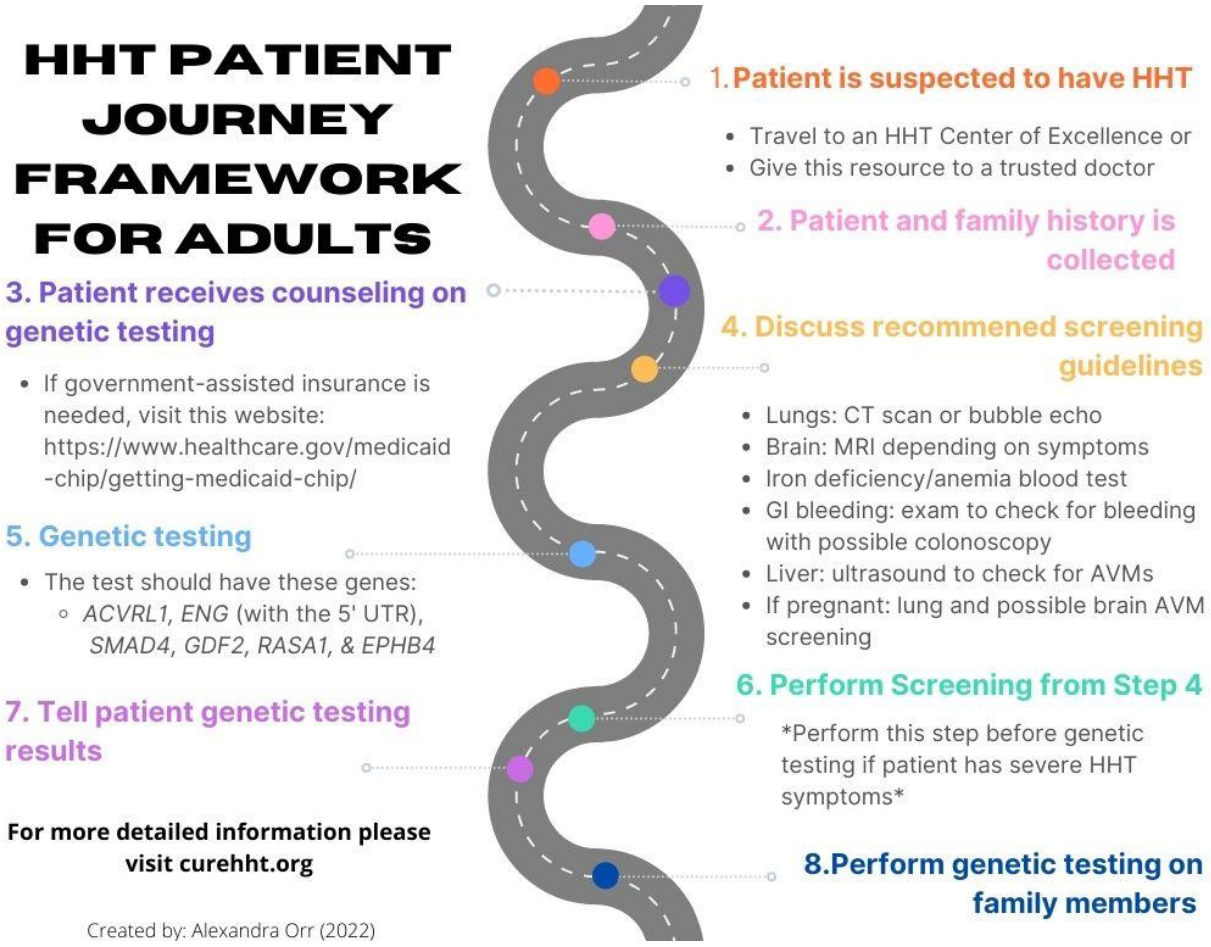

Figure 4 Adult Novel Framework Resource

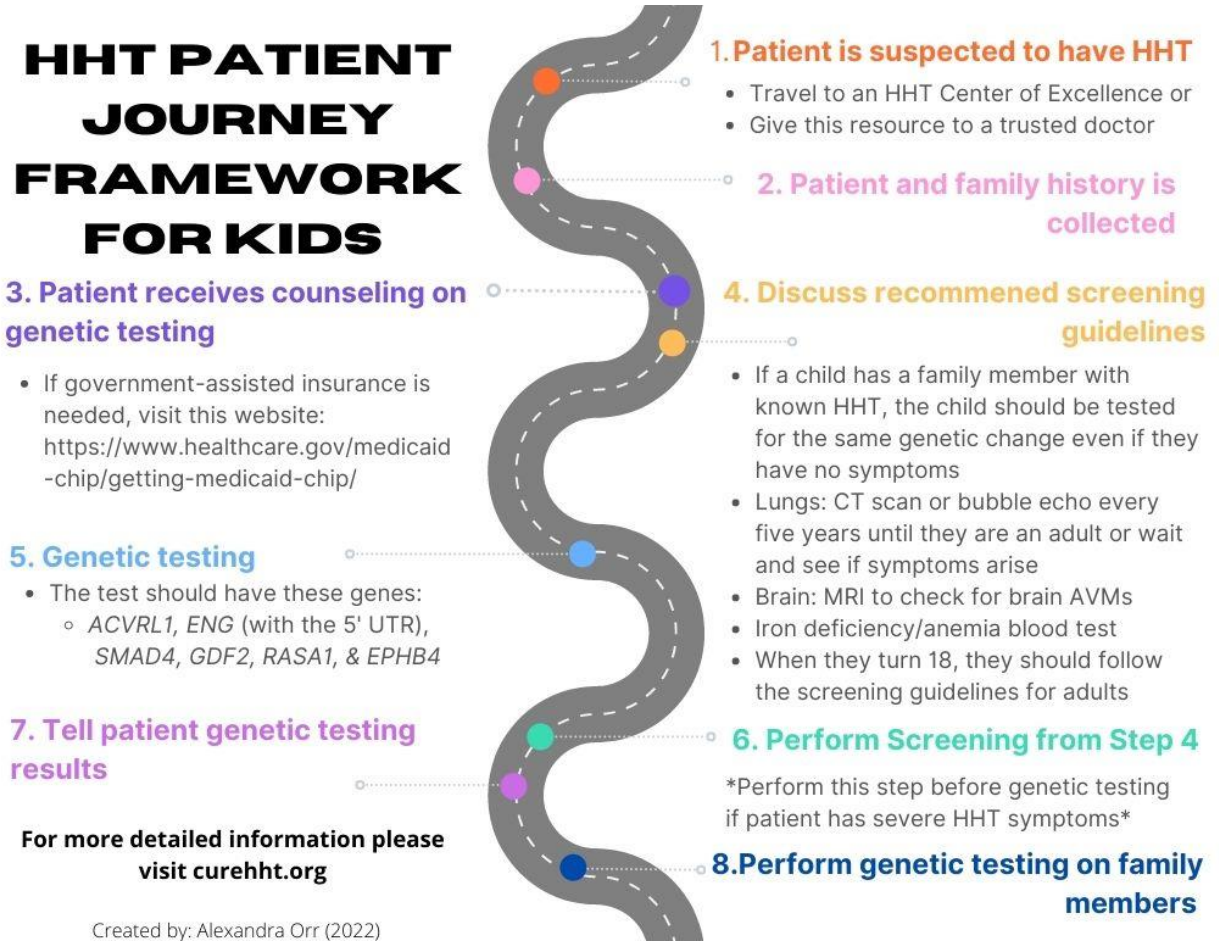

Figure 5 Pediatric Novel Framework Resource

Twenty-seven out of 34 respondents said that their COE employs genetic counselors, compared to seven out of 34 who said they did not. It needs to be mentioned that one survey respondent claimed to be a genetic counselor but answered “no” to this question on the survey. As it would be impossible for them to have access to the survey without being employed at the COE, this data point was removed. This survey question provided insight to the research question about which providers are involved in an HHT patient’s diagnostic journey. According to the results, genetic counselors are involved in the diagnostic journey 82% of the time, similar to recently reported data (Lam et al., 2021).

Oftentimes, a clinical diagnosis is all someone needs to be considered to have HHT. However, when a clinical diagnosis is not achievable, such as in children, genetic testing is the only way to get a clear answer on a diagnosis. “Possible HHT” is a term that comes from only meeting two of the Curaçao Criteria, and people with this distinction are typically offered confirmatory genetic testing (Pahl et al., 2018) (Lam et al., 2021). Therefore, it was expected that almost all survey respondents would select this answer choice as a reason to offer genetic testing. However, only about 83% of respondents claimed this was an adequate reason to offer genetic testing. Additionally, genetic testing is offered to asymptomatic at-risk family members when a family mutation is known (Lam et al., 2021), which is corroborated by the survey results as 100% of respondents indicated that was an indication for testing. If all COEs worked in harmony and used the same thought process, either every respondent or no respondent should have selected each answer choice. The variation in this distribution suggests that COE utilization of genetic testing in patients who already have a clinical diagnosis requires standardization.

About 15% of the respondents reported that their COE was unable to provide advice and resources to a non-COE patient. This leads to a disparity in care available to those who can travel to a COE versus those who cannot. Traveling to one of the few COEs on the continent is not simple for most people (Hasan Albitar et al., 2021). Most U.S. states, for example, only have one Center in the entire state. Patients must pay to travel to the COE and stay for at least a few days to get all their necessary screenings. This highlights the utility of a novel patient framework resource, especially for patients who are of lower socioeconomic background and cannot afford to travel to a COE. The patient resource will provide them with guidance on diagnosis and screening, which they can share with a local physician. The standardized resource will help these patients receive excellent care without having to travel to a COE.

The genetic testing payment method that is typically used at COEs may shed light on the socioeconomic status of those who are able to utilize COE services. The percentages that were reported for each payment type need to be evaluated more critically because in some cases respondents from the same COE answered the question differently, in some cases drastically differently. This fact indicates that not everyone within the same COE is aware of payment methods used. Another fact to note is that almost all the Canadian COEs that responded indicated patients pay using "other." There was no opportunity to provide a description of what "other" means, but this can speak to how the Canadian and American healthcare systems are unique (Ross University, 2021). Canadians typically pay for their healthcare through their taxes instead of through insurance (Ross University, 2021), so this could be what "other" means.

Survey results indicate that private insurance is the leading payment method for the responding COEs. This result implies that those who visit COEs can afford private insurance premiums, deductibles, and co-payments. Medicaid is used much less according to survey respondents. This is likely because individuals of low socioeconomic status who are eligible for Medicaid cannot afford to travel to distant COEs or access them even if they are close by. They also do not have the time to dedicate to their healthcare, as also noted in prior research (Hasan Albitar et al., 2021).

Overall, these genetic testing payment method results prove the necessity of the novel HHT patient resource frameworks. It is crucial to provide resources that can reduce inequities between patients of different socioeconomic status and these resources are a way to try to begin that process. As indicated by the survey responses to this payment method question, not everyone involved at each COE is aware of the payment method breakdown, and therefore, may not be aware of the economic demographics of their patients. While physicians should not be faulted for prioritizing

the healthcare of patients who come in to see them, it is important they are aware of any gaps in accessibility to their services. If COE directors and medical providers were more aware of these accessibility gaps, they could begin to create ways close that gap.

5.1 Limitations

Survey collection comes with a set of limitations. For example, any ranking style question is going to be completely subjective to every person responding to the survey. Their personal experiences with the specific set of patients they have seen in their careers will certainly bias the way they feel the question should be answered. Another aspect to consider in a survey is that not every respondent will make it to the end of the survey, so they might only count for a certain number of questions.

Additionally, sending surveys out to multiple people from the same COEs can create confusion when they respond with conflicting answers. There were instances where individuals from the same COE replied differently when asked if their COE employed genetic counselors, among other questions. This could be caused by a lack of understanding of one of the respondents or a "mis-click" on the online survey where the person accidentally chose the wrong answer choice. It is difficult to resolve these kinds of confusion without directly reaching out to the survey respondents in question.

Another method of trying to resolve these discrepancies is looking on the specific webpages for each COE. While every webpage is different across all the COEs, most of them show a list of team members employed by their Center. Moreover, several Centers that claim not to have genetic counselors are associated with universities that have Genetic Counseling Training

Programs. While this would not automatically dictate that a COE employs genetic counselors, it would certainly make it easier to find people to fill that role at the Center if it is deemed beneficial by this research study.

Another limitation of the survey was that it was only asked specifically if the COEs had genetic counselors, not about any other type of medical provider. This information could have been helpful to see which Centers had certain practices and if that was determined by which medical specialists are available there. In general, COEs often have otolaryngologists, cardiologists, gastroenterologists, interventional radiologists, hematologists, dermatologists, and neurologists, among other specialists. It is not guaranteed every COE has all these specialists, however, so it would have been helpful to ask this in the survey, though that would have added more complexity to an already long survey. Most North American COEs do have at least one geneticist, otolaryngologist, interventional radiologist, pulmonologist, and hepatologist (Cure HHT, 2022a).

5.2 Future Directions

Moving beyond this research, it will be important to survey HHT patients at COEs to understand how satisfied they are with their care. The survey could ask specific questions about the utility, relevance, and convenience of the novel framework resources developed. It will also be important to analyze whether COEs with genetic counselors have a drastically different set of steps they follow compared to COEs without genetic counselors. It will shed light as to whether Centers with genetic counselors are more efficient and thorough, which could be determined by comparing patient satisfaction rates and time taken for patients to receive genetic test results. If that were seen

to be true, it could lead Cure HHT to mandating that Centers without genetic counselors hire some to improve patient care. According to the literature, it is thought that "genetic counseling…may allow for effective diagnosis of HHT among asymptomatic blood relatives of tested individuals" (Lam et al., 2021). Having a genetic counseling session performed by a licensed or certified genetic counselor can only improve the diagnostic outcomes of HHT.

Further surveys will need to be sent out to COE coordinators to learn more about the logistics new patients should know before traveling to a COE for the first time. This information could be collected and developed into another patient resource to be presented on the Cure HHT website and the websites of all COEs. Learning more about this could further highlight the inequities between individuals of differing socioeconomic status and how those who are less advantaged have a harder time receiving quality healthcare.

Cure HHT is already in the process of optimizing interventions and evidence-based guidelines for HHT disease management after cases of HHT are diagnosed, but this research and advancement should expand and continue.

Lastly, the novel resource framework should be implemented on a small scale at the University of Pittsburgh COE to determine the effectiveness of the resource before providing it to the remaining COEs across North America. After collecting feedback from the Center, adjustments could be made to the resource before widespread dissemination and online posting.

5.3 Conclusions

In summary, this research study provides enough evidence to be able to accurately create a standardized method for HHT patient diagnoses in the form of a novel framework resource for

those who are suspected to have and have been diagnosed with HHT to adequately inform them how to navigate their condition and manage follow-up care. This standardized method will need to first be put in place at the University of Pittsburgh HHT Center of Excellence on a small scale to assess its functionality and utility. If it is deemed a success, it should be implemented at all North American Centers and published on the Cure HHT website for anyone to access. As stressed before, this novel framework is crucial for patients to be able to serve as their own health advocates and to provide equitable resources to all suspected HHT patients, regardless of their socioeconomic status and whether they are a COE patient or not.

Appendix A IRB Exemption

Office of Research Protections
Human Research Protection Office

Hieber Building, Suite 106
3500 Fifth Avenue
Pittsburgh, PA 15213
412-383-1480
www.hrpo.pitt.edu

MEMORANDUM

TO: Alexandra Orr

FROM: Human Research Protection (HRP)

DATE: November 18, 2021

SUBJECT: IRB# 2111006: Creation of a Novel Framework Resource for the New Hereditary Hemorrhagic Telangiectasia Patient Journey

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The above-referenced research study has been reviewed by the University of Pittsburgh Institutional Review Board. Based on the information provided to the IRB, this project includes no involvement of human subjects, according to the federal regulations [45 CFR 46.102(e)]. That is, the investigator conducting research will not obtain data through intervention or interaction with the individual, or will not obtain identifiable private information. Should that situation change, the investigator must notify the IRB immediately.

Appendix B Patient Journey Survey

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The Cornerstone of the HHT Community

Patient Journey at HHT Centers of Excellence

We are surveying the patient journey at the North American COEs. Please take a few minutes to provide information about the patient journey at your center.

* 1. With which HHT Center are you affiliated?

* 2. What is your role at your Center of Excellence (COE)? Select all that apply.

- [ ] Center Director / Co-Director
- [ ] Geneticist
- [ ] Genetic Counselor
- [ ] Other Medical Provider
- [ ] Other role (please specify)

* 3. Does your COE have genetic counselors?

- ( ) Yes
- ( ) No

* 4. Is there anyone at your COE who provides advice, resources or recommendations to someone who potentially has HHT but has never been seen at a COE (non-HHT Center patients), i.e., a new patient and/or providers?

- ( ) Yes
- ( ) No

Patient Journey at HHT Centers of Excellence

Patient and Provider Discussions with Your HHT Center

* 5. Which of the following is discussed with **non-HHT Center patients** (potential new patients) and/or providers by someone at your center? Select all that apply.

- [ ] What is genetic counseling and why is it important
- [ ] What HHT genetic testing entails
- [ ] HHT screening guidelines
- [ ] How to find a genetics provider in their area
- [ ] How to find the CureHHT website for more information about HHT
- [ ] Other discussion points (please briefly specify)
- [ ] None of the above

* 6. For **non-HHT Center patients** who contact your COE about genetic testing, what information do you provide to help facilitate testing? (If your center does not provide this type of information, please type N/A.)

* 7. For HHT Center **patients of record** who contact you about getting genetic testing outside your HHT Center, what information do you provide to help facilitate testing that differs from your answer to Question 6? (If your center does not provide this type of information, please type N/A.)

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Patient Journey at HHT Centers of Excellence

Steps in the Patient Journey

* 8. Rank the following from first (1) to last (8) in the typical HHT diagnostic journey a patient takes at your center. If a step does not apply to your center, please choose N/A.

Patient is referred/patient self refers to the COE

☐ N/A

Patient and family history is taken

☐ N/A

Patient is screened for AVMs

☐ N/A

Patient is counseled on genetic testing

☐ N/A

Patient is offered genetic testing to identify their HHT variant or targeted variant testing if family mutation is already known

☐ N/A

Results of genetic testing are disclosed

☐ N/A

Recommended screening guidelines are discussed

☐ N/A

Family members are seen at the COE and targeted testing is offered to them

☐ N/A

9. Please list any steps in the patient diagnostic journey at your center that were not mentioned in the previous question.

* 10. Please briefly mention how steps differ if a person is not a current COE patient. (Please write N/A if not applicable).

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Patient Journey at HHT Centers of Excellence

Clinical Diagnosis

* 11. Approximately what percentage of your patients have a clinical diagnosis only (no genetic testing) of HHT?

- ○ 0%
- ○ 1-20%
- ○ 21-40%
- ○ 41-60%
- ○ 61-80%
- ○ 81-99%
- ○ 100%

* 12. Which of the following are done at your COE to help with a clinical diagnosis of HHT? (Select all that apply.)

- ☐ Lung AVM Screening
- ☐ Brain AVM Screening
- ☐ Obtain a family history
- ☐ Obtain a personal health history
- ☐ Physical exam
- ☐ Other (please specify)

- ☐ None of the above

* 13. Which of the following have been a reason to not want to proceed with genetic testing if a patient has a clinical diagnosis? (Select all that apply.)

- [ ] No family members interested in genetic testing
- [ ] Concerns about cost/insurance
- [ ] Would not change their medical management
- [ ] Other reason(please specify)

None of the above

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Genetic Diagnosis

* 14. Approximately what percentage of your patients go through your HHT Center to complete genetic testing?

- ( ) 0-20%
- ( ) 21-40%
- ( ) 41-60%
- ( ) 61-80%
- ( ) 81-100%

* 15. Approximately what percentage of your patients utilize the following payment options for genetic testing when testing is coordinated through your HHT center? (Please approximate so your total percentages equal 100%).

Institutional (Corporate Account)	
Private insurance	
Medicaid	
Medicare	
Self-pay	
Other	

* 16. Which of the following are reasons why you would order genetic testing for a patient already clinically diagnosed? (Select all that apply.)

- [ ] To determine a family genetic mutation to better screen at risk family members
- [ ] To determine medical management (i.e. SMAD4 mutations)
- [ ] Genetic diagnosis is requested for confirmation of HHT because the Curaçao Diagnostic Criteria determines them to have "possible HHT"
- [ ] Other (please specify)

* 17. Would you recommend that a self-diagnosed or suspected HHT patient, referred by a local physician, receive genetic testing before traveling to an HHT COE for clinical diagnosis and screening?

- ( ) Yes
- ( ) No
- ( ) Maybe (Please briefly explain why you did not choose yes or no.)

* 18. Do patients typically obtain genetic testing locally before they travel to see you at your COE?

- ( ) Yes
- ( ) No
- ( ) Sometimes (Please specify the approximate percentage of patients who do receive testing before visiting your COE.)

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Local Genetic Testing Prior to Travel to an HHT Center

* 19. What percent of the time do you approximate that patients obtain local genetic testing in the following different ways before traveling to your HHT Center?

	0-20%	21-40%	41-60%	61-80%	81-100%	N/A
Your HHT Center refers them to a local genetics clinic/genetics professional	○	○	○	○	○	○
Their primary care provider orders genetic testing or refers them to a genetics professional	○	○	○	○	○	○
Their specialist (Hematologist, Dermatologist, Pulmonologist, etc.) orders testing or refers them to a genetics professional	○	○	○	○	○	○
They self-refer to a genetic counselor/remote genetic counseling service	○	○	○	○	○	○

Other ways to receive local genetic testing (please specify)

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Roles at your HHT Center

* 20. Who at your center usually performs the following steps in obtaining genetic testing? You may select more than one person for each step.

	Center Director	Geneticist	Genetic Counselor	Other medical provider	None of these
Provides genetic counseling	☐	☐	☐	☐	☐
Coordinates genetic testing	☐	☐	☐	☐	☐
Provides pre and post testing counseling	☐	☐	☐	☐	☐
Obtains informed consent for genetic testing	☐	☐	☐	☐	☐
Discusses insurance and cost related issues regarding genetic testing	☐	☐	☐	☐	☐

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Contact Information

* 21. Please provide your contact information below:

Name

Email Address

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Thank you!

Your participation in this survey is greatly appreciated.

Please click "Done" to complete the survey.

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