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Experiences, Attitudes, and Knowledge within the Hemoglobinopathy Community

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Experiences, Attitudes, and Knowledge within the Hemoglobinopathy Community

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Genetic Counseling

by

Anusha Beth Klinder

Thesis Committee:
Professor Moyra Smith, Chair
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2022

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ABSTRACT OF THE THESIS

Experiences, Attitudes, and Knowledge within the Hemoglobinopathy Community

by

Anusha Beth Klinder
Master of Science in Genetic Counseling
University of California, Irvine, 2022
Professor Moyra Smith, Chair

Hemoglobinopathies are highly prevalent conditions, with a global carrier rate of about 7%, and where carriers often present with microcytic anemia. Despite this, a standard of care or treatment is not yet established for cases of hemoglobinopathies within the U.S. Countries outside of the U.S. with a high in-nation carrier rate have long-established guidelines for hemoglobinopathy care. Through interview-style studies, previous research has demonstrated that satisfaction of care is attainable within the hemoglobinopathy community if appropriate diagnostic procedures, such as newborn and prenatal screening, are implemented. For this reason, the aims of this research were as follows: 1. Evaluate the gaps in genetic knowledge of both carriers and individuals affected by hemoglobinopathy as well as their family members and 2. Measure satisfaction with coordinated care by individuals affected by hemoglobinopathies, especially in terms of treatment options and preconception planning. An anonymous survey designed to assess a participant's knowledge and experience regarding anemia or their hemoglobinopathy diagnosis was created and distributed to various clinical groups including the University of California Irvine Center for Fetal Evaluation and the Thalassemia Center: UCSF Benioff Children's Hospital Oakland. In total, 92 participants completed the survey in its

entirety, 54 of these individuals completed the anemia experience portion, and 19 of these individuals completed the hemoglobinopathy experience portion. A majority of these participants held a bachelor's degree or greater and had some relation to the healthcare industry; despite this, the knowledge score, with a possible range of zero to seven, had a mean of 3.7 and median of 3.8. Additionally, the highest score recorded by a participant was a 6.5. Genetic counseling is thought to help breakdown the complex information surrounding hemoglobinopathies. However, many survey respondents reported no genetic counseling at their initial or follow-up appointments for their hemoglobinopathy. Thus, to increase satisfaction and knowledge of hemoglobinopathies within this community, more detailed screening within the U.S. and access to genetic counseling services may be recommended.

INTRODUCTION

1.1 Overview of Hemoglobinopathies

Hemoglobinopathies are a group of single-gene disorders which affect the ability of hemoglobin to carry oxygen in our red blood cells to other organ systems. Hemoglobin is a tetramer composed of two alpha chains paired most frequently with beta, delta, or gamma chains, which make up the oxygen-carrying protein. These types of hemoglobin are referred to as hemoglobin A, hemoglobin A2, and hemoglobin F, respectively. In an unaffected individual, approximately 97% of the hemoglobin in adult red blood cells is type A, about 2% is type A2, and type F comprises less than 1%. Hemoglobin F is fetal hemoglobin and is the least prevalent type of hemoglobin in adults but the most prevalent type of hemoglobin beginning in the 2nd to 4th week of gestation until about 5 months after birth (Edoh et al., 2006). In an individual affected by a hemoglobinopathy, these percentages may vary; examples of this include individuals with alpha or beta thalassemia major or minor. An individual with beta thalassemia has deficiencies of beta chains, while an individual with alpha thalassemia has deficiencies of alpha chains. For this reason, someone with beta thalassemia major will have elevated A2 and F hemoglobin and lowered levels of hemoglobin type A since their type A hemoglobin would contain deficient beta chains and not be sustained at a high level in their body. As an example, typically symptoms of beta thalassemia do not present until around 5 months after birth, when hemoglobin A (adult hemoglobin) is produced more than hemoglobin F (fetal hemoglobin) (Edoh et al., 2006). For this reason, some hemoglobinopathies are not as easily diagnosable via routine bloodwork until after fetal hemoglobin (type F) reduces in prevalence. Importantly,

hemoglobinopathies are typically diagnosable at any point through molecular, or genetic, testing.

Hemoglobinopathies fall into two broad categories of either structural hemoglobin variants (qualitative) or deficiencies in globin production (quantitative) changes (Weatherall et al., 2012). Qualitative hemoglobinopathies are conditions which affect the structure of the hemoglobin whereas quantitative hemoglobinopathies affect the production of hemoglobin chains. Further information about individual variants and their phenotypes can be found in the Human Hemoglobin Variant Server (Giardine et al., 2014).

1.11 Inheritance

There are more than 750 variants in the *HBB, HBA1,* and *HBA2* genes which can cause deficiencies in quantity or quality of hemoglobin and cause hemoglobinopathies (Firth and Hurst 2017). In this context, a variant refers to a genetic change in a gene which affects hemoglobin chains. Within the larger category of hemoglobinopathies are more common conditions including beta thalassemia, alpha thalassemia, and sickle cell disease. These, and most other, hemoglobinopathies are inherited in an autosomal recessive pattern, meaning that, in an affected individual, variants are present in both copies of a gene, with one copy inherited from each carrier parent. For example, both sickle cell disease and beta thalassemia are inherited in an autosomal recessive pattern, where each parent of an affected individual typically has one variant in the *HBB* gene and is referred to as a carrier. Carriers are typically asymptomatic or have only a very mild phenotype. It is notable that some hemoglobinopathies, such as Hb Hakkari and other rare hemoglobinopathies, are inherited in an autosomal dominant pattern (Nair et al., 2014), meaning individuals who are heterozygous for a variant present with symptoms.

The inheritance of alpha thalassemia is more complex than other hemoglobinopathies; there are multiple different phenotypic outcomes from differing amounts of functional alpha globin. The alpha globin genes are called *HBA1* and *HBA2,* and since everyone inherits one copy of each alpha globin gene from each parent, a typical individual would have four functional alpha globin alleles. There are four different sub-types of alpha thalassemia, described by how many globin alleles are deleted: alpha thalassemia silent carrier (three functional alpha globin copies), alpha thalassemia trait (two functional alpha globin copies), hemoglobin H disease (one functional alpha globin copy), and alpha thalassemia major or hemoglobin Barts (Hb Barts) hydrops fetalis syndrome (no functional copies of alpha globin).

1.12 Symptoms

Individuals with hemoglobinopathies will generally have similar physical characteristics which may include enlarged spleen (splenomegaly), abdominal pain, fatigue, microcytic hypochromic anemia, chronic hemolytic anemia, hydrops fetalis without other known etiology, bone changes, and erythrocytosis (Kohne et al., 2011). However, each hemoglobinopathy type has its own more nuanced phenotype as well, dependent on the specific genetic variants and molecular mechanism of the gene(s) impacted. Since there are more than a thousand variants that have been described to cause a hemoglobinopathy, this section will focus primarily on discussing the phenotypes of the three most common hemoglobinopathies: sickle cell disease, beta thalassemia, and alpha thalassemia.

Individuals with sickle cell disease (any hemoglobinopathy that includes production of hemoglobin S) may be the most well-studied group within the hemoglobinopathies. Episodes and attacks of pain are common among affected individuals and are thought to occur because of vascular occlusion (inability of blood to pass through vessels) and an increase in inflammation

(Ataga et al., 2017). Additionally, sickle cell anemia is characterized by recurrent infections, strokes, increased hemolysis, splenomegaly, fatigue, and chest pain. Sickle cell anemia is due to an abundance of abnormal hemoglobin within an individual's red blood cells, called HbS ("hemoglobin S"). Carriers of sickle cell anemia (those with a heterozygous variant in *HBB* that leads to abnormal structural changes or an abundance of "hemoglobin S") are usually not symptomatic but may exhibit iron deficiency or fatigue and dizziness due to increased hemolysis, and also have an increased risk for heat stroke and muscle breakdown after intense exercising.

The clinical features of beta thalassemia and alpha thalassemia can be similar to each other, although they are caused by variants in different genes. Variants causing beta thalassemia are in the *HBB* gene, whereas variants causing alpha thalassemia involve the *HBA1* and *HBA2* genes. In both cases, if an individual has a single globin variant (a heterozygous variant in *HBB* or a single globin deletion of *HBA1* or *HBA2*), they may be referred to as having thalassemia minor, trait, or called a carrier of thalassemia; these individuals may still have some clinical features of a hemoglobinopathy albeit less severe than in individuals with two globin variants. If a single individual has both alpha and beta globin pathogenic variants, they may have hemolytic anemia, jaundice, splenomegaly, and reticulocytosis. When alpha and beta globin pathogenic variants occur together, these conditions can cause unique phenotypes, which may be difficult to diagnose (Yates et al., 2015).

As mentioned previously, the term carrier is used interchangeably with beta thalassemia minor or trait. Beta thalassemia can present as either beta thalassemia minor, beta thalassemia intermedia, or beta thalassemia major. Beta thalassemia minor or trait is where an individual only has one copy of *HBB* with a variant (heterozygous). Beta thalassemia intermedia, where an individual has homozygous or compound heterozygous variants in *HBB* with or without variants

in *HBA1* and *HBA2*, varies in severity and phenotype, but individuals with the condition typically do not require blood transfusions for management or treatment. Beta thalassemia major is where an individual has homozygous or compound heterozygous variants in *HBB* and is blood transfusion dependent (Needs et al., 2021). Typically, those with beta thalassemia intermedia and major will have the most noticeable phenotype including molecular features, such as a hereditary persistence of fetal hemoglobin (HPFH), and physical features, such as general failure to thrive and regular fevers in the first year of life. Individuals with beta thalassemia major may have hemoglobin levels ranging from 2-8g/dL (for reference, normal hemoglobin ranges are 14 to 18 g/dL for males and 12 to 16 g/dL for females) and are generally transfusion-dependent (Adamson and Finch, 1975). Individuals with beta thalassemia intermedia, will often have hemoglobin levels around 6-9g/dL and are not necessarily transfusion dependent, so they may have milder phenotypes (Firth et al., 2005).

Most individuals with three functional alpha globin alleles (alpha thalassemia silent carrier) will not experience any symptoms and often go undetected for their entire life, hence the term silent carrier. Individuals with two functional alpha globin alleles have alpha thalassemia trait (also called alpha thalassemia minor). They may experience mild fatigue related to microcytic anemia, but are often asymptomatic. These *HBA1/HBA2* variants can both be present on the same allele (*in cis*) or can be present on opposite alleles (*in trans*). Notably, variants *in cis* are more frequently found in Asian populations, while variants *in trans* are more common in African populations. Figure 1 provides a visual depiction of these two different variant configurations. Individuals with one functional alpha globin allele have hemoglobin H disease and typically experience more severe symptoms and typically require transfusions of healthy red blood cells on a consistent basis over their lifetime (Cappellini and Motta, 2017). Individuals

with no functional alpha globin alleles have alpha thalassemia major (also called Hb Barts), which typically presents prenatally or early in infancy with severe anemia, intrauterine growth restriction, and often fetal or neonatal demise. It was previously considered perinatal lethal; however, recent advancements in research have demonstrated the condition can be treated via *in-utero* hematopoietic stem cell transplant (HSCT) (Curran et al., 2020). Figure 1 depicts these four subtypes of alpha thalassemia.

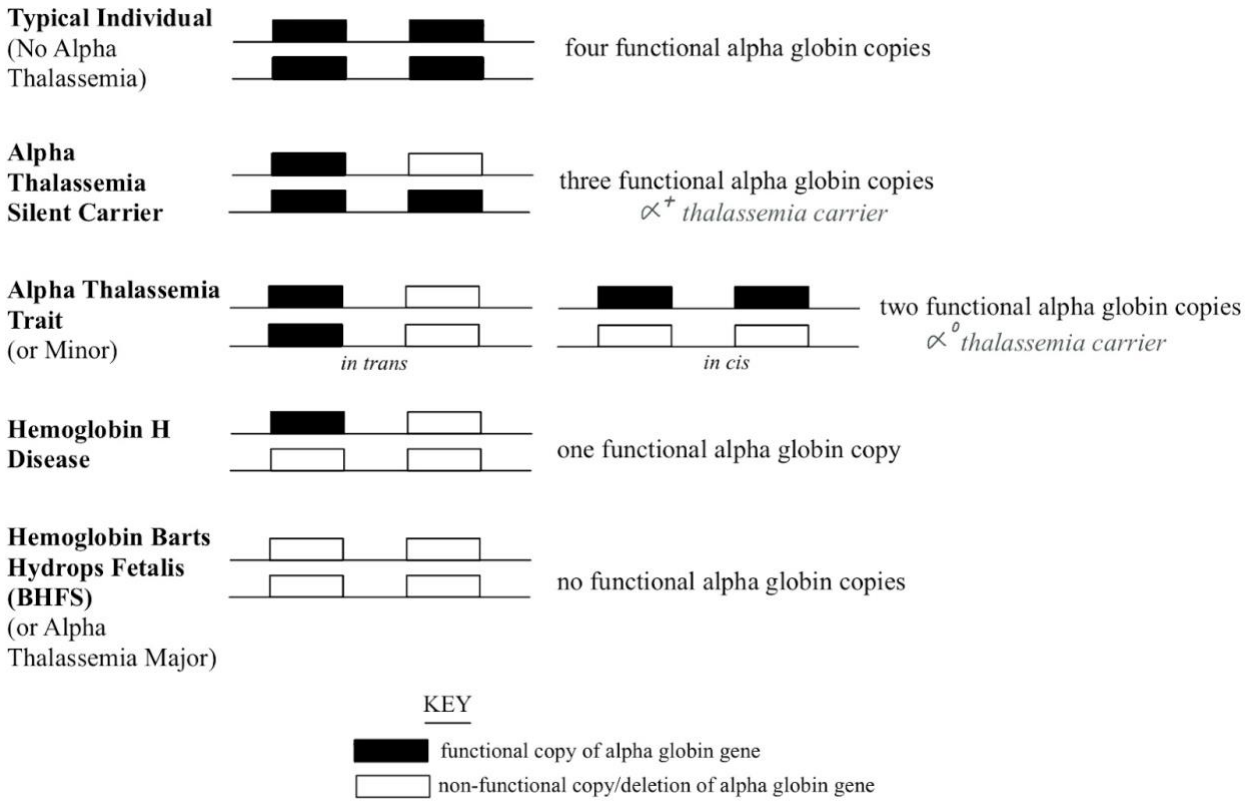

Figure 1: Alpha Thalassemia Visual Diagram

The four possible sub-types of alpha thalassemia as compared to a typical individual with no alpha thalassemia. This diagram was prepared based on published information (Williams and Weatherall 2021).

It is important to note that two variants of different hemoglobinopathies can interact, resulting in a more complex phenotype (Yates et al., 2015). A frequent occurrence of this is an

individual with two variants in the beta globin gene (*HBB)* that does not lead to a beta thalassemia phenotype. For example, an individual with both a variant that results in sickle cell (HbS) and another rarer variant, c.83C>A (p.Ala27Asp), which results in Hb Volga, may present with increased reticulocyte counts (immature red blood cells) due to increased hemolysis. Another more common example would be an individual with two variants in *HBB*, HbS in conjunction with HbC, whose clinical features include hepatosplenomegaly and anemia. Splenomegaly, anemia, and sickle-shaped red blood cells could be expected in this aforementioned individual as well (Yates et al., 2015). There are many variants which have only been clinically observed in one individual, but these rare variant combinations often have a lot of overlapping features with other hemoglobinopathies.

1.2 Diagnostic Process

To accurately determine whether an individual has or is a carrier of a hemoglobinopathy, the diagnostic process is usually broken down into multiple steps. Importantly, both carriers and affected individuals can have abnormal test results (these specific tests are detailed below). An accurate diagnosis is important for family planning and management of potential symptoms, such as dizziness and anemia, that may arise as a result of one or more deficient copies in the *HBB, HBA1,* or *HBA2* genes. Therefore, it is necessary to differentiate between isolated iron deficiency (which can mimic a hemoglobinopathy) and clinical features of hemoglobinopathies through a primary test of iron studies. If iron studies are normal, subsequent thorough testing should include a complete blood count (CBC), isoelectric focusing (IEF), hemoglobin electrophoresis, and molecular (genetic) testing. Additionally, even if iron studies show a deficiency, subsequent testing should be considered in some cases since individuals with hemoglobinopathies can likewise present with iron deficiency. More recently, high-performance

liquid chromatography (HPLC) has replaced hemoglobin electrophoresis, but the testing is often still referred to as hemoglobin electrophoresis (Antonarakis et al., 2019). Specific results from each step, which will be discussed in subsequent paragraphs, determine whether the next protocol is undertaken.

If a complete blood count shows a low mean corpuscular volume (MCV) of the red blood cells with either a low count of hemoglobin protein (Hb) or a high count of red blood cells (RBC), it can be indicative of microcytic anemia. Microcytic anemia presents with red blood cells smaller than expected, being produced at a greater rate, and lacking in effective hemoglobin. While the majority of hemoglobinopathy carriers will be "silent," meaning they do not show symptoms of anemia, many may eventually be suggested as possible carriers through an initial CBC (Bender et al., 2021). Not all individuals with anemia will have a hemoglobin variant, but specific forms of anemia, such as microcytic anemia, in the setting of normal iron levels and/or in an individual from a high-risk ethnic group may be more clinically suspicious as having been caused by molecular variants in hemoglobin genes, and should prompt further testing.

Isoelectric focusing (IEF) may be the next screening test following a CBC, which allows for separation of molecules by the pH at which they no longer carry an electrical charge. This screening method is not always used clinically; in some settings, this serves as an intermediate step between a CBC and HPLC (Bender et al., 2021), and in others it is skipped entirely.

Following abnormal CBC and/or IEF results, an HPLC, which is a laboratory test that measures the percentage of each type of hemoglobin (HbF, HbA, HbA2, HbC, HbS, etc.) in one's red blood cells, can be performed. Even if CBC results are normal, an HPLC may still be recommended in some scenarios, since some hemoglobinopathies, such as sickle cell, may not

have abnormal results on a CBC. Through this test, a better ascertainment can be made of which hemoglobin types are deficient as well as the percent of atypical hemoglobin variants present in that individual. Sometimes, the order of these tests may be reversed, so iron studies may be done prior to a CBC or between a CBC or HPLC. If an HPLC is normal, further testing, such as iron studies can be done to determine if the abnormal CBC results are due to non-inherited forms of anemia rather than a hemoglobinopathy. In some cases, an individual may have a normal HPLC following an abnormal CBC, which can be an indication of alpha thalassemia trait or silent carrier status, in which case further genetic testing is warranted. This HPLC may appear normal because only a small percentage of alpha globin chains may be missing if two or fewer copies of alpha globin genes are deleted in the individual. For this reason, an HPLC may show normal levels of hemoglobin types A2, A, and F even if upon further genetic testing this is not the case.

After the CBC, HPLC, IEF, or iron studies are conducted, follow-up testing may include genetic testing. Multi-gene panels designed to identify possible hemoglobin defects, marketed as "anemia panels," are available through commercial laboratories. These panels may or may not include sequencing and deletion/duplication analysis of the alpha globin genes, *HBA1* and *HBA2*, and beta globin gene, *HBB*. Some symptomatic individuals with a hemoglobinopathy have rare variants in the beta globin gene that are best detectable by sequencing and, more rarely, deletion/duplication analysis. For this reason, sequencing of the *HBB* gene is recommended for those with abnormal CBC and HPLC results to further evaluate for any beta globin changes. In instances of abnormal hemoglobin on HPLC, genetic testing of specific variants that cause the abnormal hemoglobin may be recommended. The beta globin gene, *HBB*, houses many of the pathogenic variants found in individuals who either carry or have a hemoglobinopathy. For individuals with suspected alpha globin genetic variants, deletion/duplication testing is

recommended as the initial test because of the frequency of common deletions in many different populations; sequencing of *HBA1* and *HBA2* can identify rarer variants.

Importantly, some individuals may be screened through population-based screening programs, such as newborn screening, and may be recommended to undergo genetic testing without moving through all of the above steps. Some carriers may also be identified through population-based or ethnicity-based carrier screening (often offered through prenatal or preconceptional consultations) in which some of the above steps may be used but genetic testing is increasingly being used earlier in the process.

1.21 Newborn Screening

Individuals affected by hemoglobinopathies can be detected via newborn screening. As of 2006, all 50 states within the U.S. screen for sickle cell disease as recommended by the American College of Medical Genetics (ACMG) (Hoppe, 2009). All 53 U.S. states and territories that have implemented newborn screening for hemoglobinopathies screen for Sickle Beta Thalassemia (HbS/ßTh); Sickle Cell, Hemoglobin C Disease (HbS/C), and Sickle Cell Anemia (HbSS). As of 2022, the only state or territory which does not screen for any hemoglobinopathies is the U.S. Virgin Islands. Currently, all but six states (Arizona, Colorado, Kansas, Montana, New Hampshire, Rhode Island, and Virginia) and two territories (Guam and U.S. Virgin Islands) screen for other hemoglobin variants as well. Since newborns will have high levels of fetal hemoglobin (Hb F) for up to 5 months after birth, and beta thalassemia is diagnosed via high levels of type F and A2 hemoglobin via HPLC, this will result in high false positive rates on HPLC tests (Firth et al., 2005). Historically, for this reason, beta thalassemia is difficult to detect via newborn screening.

1.3 Treatment

Treatment of a hemoglobinopathy depends on type and whether an individual is exhibiting symptoms. Management and treatment may include preventative and symptom-based splenectomies, targeted medication, blood transfusions, gene therapies, or hematopoietic stem cell transplants (HSCT).

Occasionally, due to the cholelithiasis associated with these conditions, cholecystectomy may be recommended to prevent onset of more severe symptoms (Yates et al., 2015). This is because, especially with increased hemolysis observed in sickle cell disease, excess bilirubin can lead to a buildup of gallstones or bladder disease. Therefore, a cholecystectomy would inhibit future severe symptoms in an individual with elevated levels of hemolysis. This procedure is recommended in the 30-70% of individuals with sickle cell who exhibit this phenotype (Diarra et al., 2008). On this same note, due to the hepatosplenomegaly associated with these conditions, removal of the spleen (splenectomy) may be recommended to reduce excess inflammation and recurrent infection (Kanter and Kruse-Jarres 2013). Importantly, these prophylactic surgeries are generally reserved for individuals who are suspected to have later onset of severe symptoms.

Hydroxyurea is an example of a targeted treatment used to treat patients with sickle cell disease who experience severe episodes of vascular occlusion (colloquially referred to as pain crises). When taken consistently over the course of an individual's life, hydroxyurea results in a reduced frequency of these painful occlusions (Kanter and Kruse-Jarres 2013). This treatment works by reducing the number of reticulocytes in circulation, while increasing the amount of healthy fetal hemoglobin. A study established support for the efficacy of hydroxyurea when it found an increased risk of thromboembolic events (blood clots) amongst individuals with

hemoglobin C abnormalities or sickle cell disease who were not taking the medication (Colella et al., 2015).

Crizanlizumab is a newer treatment with clinical trials in 2016 to evaluate efficacy alongside hydroxyurea treatment. Among 198 patients in one study, crizanlizumab was found to have a significant effect on reducing the length of time between pain crises and adverse effects such as diarrhea, joint pain, chest pain, and vomiting (Ataga et al., 2017).

In addition to targeted medication, biweekly transfusions of healthy red blood cells from donors have been effective in reducing crises and improving the quality of life for patients with sickle cell and thalassemia (Porter 2018). The transfusion of healthy red blood cells is generally used sparingly for most minor clinical symptoms of hemoglobinopathies (e.g. fatigue, dizziness, or anemia) but is a significant preventative measure prior to major surgeries or for oncoming vascular occlusion in sickle cell patients (Kohne 2011).

HSCT is a newer method of treatment for sickle cell disease, alpha thalassemia, and related hemoglobinopathies. This management method aims to prevent future onset of symptoms through a transplant of stem cells *in-utero*, in infancy, or in early childhood. In this way, HSCT is able to essentially rewrite and provide new instructions for the individual's hemoglobin to bind to oxygen. Since an individual's stem cells belong to a specific human leukocyte antigen (HLA) family, it is essential to find a transplant donor whose HLA matches that of the recipient (Park and Seo 2012). HSCT has been found to be especially effective as an *in-utero* treatment for fetuses with Hb Barts. A recent study discovered that IUHCT (*in-utero* hematopoietic stem cell transplant) from the mother to the fetus in the second trimester of pregnancy, starting around the 23rd week of gestation and every three weeks until term, significantly improved fetal survival rate and lowered the chance of stem-cell rejection (Derderian et al., 2015). However, due to high

rates of mortality and morbidity with histocompatability locus matched but unrelated donors, this treatment is generally only implemented if a matching and related donor can be established (Park et al., 2019). When a transplant from a matched sibling donor is established prior to 14 years old, mortality has been found to be less than 10% (Porter 2018).

1.4 Background and Significance

1.41 Global Prevalence

Notably, some hemoglobinopathies may occur more frequently in specific populations and individuals of certain ethnic backgrounds. Hemoglobinopathies are common in specific regions of the world, generally in those situated along the equator. Carriers are thought to be present in higher frequencies within these regions due to the hypothesized heterozygote advantage that carriers have against malaria (Williams and Weatherall 2021). It is thought that because of the physiology of the changed red blood cells, the hemoglobin in individuals who are carriers is not as receptive to the growth of *P. falciparum*, the parasite responsible for malarial disease (Williams and Weatherall 2021). Countries where hemoglobinopathies are higher in prevalence are situated in the Mediterranean, Southeast Asia, Southern Asia, sub-Saharan Africa, Central and South America, the Caribbean, and the Pacific Islands. In Central and South America, these countries include El Salvador, Guatemala, the Dominican Republic, Brazil, Costa Rica, and Venezuela. More severe variants of alpha thalassemia are most common in many Southeast Asian countries, such as Vietnam, Cambodia, Laos, Thailand, and Malaysia (Goh et al., 2020). Carriers of a single alpha globin deletion are common in countries like Cyprus, which are located in the Mediterranean, as well as in parts of northern India and sub-Saharan countries (Ashiotis et al., 1973). Around 15% of the Cyprus population, for example, was found to be a carrier for a thalassemia, either beta or alpha (Bozkurt 2007). Beta thalassemia and sickle cell

disease are both found frequently in Southern India, parts of sub-Saharan Africa, and the Mediterranean including Bangladesh, Angola, Nigeria, Algeria, Libya, Sudan, Greece, and Italy (Wastnedge et al., 2018). As seen in the Globin Gene Server, the rarer variants found in *HBB* are named for the region in which they were found; a few examples of this include Hb Santa Ana, Hb F-Tokyo, Hb F-Oakland, and Hb Cork (Giardine et al., 2014). A more extensive list of these variants can be found in the Globin Gene Server (Giardine et al., 2014). The variety and number of countries that have high frequencies of hemoglobinopathies have large impacts within multi-cultural epicenters.

1.42 History and Moving Forward

During the 20th century, hemoglobinopathies were classified as rare diseases and often not the focus of research advancements in U.S. published or peer-reviewed literature. For example, from 1979 to 1989, a study regarding Colorado newborn screening only found 74 affected newborns after screening 528,711 individuals (Githens et al., 1990). As a result, hemoglobinopathies were not added to the nationwide Recommended Uniform Screening Panel until 2006 (Bender et al., 2021). Over time, it has become clearer that these hemoglobinopathies are, in fact, much more common than previously recognized. The prevalence of people who are carriers of hemoglobinopathies (at least one variant in *HBB*, *HBA1*, *or HBA2*) is often cited as around 7% of the world population (WHO 1989). Global carrier rates for hemoglobinopathies can be as high as 80% in specific regions of the world (e.g. alpha thalassemia in Papua New Guinea). In India, carrier rates are recorded to be as high as 15% in northern regions, with the average being around 4% of the population (Madan et al., 2010). In an 8-year study started in 2000, hemoglobinopathies were identified in 2,118 of 530,000 newborns screened in California, confirming their increasing prevalence within the U.S. due to increasing immigrant populations

(Michlitsch et al., 2009). Many research groups have cited the need to address the emerging number of patients with hemoglobinopathies, particularly regarding knowledge of clinical care. As discussed before, there are several countries globally that have high frequencies of hemoglobinopathy carriers. As people from these regions of the world immigrate to the U.S., a multi-cultural epicenter, the prevalence of hemoglobinopathies within the nation will increase as well (Boardmen et al., 2019).

1.5 Satisfaction of Care

A study evaluating the population-based screening effectiveness of 18,166 individuals, initiated by the Thalassemia Foundation, found well-established screening measures throughout West Bengal in eastern India, which greatly reduced morbidity and mortality rates (Chatterjee et al., 2015). Other countries also have robust screening programs in place to capture carrier status early in life, either in infancy or prior to marriage. Saudi Arabia's premarital screening program is an example of this, where researchers found hemoglobinopathy carrier status to be as high as 17%. A surprising majority, greater than 91% of the population studied, understood that the test would involve blood drawn and should involve both potential partners (Sulaiman et al., 2008). Saudi Arabia's educational program is akin to other screening programs in Southeast Asia, where hemoglobinopathy carrier rates are also high.

Cyprus's clinical care plans for thalassemia are a stark example of a thorough screening program with patient satisfaction in a high-prevalence country. As early as 1973, due to growing carrier rates as high as 15%, clinical care in Cyprus was altered to introduce an improved management plan for alpha and beta thalassemia. Researchers found that this change in rigor for management guidelines decreased the patient burden of the prevalent genetic condition (alpha thalassemia) and increased satisfaction of care (Ashiotis et al., 1973). In Rio de Janeiro, Brazil, a

screening program similar to the ones discussed previously was implemented to involve patients and families directly with comprehensive follow-up and detailed education about their child's needs. With their new screening implementation starting in 2000, they were able to track 2,314 children with hemoglobinopathies with only 4.4% of this population lost to follow-up (Castro Lobo et al., 2014). These different countries have found that implementation of robust carrier screening and well-managed clinical care helps reduce mortality and morbidity associated with hemoglobinopathies and improves patient perception of care quality.

About 1 in 7 people within the U.S. is foreign-born, meaning they were born overseas and immigrated to the U.S. (Straut-Eppsteiner 2021). Additionally, 1 in 8 people in the U.S. is native-born with at least one immigrant parent, contributing to a growing ethnically and culturally diverse population. A large proportion of this immigrant population originates from countries with high hemoglobinopathy carrier rates such as India, China, and the Philippines (American Immigration Council 2015). With growing immigrant rates in the U.S., hemoglobinopathies are also increasing in incidence nationwide, but unlike in other countries, large uncertainty remains regarding patient care or knowledge of these hemoglobinopathies, even among medical providers. A 2019 study by Radke et al. studied this uncertainty and found that for 76% of California-based providers surveyed, their patients with hemoglobinopathies did not have established care plans. They deduced that, due to growing immigrant populations and mixed ethnicity households, better identifiers beyond ethnicity were necessary to refer and care for these patients and families. These identifiers would include more thorough screening of clinical features, such as anemia, fatigue, and liver or spleen issues. This study focused specifically on provider perspectives regarding care. In other westernized countries with a comparable demographic and immigration rates, similar findings were discovered when focusing

on patients' perceptions of hemoglobinopathy care. In a study conducted in Australia, researchers found that there were large discrepancies when it came to genetic knowledge of hemoglobinopathies, the timing of discovery regarding carrier status, and information obtained by the patient (Cousens et al., 2013). In this particular study, timing of discovery regarding carrier status refers to population-based screening measures vs. prenatal carrier screening. Some European countries, such as Italy, have found ways to educate the growing population about hemoglobinopathies. As a direct result of increasing hemoglobinopathy rates, The Italian Society of Thalassemia and Hemoglobinopathies (SITE) implemented a cross-discipline approach in 2014 to foster collaboration amongst healthcare providers (Russo et al., 2019). Italy's ability to adapt to their increasing immigration rates with the implementation of the new hemoglobinopathy screening program demonstrates the importance of knowledge distribution for increasing patient satisfaction.

Many healthcare providers are unclear about the additional processes for diagnosing a hemoglobinopathy (Radke et al., 2019). Despite increasing immigration of populations with hemoglobinopathies, only 24% of U.S. based healthcare providers reported understanding the needs of their patients with thalassemia (Radke et al., 2019). This leaves patients with unresolved anemia or hemoglobinopathies feeling dissatisfied and receiving inadequate care, and because many of these individuals are from minority populations, further contributes to healthcare disparities.

Various studies suggest further investigation into the experiences and attitudes of these populations to better understand the pitfalls of hemoglobinopathy care in the U.S.. As Boardman et al. concluded in their 2020 paper, an exploration of patient experience, especially regarding cultural influence and stigma, is a necessary component for future research in advancing

hemoglobinopathy knowledge. Another study noted that more knowledge among both providers and patients is needed to implement effective screening and preventative programs for hemoglobinopathies (Kattamis et al., 2020). Other studies recommended exploring the knowledge of those with a carrier status for a hemoglobinopathy to help correct misunderstanding and guide future patient care (Cousens et al., 2013). For these reasons, this research will focus on patient perspectives in the U.S. in anticipation that these viewpoints will be significant in establishing more robust primary and clinical care.

1.6 Aims

This research project aims to evaluate gaps in the genetic knowledge of the general U.S. population concerning hemoglobinopathies and measure satisfaction with coordinated care within the hemoglobinopathy community. In conducting this research, it appears particularly important to analyze the data especially regarding preconception, pregnancy, and the newborn period, given the significance that a hemoglobinopathy diagnosis may have in family planning. Since it is important to know about a hemoglobinopathy diagnosis early in life, the survey seeks to estimate when individuals were diagnosed. Specifically, the survey will address the number of individuals diagnosed with anemia and the timeline of the anemia diagnosis in relation to their hemoglobinopathy diagnosis, if applicable. This will draw further insight into newborn screening efficacy and potential benefit of continued counseling and education.

In analysis of the data collected, this survey will also evaluate how demographic features of individuals are correlated with adverse or positive clinical experiences. A positive correlation between high educational level, personal relation to the healthcare industry, multiple family members affected by a hemoglobinopathy and cumulative score from the survey's knowledge section is hypothesized.

Information from the survey will provide additional insight into how patients with hemoglobinopathies in the U.S. perceive their quality of care, both at the time of initial diagnosis and any additional follow-up appointments. Part of the survey seeks to collect information about which providers are utilized by individuals with a hemoglobinopathy diagnosis. Building on this information, the survey will address whether a patient perceives providers as higher quality if the provider was available to them at the time of their initial diagnosis. This insight will help draw further conclusions about the relationship a patient with hemoglobinopathy may form with their care team. Quality of care during the initial diagnosis as compared to follow-up care will be analyzed to better evaluate the effectiveness of hemoglobinopathy care continuity in the U.S. On the same topic of nationwide care quality, while only patients residing in the U.S. were eligible to participate, the survey includes the option to discuss prior care overseas (if applicable) as compared to care received within the U.S. This may help to determine whether immigrant populations perceive differences in their clinical experience overseas or in-country care and may aid in creating standards of practice in future hemoglobinopathy care nationwide.

METHODS

2.1 Recruitment

Participants were invited to participate in an anonymous online survey generated through University of California Irvine's Qualtrics application. Recruitment was conducted online via different platforms including Twitter, Facebook groups (Sickle Cell Beta Thalassemia Disease and Sickle Cell & Thalassemia Trait), Reddit groups (r/thalassemia, r/sicklecell, r/anemic), National Society of Genetic Counselors email research distributions, Southern California Genetic Counselors conference forum, LinkedIn, and via a UCI Health email distribution. The survey and study flyer (Appendix B) were also distributed to patients with a history of anemia or a hemoglobinopathy who had genetic counseling at the UC Irvine Center for Fetal Evaluation. Patient support groups at the Thalassemia Center: UCSF Benioff Children's Hospital Oakland also received a copy of the flyer.

2.2 Participants

Eligibility for participation included any U.S. resident who was at least 18 years of age. Those who were younger than 18 or not residing in the U.S. were automatically disqualified from taking the survey. Additionally, those taking the survey were made aware that the survey was looking at experiences with anemia, which was defined symptomatically: dizziness, lightheadedness, weakness, or abdominal pain. However, individuals were eligible to participate regardless of a diagnosis of anemia or a hemoglobinopathy. The survey was only available in English; as such, the survey was limited to English-reading populations. Participants were not disqualified based on gender, educational or religious background, or ethnicity. Survey

participants from support groups were given the option to take the survey on paper and have their results scanned anonymously, but only online responses were received.

2.3 Informed Consent

Informed consent was provided at the beginning of the survey prior by selecting 'I agree' and completing the CAPTCHA, or Completely Automated Public Turing test to tell Computers and Humans Apart, to aid in differentiation between robots and humans. The informed consent page used was an IRB-approved templated page that discussed the purpose of the study, eligibility, and potential risks, discomforts, and benefits (Appendix C). Potential risks and discomforts described included the potential reminder of trauma experienced in clinical care and the possibility of breach of confidentiality. Participants were informed that information was encrypted on a password-protected personal device to reduce the latter risk and was built with few, if any, invasive questions to minimize the former discomfort. The described potential benefits included growing the understanding of hemoglobinopathy care, especially regarding clinical care and knowledge or use of screening protocols. Further, findings from this study may provide an update to genetic counseling-specific care guidelines. A more direct benefit to study participants was the opportunity to win one of ten $20 Visa gift cards through a separate linked survey (to maintain anonymity).

2.4 Survey

The survey (Appendix C) was formed using Qualtrics and accessed via a QR code or the anonymous survey link: https://uci.co1.qualtrics.com/jfe/form/SV_eG7gPIjHc6bA8n4. It was sectioned into three parts: demographics, knowledge, and clinical experience with display and skip logic present throughout the survey. This display and skip logic prompted certain

participants, depending on their answers to previous questions, to answer additional questions not displayed to other participants.

The survey consisted of 45 total questions (not including the CAPTCHA or instruction blocks) with nine "select all available" questions, 24 single-selection multiple choice questions, six fill-in questions, three dropdown select questions, and three Likert-scale questions. Of these, 14 questions were selection-based with a fill-in option and 28 were available only if the participant made a specific selection; four sections in the survey served as instructions or provided definitions that were not included in the consent page.

The demographic section totaled nine questions with one "select all available" question, five single-selection multiple choice questions, one fill-in question, and two dropdown select questions. Of these questions, three questions were selection-based with a fill-in option and two were available only if the participant made a specific selection.

The knowledge section totaled seven questions with four "select all available" questions and three single-selection multiple choice questions. Of these, one question was selection-based with a fill-in option. This section was based on previous research conducted by Dr. Felicity Boardman in a qualitative research study (Appendix D). There was no display or skip logic implemented in the knowledge section of the survey.

The experience section totaled 29 questions with four "select all available" questions, 16 single-selection multiple choice questions, five fill-in questions, one dropdown select question, and three Likert-scale questions. In the experience section, 10 questions were selection-based with a fill-in option and 26 were available only if the participant made a specific selection.

2.41 Survey Analysis

The data were analyzed through Statistical Package for Social Sciences (SPSS) software. Statistical significance was determined using a confidence interval of 95% and corresponding p-value of less than 0.05. In total, 123 participants began the survey, and of these participants, 4 participants completed more than half of the survey, and 92 participants completed the entire survey. If more than two groups were present for a demographic factor (e.g. age), the groups were recoded to best create equal-sized groupings for each variable, as described below, to allow for maximum statistical power.

Fisher's exact test was used to analyze differences across categorical variables, such as differences in knowledge scores across various demographic factors. When statistical analysis was not possible due to lack of power and small sample size, frequencies of dependent variables per independent variable were used to visualize data instead. Any free text answers that were considered relevant to the aims of the study are mentioned in the discussion section exclusively.

2.41.1 Demographics

Ethnicity in the survey was collected via a "select all that apply" question, as well as a free text option. Categories in the survey included Northern European, Southern European, Other European, Hispanic or Latino, Black or African American, Middle Eastern or North African, Central or East Asian, South Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Other. For data analysis, these were recoded as European (Northern, Southern, and Other), Hispanic or Latino, Black/African American/Middle Eastern/North African, Asian (Central, East, and South), Native or Indigenous (American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander), Other, and Two or More (two or more of the above categories were selected by the participant). Twelve individuals selected two or more

ethnicities and were removed from their original categories and recoded into this category. The original ethnicities and number of participants can be seen in Appendix F.

Original age categories were 18-24, 25-34, 35-44, 45-54, 55-64, and 64+, but were recoded as 18-24, 25-34, 35-44, and 45+.

For ease of reader interpretation and analysis, the categories for sex were recoded as only either “male” and “female”, with the one participant who selected “Assigned Female at Birth” recoded as “female”.

Education level of participants varied from high school level education to professional or doctorate degree level. Since the majority of survey participants were within the college level or above, this variable was recoded to provide larger sample sizes in three different groups. These new groups consisted of no college, some college, and more than college, where college was equivalent to a bachelor’s degree.

Relation to healthcare was a yes or no question and followed with display logic to ask for more specific information regarding this connection. A single individual reported “Clinical Lab Scientist”, which was recoded as “myself”.

2.41.2 Knowledge Scores

Knowledge scores were compared to demographic factors using Fisher’s exact tests or, if statistical analysis was not possible due to limited sample size or categorical variables, by frequency of passes/fails per variable category. With a value of one for each correct question, the maximum possible knowledge score was 7, and the lowest score was 0. For data analysis the knowledge scores were divided into two groups, the first group consisting of scores <5.00 points and the second group consisting of scores ≥ 5.00 points. These values were used since less than 5 points would mean that less than 71% of questions were answered correctly, indicating a

"failing" score within the knowledge section. Additionally, given that there were only 7 knowledge questions overall, if three or more questions were missed it was indicative that the respondent may not know enough about hemoglobinopathies to warrant a passing score.

2.41.3 Likert Scale Questions

Likert scale questions were analyzed regarding the participant's experiences during the initial appointment, follow-up appointment, and their experiences with the providers seen for their hemoglobinopathy care. A total of 19 individuals completed the Likert scale questions and rated their experiences.

Within the initial and follow-up appointment sections, 6 different statements were rated by each participant: "I understood my condition as it was explained to me", "I appreciated being seen by a genetic counselor", "My experience in clinic was helpful", "All of my questions were answered", "A plan for treatment of my condition was made clear to me", "I understood my condition was not my fault." Individuals rated the following statements on a 5-point scale where 1=Agree, 2=Somewhat Agree, 3=Neither Agree nor Disagree, 4=Somewhat Disagree, and 5=Disagree. Within the experiences with providers section, participants were requested to "Rate each of the following individuals regarding the quality of care with them for your hemoglobinopathy diagnosis." These providers included genetic counselor, general practitioner, obstetrician/gynecologist, hematologist, religious leader, nurse, and other provider (if applicable). Participants rated the providers on a 5-point scale where 1=Excellent, 2=Good, 3=Neutral, 4=Fair, and 5=Poor. Likert scale answers were viewed as frequencies on three histograms, one for each section of statements, since formal statistical analysis was not possible given the low sample size.

RESULTS

3.1 Sample Demographics

Ninety-two participants completed the survey, and their responses were used for data analysis. Participants were 84% (n=77) female and 16% (n=15) male. Of the total participants who completed the survey, 80% (n=74) were aged 18-44 years old. The age of the survey takers ranged from 18 to 64+ years old.

Table 1A: Demographics

Demographic characteristics of the study population, as a whole group and stratified by whether they passed or failed the knowledge assessment. Details on *specific ages at time of immigration and **relation to healthcare included in Table 1B. P-values calculated using Fisher exact test.

TABLE 1A: DEMOGRAPHICS				
Age Group (years)	**n=92**	**Pass (≥5.00)**	**Fail (<5.00)**	**p-value**
18-24	29	5	24	
25-34	28	6	22	
35-44	17	3	14	
45+	18	6	12	N/A
Birthplace*				
Inside U.S.	78	19	59	
Outside U.S.	14	1	13	0.289
Sex				
Male	15	1	14	
Female	77	19	58	0.177
Education Level				
No College	2	0	2	
Some College	43	4	39	
More than College	47	16	31	N/A
Ethnicities				
European	35	15	20	
Hispanic/Latino	7	0	7	
African American/Middle Eastern	7	1	6	
Asian	28	2	26	
Indigenous	1	0	1	N/A

Other	2	0	2	
Two or More	12	2	10	
Pregnancy History				
Never Been Pregnant	56	13	43	
Previously Pregnant	22	7	15	
Not Applicable	14	0	14	N/A
Relation to Healthcare**				
Yes	69	19	50	
No	23	1	22	0.02

Table 1B: Detailed Demographics

Extension of previous Table 1A shows *age at immigration for individuals not born inside the U.S. and **relationship to healthcare for participants and their family members

TABLE 1B: DETAILED DEMOGRAPHICS	
Age Arrived in U.S. (years)*	**n=14**
1	1
2	1
10	1
12	1
13	2
15	1
20	1
23	2
24	1
26	1
28	1
60	1
Specified Relation to Healthcare**	**n=69**
Myself	47
Family Member	15
Close Friend	5
Myself and Family Member	1
Significant Other and Family Member	1

Eighty-four participants, 91%, reported a bachelor's degree or greater as their highest educational level. There were two individuals (2%) who were in the “no college” category, 47%

of participants (n=43) reported “some college”, and 51% of participants (n=47) reported “more than college”.

When asked about pregnancy history, 61% (n=56) reported no previous pregnancies (never been pregnant), 24% (n=22) reported they were previously pregnant, and 15% (n=14) reported this was not applicable to them.

When asked about ethnicity, thirty-five participants were European. Seven individuals were Hispanic/Latino, and seven individuals were Black/African American/Middle Eastern/North African. Twenty-eight individuals were Asian, which includes Central or East Asian and South Asian. A small portion of individuals were Indigenous and Other, making up one and two participants, respectively. From these above categories, if an individual selected two or more ethnicities, they were counted as “Two or More”. Of these individuals, two reported Hispanic/Latino and Asian, two reported Asian and Black/African American/Middle Eastern/North African, three reported Asian and European, one reported Black/African American/Middle Eastern/North African and Hispanic/Latino, two reported Hispanic/Latino and European, one reported European and Black/African American/Middle Eastern/North African, and one reported European and Other (Caucasian).

Most survey takers were born within the U.S. at 85% (n=78), with a minority of 15% (n=14) born outside the U.S. These individuals arrived to the U.S. between the ages of 1-60 years old, with a majority arriving before the age of 30 years old, as depicted in Table 1B.

Seventy-five percent of participants (n=69) reported a personal connection to the healthcare industry, with 93% (n=64) of these individuals reporting that this connection was either themselves or a family member.

3.2 Knowledge Scores

Figure 2 below depicts the percentage of answer choices selected correctly or incorrectly by participants per each knowledge section question. In chronological order, these were: "12. A carrier of a hemoglobinopathy is someone who…, 13. Which is an example of a hemoglobinopathy?, 14. Who should be offered testing for a hemoglobinopathy?, 15. Which of the following is the most effective treatment for a hemoglobinopathy?, 16. Which of the following tests are commonly used for a hemoglobinopathy diagnosis:, 17. A CBC (Complete Blood Count) is…, 18. Carrier screening is…". All questions were "select all applicable" aside from questions 15, 17, and 18.

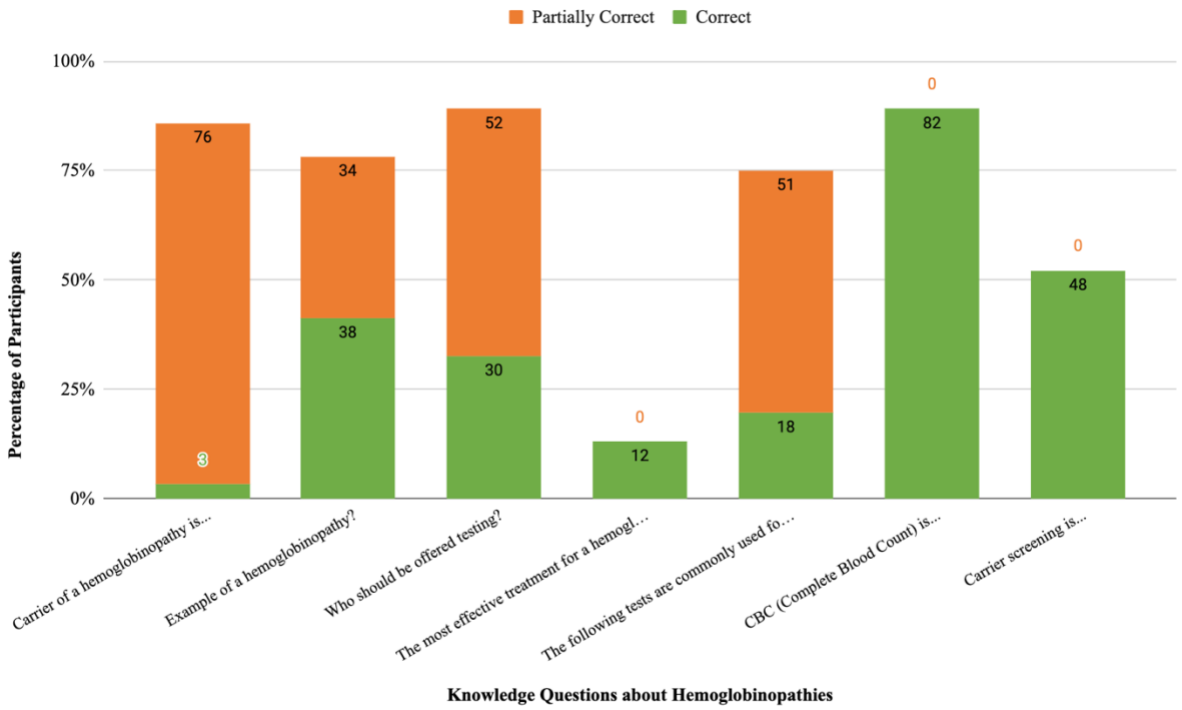

Figure 2: Individual Knowledge Question Scores

There were seven total questions that comprised the knowledge section of the survey. The questions are shown along the x-axis, with the percentage of 92 participants who answered the

question along the y-axis. Orange depicts the percentage of partially correct answers and green depicts the percentage of correct answers. Each bar is labeled with the count of individuals who had the correct answer (green) or partially correct answer (orange) for each question.

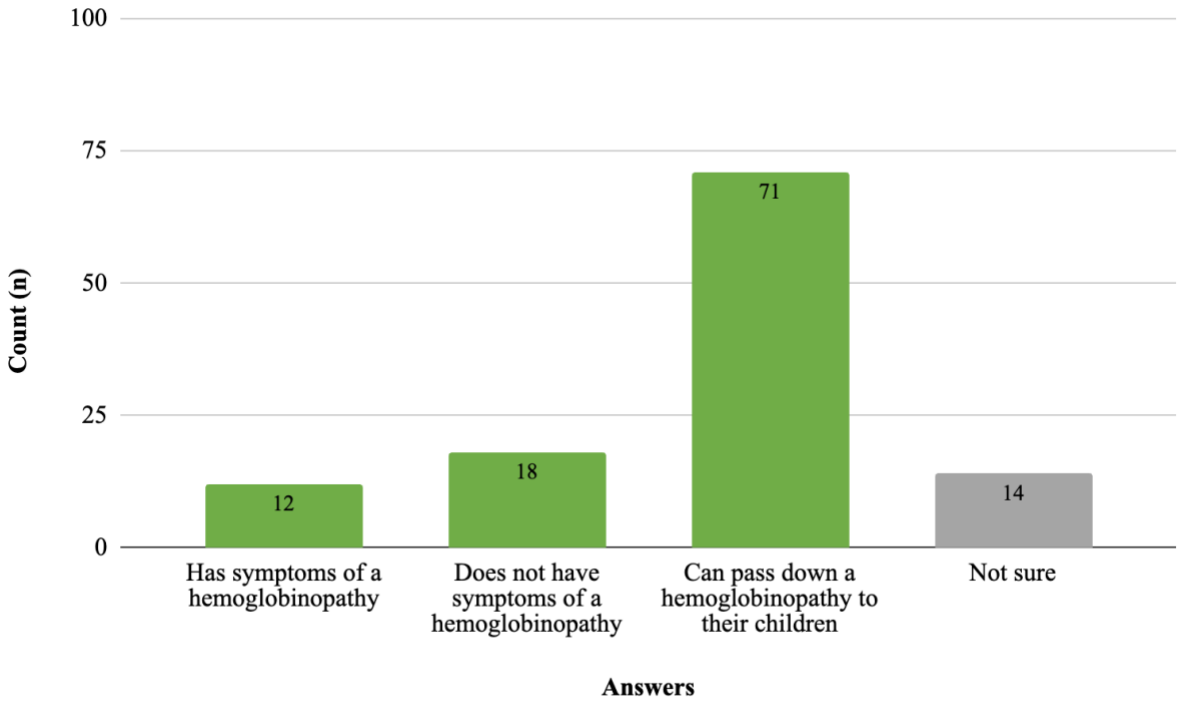

Figure 3A: Question 12. "A carrier of a hemoglobinopathy is someone who…"

Distribution of correct (green bars) and incorrect answers (gray bars) to question 12 from 92 total participants (count on the y-axis). Each bar is labeled with the count of individuals who passed (green) or failed (gray) within each selection. Answers were recorded as correct only if a participant selected all three green options, "has symptoms of a hemoglobinopathy, does not have symptoms of a hemoglobinopathy, and can pass down a hemoglobinopathy to their children". Partially correct answers were given a fraction of points out of one for every correct answer selected. (e.g. if only "can pass down a hemoglobinopathy to their children" a participant would have received 0.33 of a point).

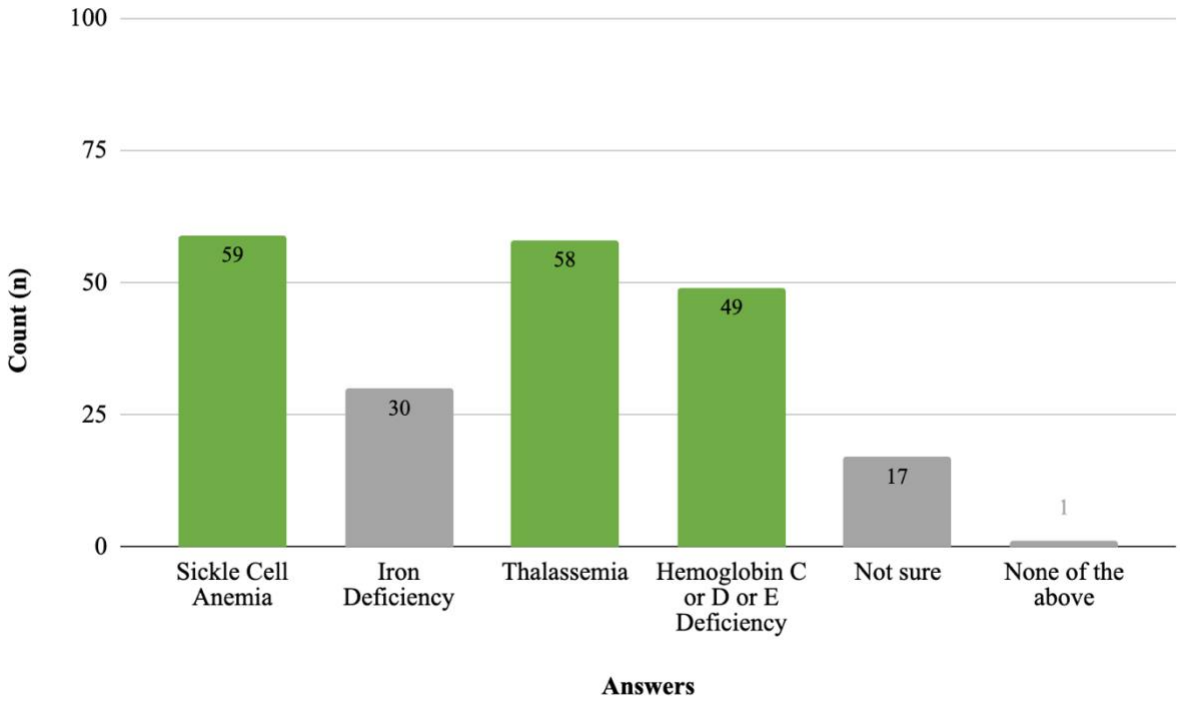

Figure 3B: Question 13. "Which is an example of a hemoglobinopathy?"

Distribution of correct (green bars) and incorrect answers (gray bars) to question 13 from 92 total participants (count on the y-axis). Each bar is labeled with the count of individuals who passed (green) or failed (gray) within each selection. Answers were recorded as correct only if a participant selected all three options, "Sickle Cell Anemia, Thalassemia, and Hemoglobin C or D or E Deficiency". Partially correct answers were given a fraction of points out of one for every correct answer selected. (e.g. if only "Sickle Cell Anemia" was selected, a participant would have received 0.33 of a point).

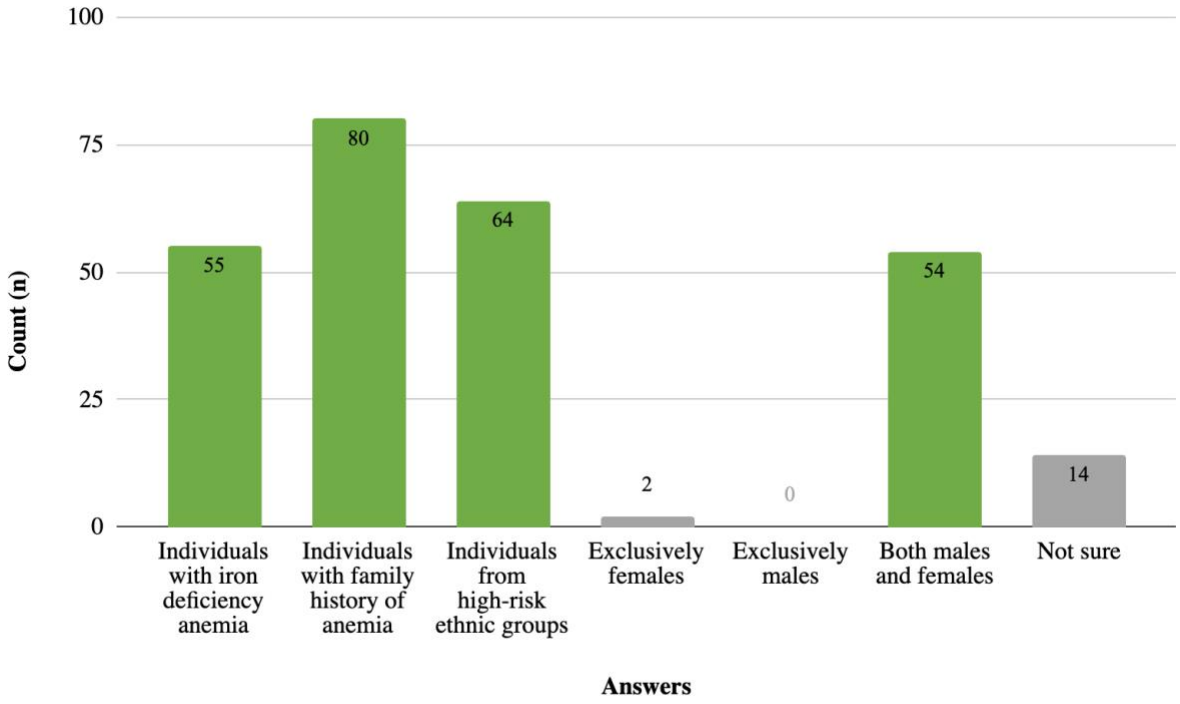

Figure 3C: Question 14. "Who should be offered testing for a hemoglobinopathy?"

Distribution of correct (green bars) and incorrect answers (gray bars) to question 14 from 92 total participants (count on the y-axis). Each bar is labeled with the count of individuals who passed (green) or failed (gray) within each selection. Answers were recorded as correct only if a participant selected all four options, "Individuals with iron deficiency anemia, Individuals with family history of anemia, Individuals from high-risk ethnic groups, and Both males and females". Partially correct answers were given a fraction of points out of one for every correct answer selected. (e.g. if only "Both males and females" was selected, a participant would have received 0.25 of a point).

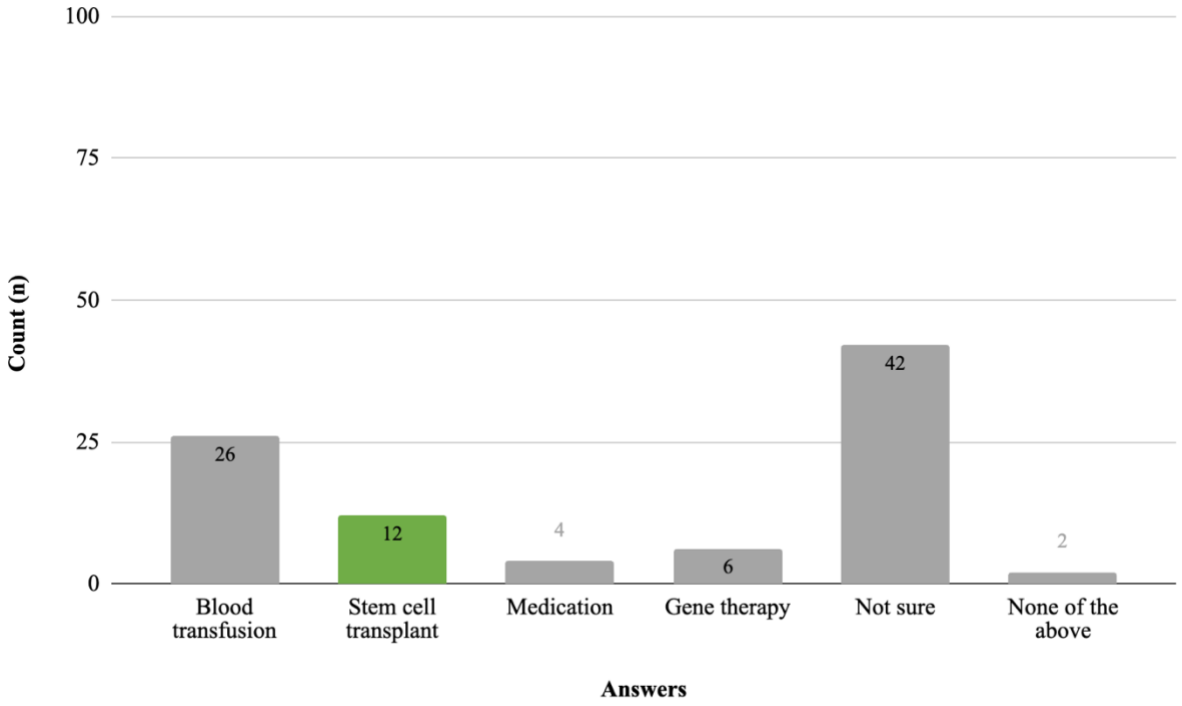

Figure 3D: Question 15. "Which of the following is the most effective treatment for a hemoglobinopathy?"

Distribution of correct (green bar) and incorrect answers (gray bars) to question 15 from 92 total participants (count on the y-axis). Each bar is labeled with the count of individuals who passed (green) or failed (gray) within each selection. Answers were recorded as correct only if a participant selected the correct option since this was a multiple-choice and not select all applicable question. If an individual selected any other answer, they were given a score of zero out of one for this question.

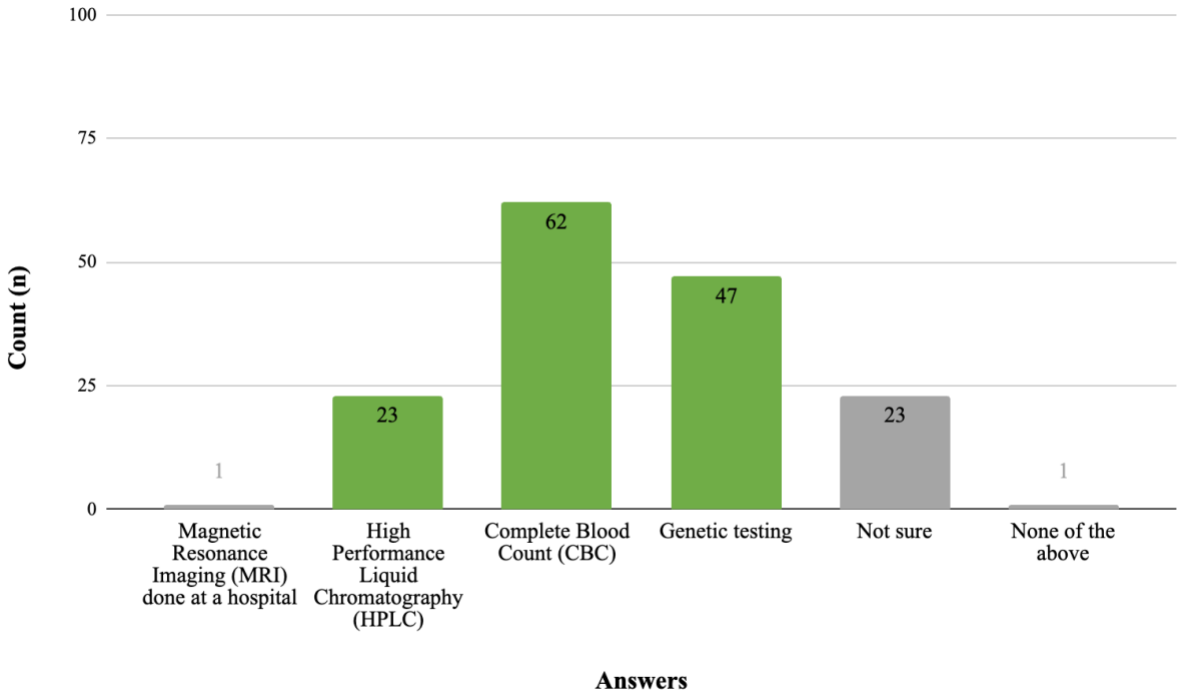

Figure 3E: Question 16. "Which of the following tests are commonly used for a hemoglobinopathy?"

Distribution of correct (green bars) and incorrect answers (gray bars) to question 16 from 92 total participants (count on the y-axis). Each bar is labeled with the count of individuals who passed (green) or failed (gray) within each selection. Answers were recorded as correct only if a participant selected all three correct options, "High Performance Liquid Chromatography (HPLC), Complete Blood Count (CBC), and Genetic testing". Partially correct answers were given a fraction of points out of one for every correct answer selected. (e.g. if only "genetic testing" was selected, a participant would have received 0.33 of a point).

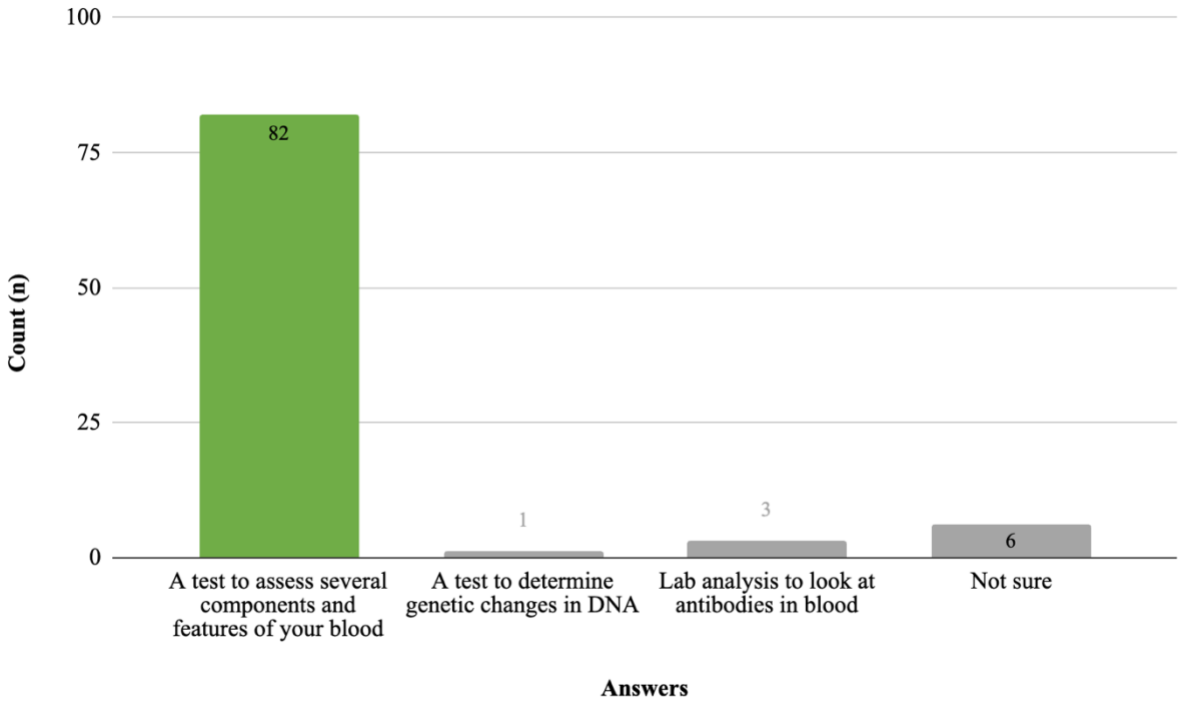

Figure 3F: Question 17. "A CBC (Complete Blood Count) is…"

Distribution of correct (green bars) and incorrect answers (gray bars) to question 17 from 92 total participants (count on the y-axis). Each bar is labeled with the count of individuals who passed (green) or failed (gray) within each selection. Answers were recorded as correct only if a participant selected the correct option, "A test to assess several components and features of your blood" since this was a multiple-choice and not select all applicable question. If an individual selected any other answer, they were given a score of zero out of one for this question.

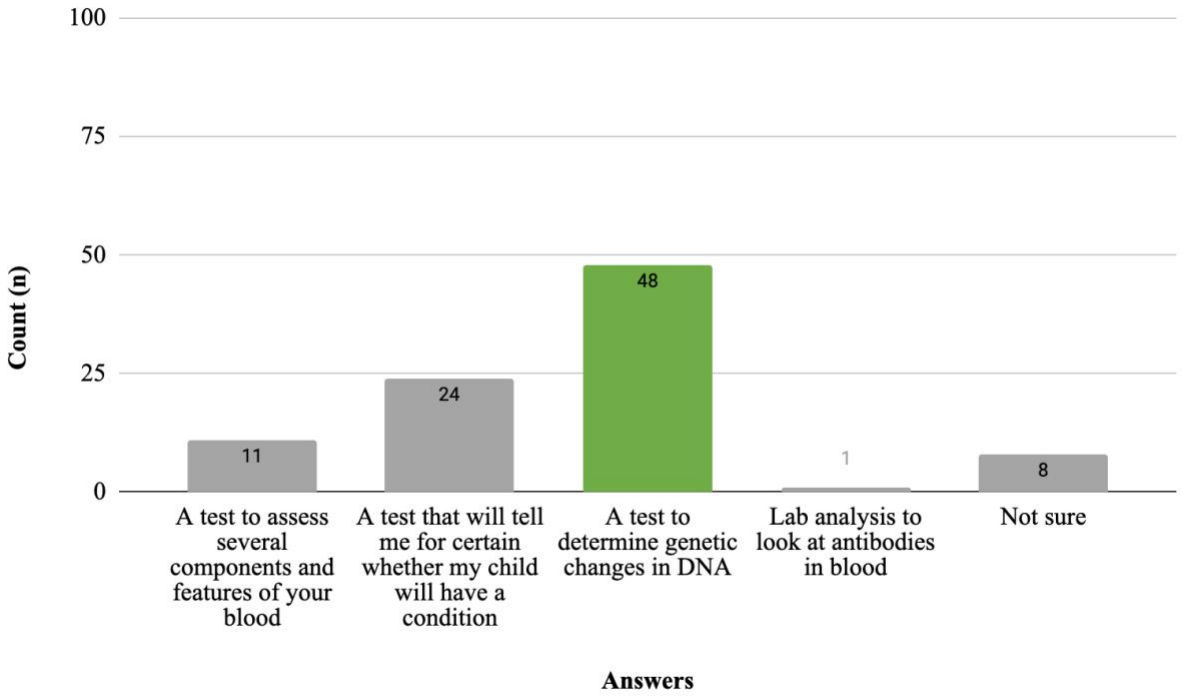

Figure 3G: Question 18. "Carrier screening is…"

Distribution of correct (green bars) and incorrect answers (gray bars) to question 18 from 92 total participants (count on the y-axis). Each bar is labeled with the count of individuals who passed (green) or failed (gray) within each selection. Answers were recorded as correct only if a participant selected the correct option, "A test to determine genetic changes in DNA" since this was a multiple-choice and not select all applicable question. If an individual selected any other answer, they were given a score of zero out of one for this question.

As mentioned previously, scores for each individual question were weighted evenly. Each participant taking the survey missed a portion of at least one question. In other words, there were no participants who had a full score of seven. The highest recorded score was 6.5, and was achieved by only one individual. Only a minority of individuals, 26% (n=24), had a passing score (defined as ≥5) in the knowledge section, and 74% individuals (n=68) did not have a passing score. As visible from Figure 3A question 12, "A carrier of a hemoglobinopathy is someone who…" was the most frequently missed question followed by question 15, "Which of the following is the most effective treatment for a hemoglobinopathy?" (Figure 3D). Question

17, “A CBC (Complete Blood Count) is…” was the most frequently correctly answered question.

3.21 Age

A majority of the participants (n=57) were 34 and under with the remaining participants 35 and older. There was not enough power given the small sample sizes to run statistical analysis, but Figure 4 displays the frequency of passing scores per age group. There appears to be a positive trend with more passing knowledge scores in the oldest age group, but this could not be assessed for statistical significance.

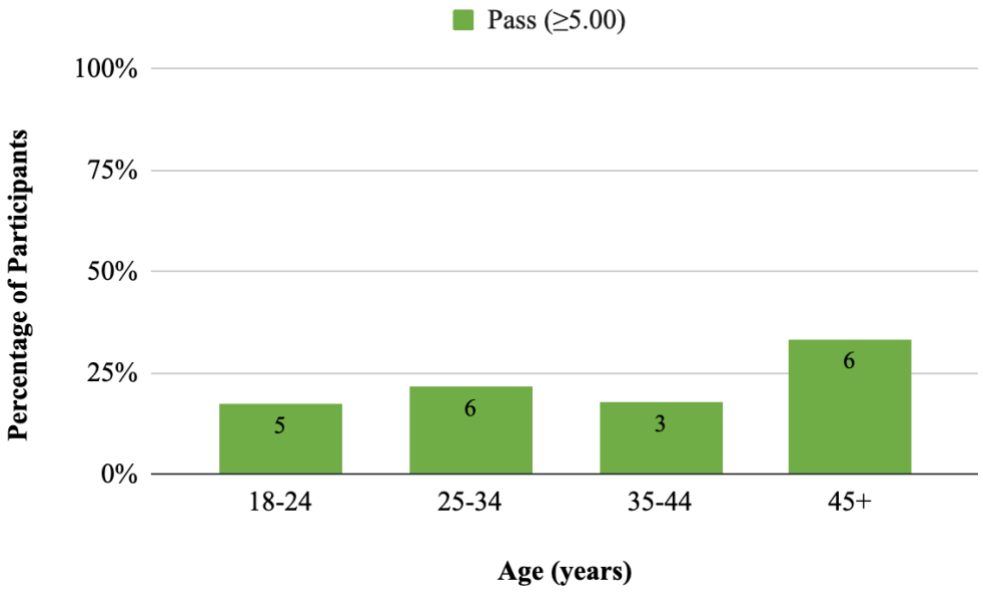

Figure 4: Distribution of Passing Knowledge Scores Across Age Groups

Green bars show the percentage of individuals who passed the knowledge section per age group (18-24, 25-34, 35-44, and 45+). Each bar is labeled with the count of individuals who passed in each category. Participants in the older age group appeared slightly more likely to pass.

3.22 Sex

A Fisher exact test was used to compare the knowledge scores between the sexes. As visible in Table 1a, there was not a statistically significant difference between the passing knowledge scores of either sex, potentially due to the small sample size of the male group (p=0.177). Females appeared to be more likely to pass when compared to the male group.

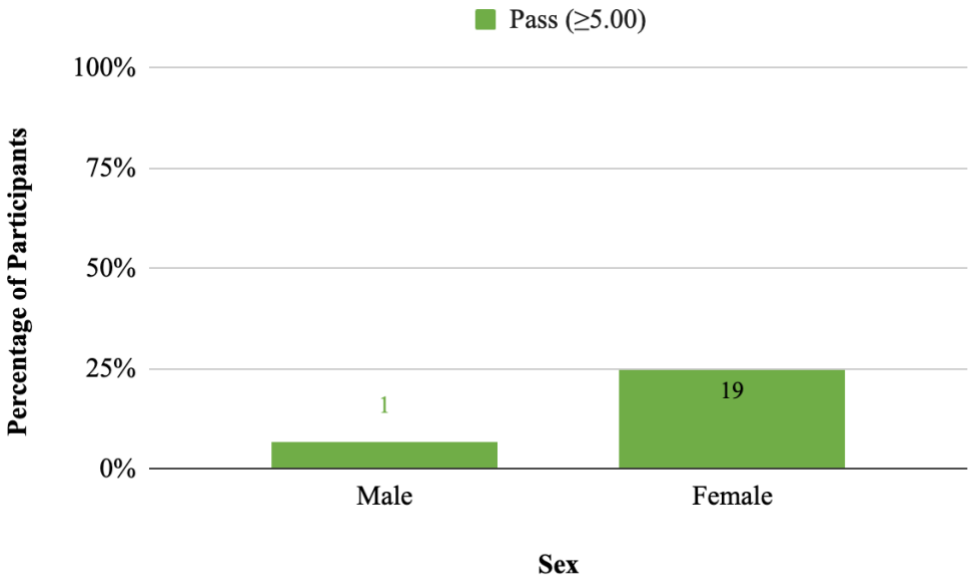

Figure 5: Passing Knowledge Scores Across Sexes

Green bars depict the percentage of individuals who passed the knowledge section per sex (male/female). Each bar is labeled with the count of individuals who passed in each category. There was no statistically significant difference in knowledge score between the sexes (p=0.177).

3.23 Education Level

Statistical analysis was not possible due to small sample sizes in the education categories. However, while not statistically significant, a trend can be seen in Figure 6, which indicates a positive trend of knowledge score with education level.

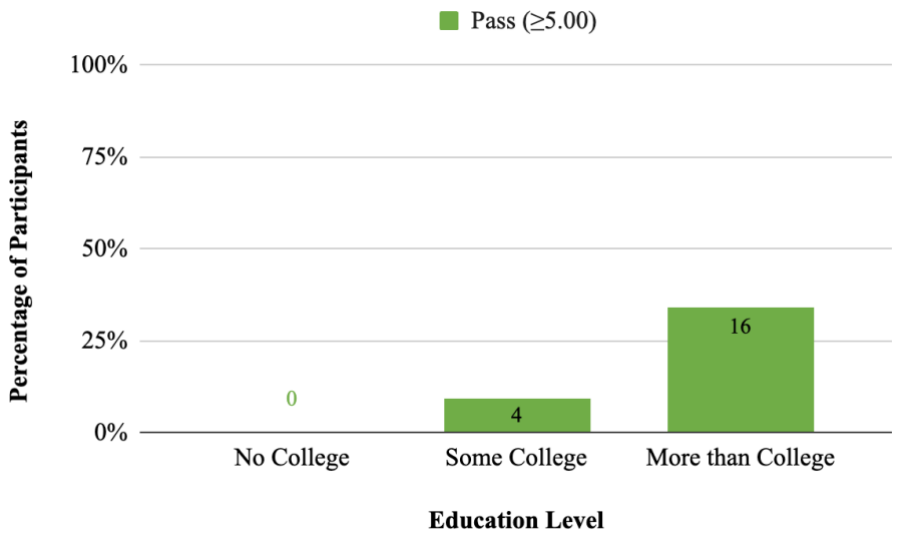

Figure 6: Distribution of Passing Knowledge Scores Across Education Levels

Green bars display percentage of passing knowledge score for each category of education: no college, some college, and more than college. Each bar is labeled with the count of individuals who passed in each category.

3.24 Ethnicity

Due to small sample size for some categories of ethnicity, they were recoded as listed in the methods section previously. Even by consolidating ethnicities into fewer categories to try to maximize statistical power, there was still insufficient power to assess for a statistically significant difference in passing knowledge scores between ethnicities. Figure 7 displays passing knowledge score counts for each ethnic group.

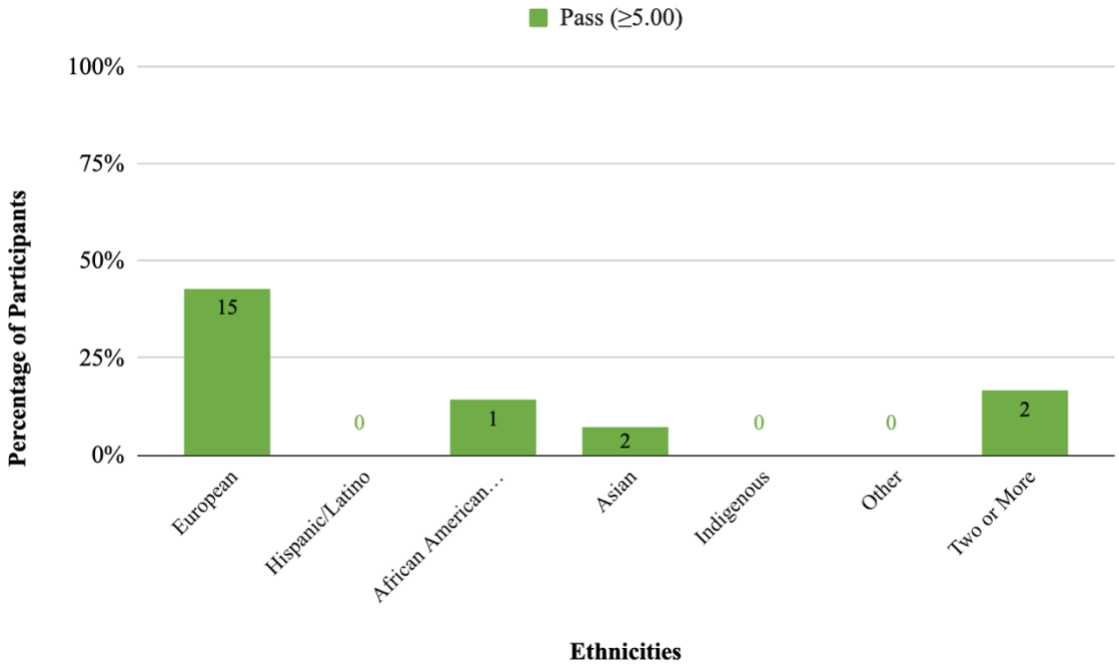

Figure 7: Distribution of Passing Knowledge Scores Across Ethnicities

Green bars show the percentage of individuals who passed the knowledge section per ethnic group (European, Hispanic/Latino, African, Asian, Indigenous, Other, and Two or More). Each bar is labeled with the count of individuals who passed in each category.

3.25 Relation to Healthcare

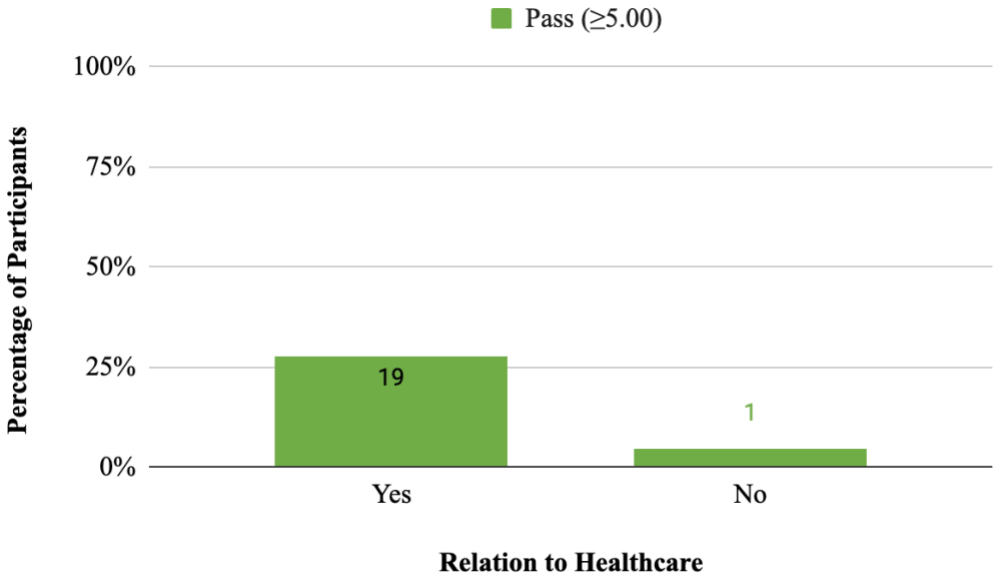

Figure 8: Distribution of Passing Knowledge Scores When Considering Participants' Relation with Healthcare

Green bars show the percentage of individuals who passed the knowledge section compared to relation to healthcare (Yes/No). Each bar is labeled with the count of individuals who passed in each category. Individuals with a connection to healthcare were significantly more likely to have a passing score (p=0.02)

Of the total participants who took the survey, a majority had some relation to the healthcare industry. Individuals with a relation to healthcare were significantly more likely to have a passing knowledge score than those without a relation to the healthcare industry (p=0.02).

3.26 Affected Family Members

Within the clinical experience section, a participant was given the option of reporting family members who are affected with a hemoglobinopathy or carriers of a hemoglobinopathy. No statistically significant difference was observed in passing knowledge scores between individuals with an affected family member and individuals without an affected family member. While not statistically significant, a trend was observed in a likelihood ratio such that when an individual had an affected family member, knowledge score was more likely to be passing (p=0.11). The visual representation of this can be seen in Figure 9.

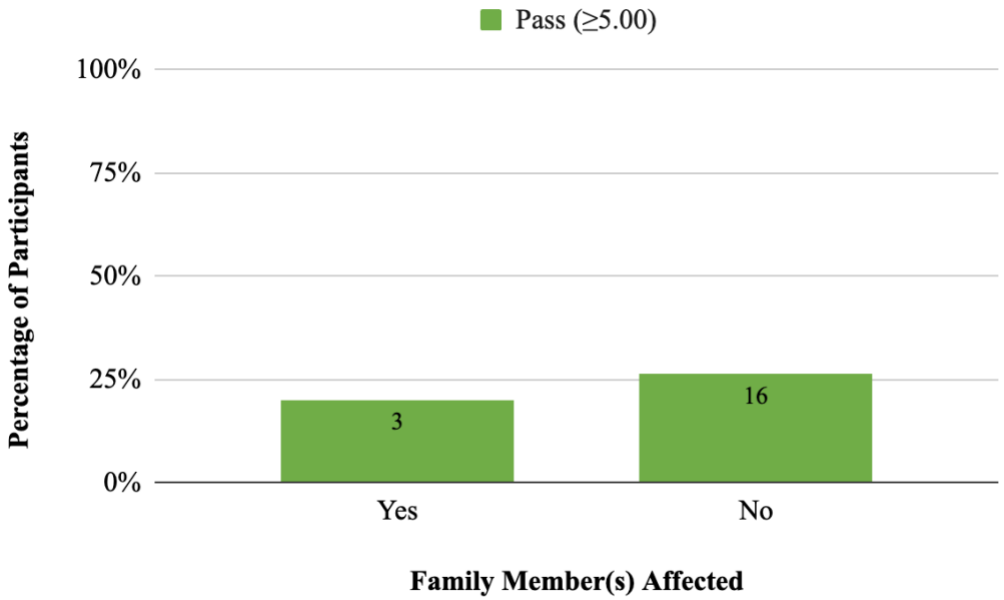

Figure 9: Distribution of Passing Knowledge Scores when Considering Participants' Affected Family Member(s)

Green bars show the percentage of individuals who passed the knowledge section compared to having one or more affected family members (Yes/No). Each bar is labeled with the count of individuals who passed in each category. There was no statistically significant difference in passing knowledge score between those with an affected family member and those without an affected family member (p=0.11).

3.3 Clinical Experiences

The clinical experiences section of the survey included several Likert scale questions as well as particular questions about an individual's specific anemia and hemoglobinopathy care. Due to display logic in the survey, a smaller subset of the 92 individuals were asked to complete the clinical experience section. For this reason, only 19 individual responses were recorded for the clinical experience section.

3.31 Anemia Diagnosis

Table 2A: Anemia Experience

Answers to the clinical experience section of the survey, which directly asked about a participant's experience with an anemia diagnosis.

TABLE 2A: ANEMIA EXPERIENCE		
Question	**Answers**	**n**
Diagnosed with anemia?		**n=92**
	Yes	54
	No	38
Context of diagnosis?		**n=54**
	Routine doctor's visit	32
	Pregnancy-related visit	7
	Genetic carrier screening	5
	Medical encounter for symptoms	20
	Newborn screening	2
	Blood donation	7
	Cannot remember	2
	Other*	3
Received care outside U.S.?		**n=54**
	Yes*	6
	No	48
Difference in care perceived?		**n=6**
	Yes*	3
	No	2
	Not sure	1
Underlying cause determined?		**n=54**
	Yes	39
	No	12
	Not sure	3
Underlying cause?		**n=42**
	Hemoglobinopathy	13
	Iron deficiency	20
	Other*	9
Further testing done?*		**n=54**
	Yes	21
	No	27
	Not Sure	6

Treatment required?		**n=6**
	Yes	5
	No	1
Iron supplement prescribed?		**n=5**
	Yes	3
	No	2
Iron prescription resolved anemia?		**n=3**
	Yes	2
	Not sure	1

Table 2B: Detailed Anemia Experience Part One

Free text answers to the clinical experience section of the survey, which directly asked about a participant's experience with an anemia diagnosis.

TABLE 2B: DETAILED ANEMIA EXPERIENCE PART ONE	
Context of Anemia Diagnosis? Other	**Type of further testing done**
"Routine visits and March 2021 collapsed and was hospitalized for low blood count, followed up with iron transfusions at the OC blood and cancer center to stabilize my levels."	"alpha thalassemia"
"Miscarriage"	"don't remember what test ordered"
"Post-COVID"	"electrophoresis"
Underlying cause? Other	"endoscope and colonoscopy"
"blood loss"	"ferritin levels"
"celiac disease"	"ferritin levels + other tests (not sure which)"
"I am a long distance runner and grew anemic (iron deficiency) while running. It lasted for 6 years and then one day I decided to take Vitamin D and all of a sudden my iron started going up."	"genetic test"
"Lack of iron absorption and B12 due to gastric ulcer and loss of iron due to heavy menstruation"	"genetic testing"

"on separate occasion iron deficiency and hemoglobinopathy"	"hemoglobin electrophoresis"
"platelet dysfunction leading to too much blood loss during menses"	"hgb elextrophoresis"
	"iron studies, hemoglobin electrophoresis with hemoglobin A2 and F"
	"not sure what it was"
	"not sure which tests were performed but platelet dysfunction was discovered"
	"started seeing a hematologist"
	"thalassemia"
	"ttg iga blood test"
	"WGS as part of a research study then qualitative assay to determine symptoms as a carrier"

Table 2C: Detailed Anemia Experience Part Two

Free text answers to the clinical experience section of the survey asking about care received outside of the U.S.

TABLE 2C: DETAILED ANEMIA EXPERIENCE PART TWO	
Care outside U.S.? Yes	**Difference in care perceived? Yes**
"Argentina"	
"Canada"	"Different way of testing and testing for more, ex) coming in couple days before transfusion, doing more labs"
"Cyprus"	"In Cyprus, thalassemia is very well known and there is established, government-funded, widespread premarital and prenatal genetic testing. I found that doctors were more familiar with the condition and how it should be treated. In the US I've had very many doctors that have no idea what it is or how to treat it"
"Egypt"	"Outside US: only PO iron Inside US: IV iron"
"Germany Air Force Base"	
"India"	

3.32 Hemoglobinopathy Diagnosis

Table 3A: Hemoglobinopathy Experience
Answers to the clinical experience section of the survey, which directly asked about a participant's experience with a hemoglobinopathy diagnosis.

TABLE 3A: HEMOGLOBINOPATHY EXPERIENCE		
Question	**Answers**	**n**
Diagnosed with hemoglobinopathy?		**n=92**
	Yes	19
	No	70
	Not sure*	3
Condition/trait?		**n=19**
	Beta thalassemia	7
	Alpha thalassemia	4
	Sickle cell anemia	2
	Other*	6
When diagnosed relative to iron deficiency?		**n=15**
	Prior to	5
	At same time	4
	After	6
Context of diagnosis?		**n=15**
	Routine doctor's visit	1
	Pregnancy-related visit	4
	Genetic carrier screening	6
	Medical encounter for symptoms	4
	Newborn screening	0
	Blood donation	0
	Cannot remember	2
	Other*	2
Told hemoglobin or red blood cell levels were low?		**n=15**
	Yes	13
	No	2
Family member is a carrier or diagnosed with hemoglobinopathy?		**n=92**
	Yes	15
	No	61
	Not sure*	16
Currently undergoing treatment?		**n=19**

	Yes	7
	No	12
Current treatment?*		**n=9**
	HSCT	0
	Medication	3
	Blood transfusions	4
	Other	2
How often do you receive blood transfusions as part of treatment?		**n=6**
	Frequently (i.e. several times a year)	4
	Never	2
Religion influence treatment choice?		**n=19**
	Yes	0
	No	15
	Not sure	0
	I do not identify with a religion	4
	Other	0

Table 3B: Detailed Hemoglobinopathy Experience

Free text answers to the clinical experience section of the survey, which directly asked about a participant's experience with a hemoglobinopathy diagnosis.

TABLE 3B: DETAILED HEMOGLOBINOPATHY EXPERIENCE	
Context of hemoglobinopathy diagnosis? Other	**Family member diagnosed? Not sure**
"Ashkenazi panel during pregnancy"	"it was never mentioned by family members; the specificity of their anemia; it just runs in the family"
"Visited hematologist after getting abnormal CBC results on other visit"	"Family never got tested"
Condition or trait? Other	"I do not have a relationship with extended family"
"Black fan diamond anemia"	"I don't think anyone has it that I know of"
"G6PD deficiency"	"I don't know, family haven't been tested"
"Hemoglobin e trait deficiency"	"i think some family members are anemic but i'm not sure of any specific diagnosis or carrier screening"

"Hereditary Spherocytosis"	"Immediate family members are not carriers, but unsure if extended family (aunts/uncles/cousins) are or are not"
"thalassemia - not sure beta or alpha"	"Maybe"
"Thalassemia minor"	"My family does have Anemia, but I don't know them close enough"
Diagnosed with hemoglobinopathy? "Not sure"	"My family has not been tested for this to my knowledge"
"I was tested for sickle cell anemia, it was mandatory to play a sport at my university but I am not sure what tests determine hemoglobinopathy"	"My mother is Anemic but it isn't sickle cell."
"My anemia is mild I wasn't sure if that counted."	"My parents died early. I do not know much regarding my family medical history."
"on separate occasion iron deficiency and hemoglobinopathy"	"Never came up"
"Thals/Alpha"	"Not sure what it is"
"thelsemia"	"note sure"
Current treatment?	"Uncertain on family history"
"Chelation"	
"desferasirox"	
"Hydroxyurea"	
"Celiac disease, gluten free diet resolve iron deficiency anemia"	
"Ferrous sulphate"	

A small percentage of the overall participant population reported a hemoglobinopathy diagnosis, 21% (n=19) (Table 3A). There was a fairly equal representation of the more common hemoglobinopathies with seven individuals reporting beta thalassemia, four individuals reporting alpha thalassemia, and two individuals reporting sickle cell anemia. Within the "other" category, two individuals reported unknown thalassemia, and one individual reported a hemoglobin C or E deficiency. Notably, no individuals reported the context of their hemoglobinopathy diagnosis as newborn screening or blood donation. Many individuals did not report a family member with a hemoglobinopathy, although some reported uncertainty about this, which can be seen in Table

3a. Less than half of the 19 individuals reported currently undergoing treatment (n=7). Of the individuals who reported undergoing treatment, none reported a religion influencing their treatment choice (those not undergoing treatment were not asked this question).

3.32.1 Hemoglobinopathy Diagnosis Relative to Anemia Diagnosis

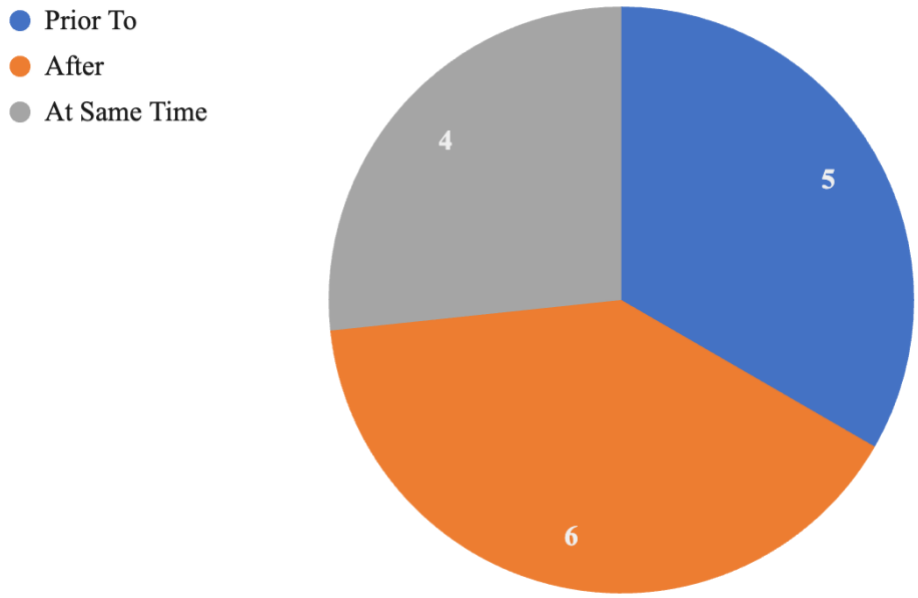

Figure 10: Diagnosis of Hemoglobinopathy Relative to Anemia Diagnosis

Pie chart showing breakdown of participants' hemoglobinopathy diagnosis relative to anemia. There were four individuals who were diagnosed with a hemoglobinopathy prior to their diagnosis of anemia, five individuals who were diagnosed at the same time, and six individuals who were diagnosed after their anemia diagnosis.

Individuals were asked about the timing of their hemoglobinopathy diagnosis relative to their diagnosis of anemia, if applicable. The intended purpose of this question was to better characterize the stepwise diagnosis process for hemoglobinopathies. Since diagnosis of a hemoglobinopathy often, but not always, follows a diagnosis of microcytic anemia first, it was expected that more individuals would be diagnosed with a hemoglobinopathy after a diagnosis of anemia. Five individuals (33%) were diagnosed with a hemoglobinopathy prior to an anemia

diagnosis, four individuals (27%) were diagnosed with a hemoglobinopathy and anemia at the same time, and six individuals (40%) were diagnosed with a hemoglobinopathy after an anemia diagnosis (Figure 10).

3.33 Initial, Follow-Up Appointment, and Providers Comparisons

Likert scale analysis was utilized to best assess satisfaction of hemoglobinopathy care among those who reported a hemoglobinopathy diagnosis.

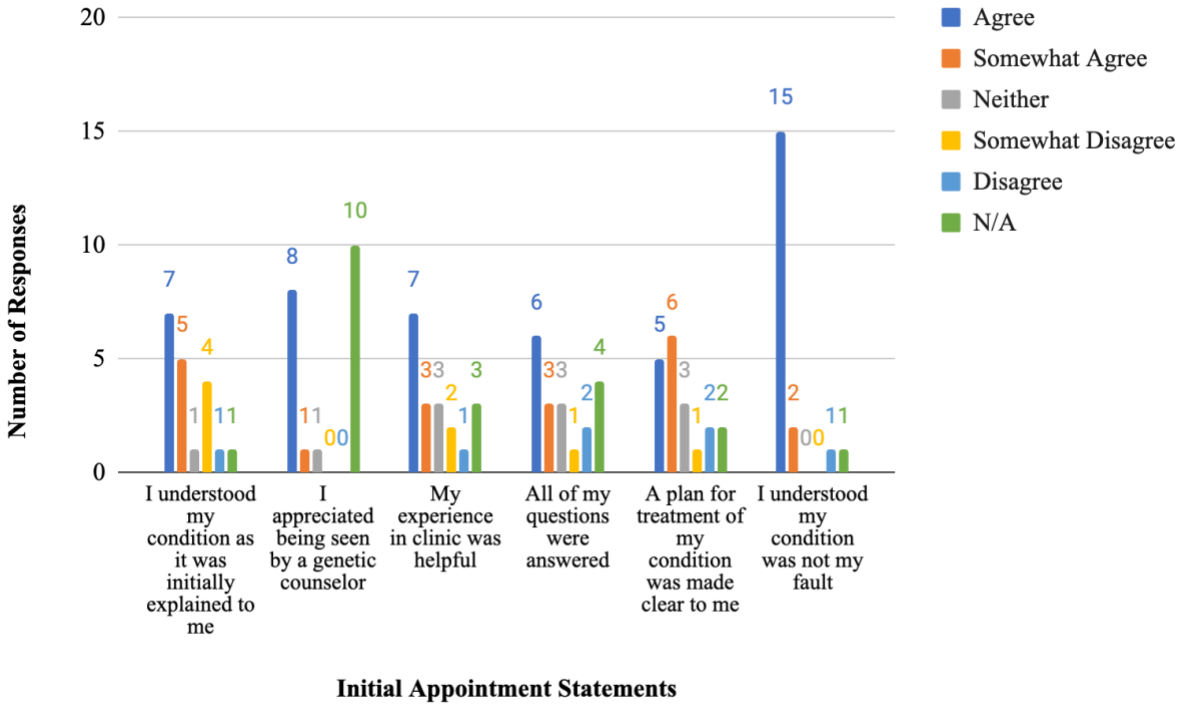

Figure 11: Satisfaction Measured from Initial Appointment Experience

This chart shows the number of responses for each selection (ranging from Agree to Disagree, left to right, followed by not applicable) for each statement about their initial appointment for a hemoglobinopathy diagnosis. In total, 19 participants completed this section of statements.

Participants were asked to rate, on a 5-point scale from Agree to Disagree, their satisfaction of care received at their initial appointment for hemoglobinopathy care. Notably, a majority of participants reported not applicable for a genetic counseling interaction (n=10),

indicating that they were not seen by a genetic counselor for their initial and/or follow-up appointments. Importantly, the satisfaction of care trended positively, with more individuals reporting that they agree or somewhat agree with each statement. For the statement, "I understood my condition was not my fault" most participants selected "agree" for both initial (n=15) and follow-up (n=12) appointments.

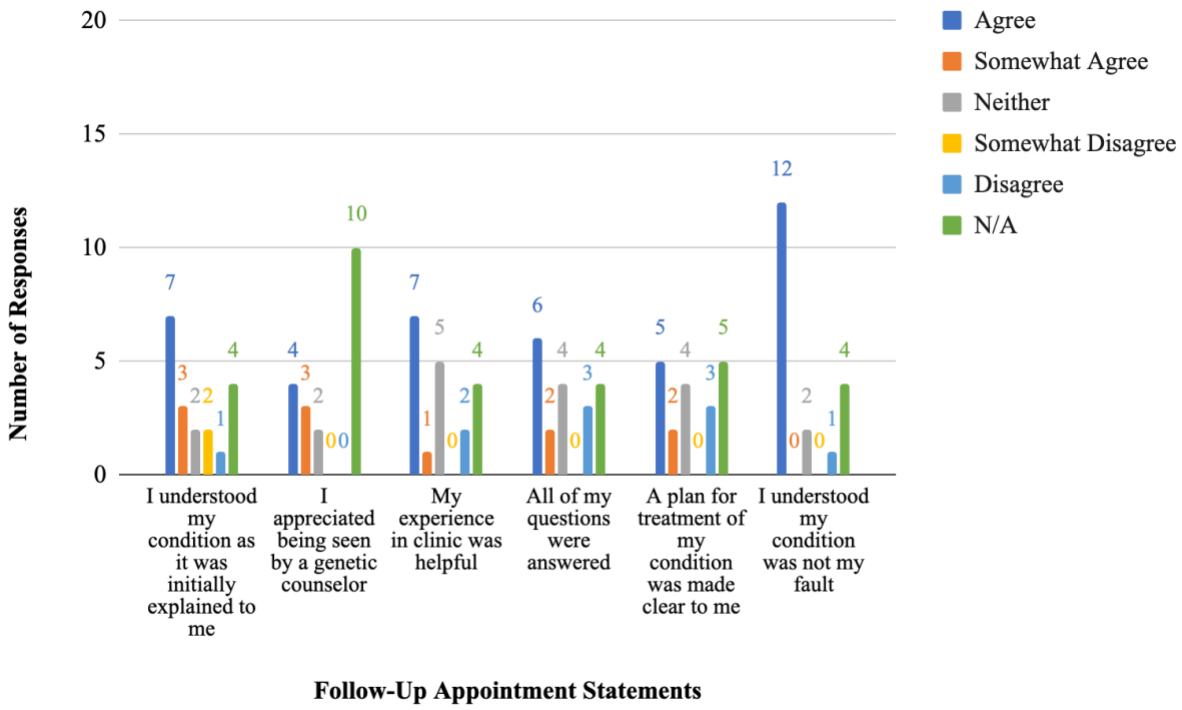

Figure 12: Degree of Satisfaction of Follow-Up Appointment Experience

This chart shows the number of each selection (ranging from Agree to Disagree, left to right, followed by not applicable) for each statement. In total, 19 participants completed this section of statements.

3.34 Providers Involved in Care

Participants were asked to rate the hemoglobinopathy care received from their providers on a scale from Excellent to Poor with the option to select "not applicable". While determining statistical significance was not possible due to an underpowered sample, data from this portion of

the survey is displayed in Figure 13. Notably, most participants reported “not applicable” for care/services from a genetic counselor (n=10), indicating that they were not seen by a genetic counselor for their care. Importantly, most participants reported “not applicable” for several other providers as well, including hematology (Figure 13). Most notably, a majority of participants (n=17) selected not applicable for religious leaders.

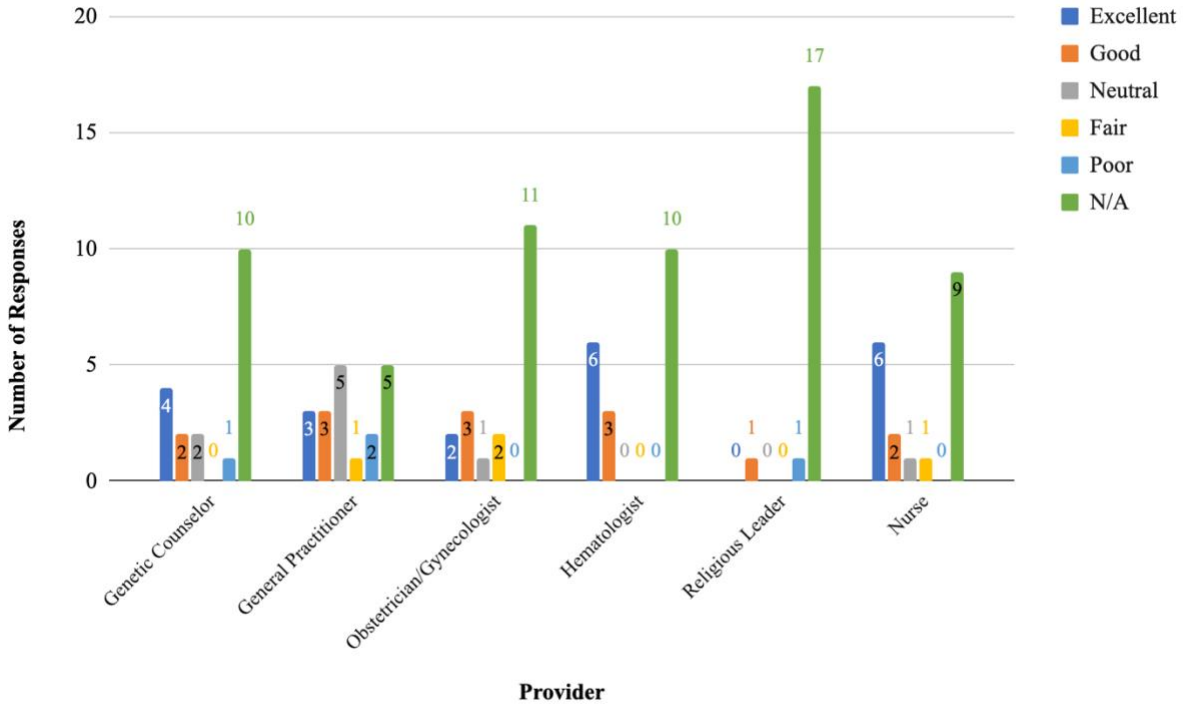

Figure 13: Degree of Satisfaction with Providers

This chart shows the number of each selection (ranging from Excellent to Poor, left to right, followed by not applicable) for each provider. In total, 19 participants completed this section of statements.

DISCUSSION

There is large variability in hemoglobinopathy care and knowledge across the general population. Previous studies in westernized countries outside of the U.S. have demonstrated that variability in management can make a hemoglobinopathy diagnosis daunting, difficult, and stressful for patients in these settings (Cousens et al., 2013 and Russo et al., 2019). However, there are limited studies within the nation that address the patient experience and satisfaction with treatment and care for hemoglobinopathies. For this reason, this study aimed to: 1. Evaluate the gaps in genetic knowledge of both carriers and individuals affected by hemoglobinopathy as well as their family members and 2. Measure satisfaction with coordinated care by individuals affected by hemoglobinopathies, especially in terms of treatment options and preconception planning. To do so, the following research questions were explored in detail: Is there a difference in level of satisfaction between patients who received care outside of the U.S. and those who received care inside the U.S.? How does quality of care during initial diagnosis compare with quality of care in follow-up appointments? Which individuals are involved in the care of patients with hemoglobinopathies? Do a patient's religious beliefs influence specific treatment choices/options? Does education level or relation to someone in the healthcare industry correlate with knowledge score? Are the number of affected family members associated with a higher individual knowledge score? Which demographic features are most associated with negative clinical experiences amongst individuals with hemoglobinopathies? Are individuals more likely to be diagnosed with a hemoglobinopathy after an iron deficiency anemia diagnosis?

4.1 Notable Findings

Although numbers were small, findings from this study illuminate some shared experiences among participants. Primarily, individuals who experienced hemoglobinopathy care outside of the U.S. reported quality care in these countries, but not necessarily within the U.S.. An overwhelming number of participants, regardless of where they received care, had low knowledge scores. They shared a wide range of free text responses about complicated diagnostic odysseys, variable care received, and treatment regimen. These survey results illustrated a lack of understanding of hemoglobinopathies and anemia, especially in terms of treatment and established standards of care. Interestingly, this appears to extend beyond the general population, as a majority of the individuals who completed the survey had some relation to healthcare. Many of the participants reported that they did not receive genetic counseling as part of their care, which is notable as hemoglobinopathies are most well understood in the context of such appointments (Boardman et al., 2019).

4.2 Clinical Experiences

4.21 Differences in Care Inside or Outside U.S.

Individuals were asked about differences in their care received if some of their care was received outside of the U.S. Three individuals from Egypt, Canada, and Cyprus, respectively, reported a difference in this care: “Outside US: only PO iron Inside US: IV iron”, “Different way of testing”, and, most striking,

> “[In] Cyprus, thalassemia is very well known and there is established, government-funded, widespread premarital and prenatal genetic testing. I found that doctors were more familiar with the condition and how it should be treated. In the US I’ve had very many doctors that have no idea what it is or how to treat it”.

Cyprus established screening for hemoglobinopathies as early as 1973 to combat growing carrier rates in their population. A study in 1973 found that this did address patient satisfaction appropriately and decreased the burden of the genetic condition in the country (Ashiotis et al., 1973). However, patient experiences in Cyprus have not been previously studied in comparison to hemoglobinopathy care within the U.S. The above participant's anecdotal report of the lack of knowledge in U.S. healthcare regarding hemoglobinopathies, especially in terms of treatment is, therefore, crucial in understanding the quality of hemoglobinopathy care in the U.S. If this individual's experience was representative of others, it would suggest that hemoglobinopathy care in the U.S. is not as detailed when compared to countries with a higher prevalence such as Cyprus.

4.22 Initial and Follow-Up Appointment Experiences

When asked about experiences at initial appointments and follow-up appointments for hemoglobinopathy care, participants' responses trended similarly in both Likert scale sections; if an individual rated their experience high at the initial appointment setting, they were more likely to rate their follow-up appointment experience well. Of course, the opposite correlation was true as well, with individuals rating their follow-up appointment low if their initial appointment at the time of their diagnosis was low. This has important implications for clinical care practice, where a patient often continues to visit the same clinic for ongoing care. This finding seems to suggest that the first interaction between healthcare provider and patient is essential in building sustained satisfaction of hemoglobinopathy care.

Interestingly, given the large number of failing knowledge scores within the participant pool, depth of knowledge after being given a diagnosis was not a significant indicator of a good or bad experience in clinic. This suggests that the first interaction during hemoglobinopathy

appointments is perhaps most memorable in terms of empathy and emotional support provided by the healthcare worker as opposed to knowledge about the hemoglobinopathy. Alternatively, this suggests that more work is necessary to establish and help patients retain initial hemoglobinopathy knowledge within care settings.

4.23 Providers Involved in Care

When asked about whether participants agreed with statements regarding their initial diagnosis, genetic counselors were frequently reported as "not applicable". This may indicate that genetic counselors were either not available at the time of the initial diagnosis or not sought out as a healthcare provider for initial hemoglobinopathy care. As mentioned previously by Boardman et al, when there is an abundance of information provided to the patient in initial appointments, this ultimately causes inadequate absorption of knowledge (Boardman et al., 2019). This could be an indication that having a genetic counselor present either at the initial or follow-up consultation for a hemoglobinopathy may be helpful for dissecting useful information and care management into a more digestible format.

4.24 Role of Religion in Care

Seven individuals reported that they received treatment for their hemoglobinopathy. Of these seven individuals, it is notable none reported that religion influenced their treatment choice. However, since individuals were only asked about a religion influencing their choice if they received treatment, if an individual was not undergoing treatment, it is possible this lack of treatment may have been influenced by religion. In other words, if an individual was one of the twelve individuals who either did not receive or opted against treatment this could have been part of a religious choice and the survey would not have assessed that.

4.3 Knowledge

Most participants had low scores in the knowledge section; in fact, the highest knowledge score was a 6.5 out of 7. Knowledge scores were calculated within each demographic characteristic, but trends proved difficult to analyze. Due to the small sample sizes of some demographic categories, data such as age, ethnicity, and education level required recoding but even consolidation to fewer categories left the study underpowered to analyze for statistically significant differences across groups. While not a statistically significant finding, it is notable that there was a higher frequency of passing knowledge scores with participants who were older and more educated, with 34% of individuals passing in the "more than college" category and 9% of individuals passing in the "some college" category. Additionally, as mentioned earlier, a trend was seen in passing knowledge scores for individuals with an affected family member. A statistically significant difference was found in passing knowledge scores between those who had a relation to healthcare and those who did not, with those in healthcare more frequently passing the knowledge section overall.

Pertinent information can be drawn from patterns observed from answers to individual knowledge questions. These answers may influence how information is provided to patients in hemoglobinopathy appointments. One of the most commonly missed questions was the first: "A carrier of a hemoglobinopathy is someone who…". Of the three answers, the "can pass down a hemoglobinopathy" answer was selected by a majority of the respondents, but importantly, this is not all-encompassing for a hemoglobinopathy carrier. A key point which distinguishes hemoglobinopathies from similarly inherited conditions is that this set has a wide range of carriers who can present with severe symptoms or no symptoms at all (Abdullah et al., 2020). Question fifteen, "Which of the following is the most effective treatment for a

hemoglobinopathy?" was similarly difficult for participants to answer, with only twelve individuals selecting “stem cell transplant” as the correct response. Historically, hemoglobinopathies do not fit into a “one size fits all” for treatment, so patient care is difficult to standardize. A majority of individuals selected “not sure” for this question, which follows previous research that treatment is variable per patient and symptoms. While there is not necessarily a standard for hemoglobinopathies, stem cell transplant (HSCTs) is considered the most effective treatment due to the ability to replace defective hemoglobin (Park et al., 2019). There were many incorrect answers throughout the survey, but the most correctly answered question was “A CBC (Complete Blood Count) is…”. Only ten of the ninety-two respondents answered an option other than “A test to assess several components and features of your blood”. The CBC is a more routine tests as compared to carrier screening or high performance liquid chromatography, which were both also featured in the knowledge section of the survey. Its more common application may mean that more individuals outside of the hemoglobinopathy community are familiar with the tests.

The findings of generally low knowledge scores amongst all participants may demonstrate that hemoglobinopathies and other genetic conditions are not adequately addressed prior to pregnancy screening. This was an idea put forth by Boardman et al., which found that previous studies in the UK had addressed screening among pregnant women but not in the general population (Boardman et al., 2019). Families with an affected member (either a carrier of a hemoglobinopathy or with a hemoglobinopathy diagnosis themselves) may be exposed to the information about these hemoglobinopathies earlier and in more detail, resulting in a more robust understanding of the condition. The older and educated population also trend a higher knowledge

score, which could be because when working in healthcare at least "some college" is typically a necessary prerequisite.

4.31 Knowledge of Anemia, Hemoglobinopathies, and other Blood Conditions

Several individuals discussed the underlying reason for their anemia in the survey. The variability in these responses is incredibly enlightening for healthcare professionals who may assume that anemia is solely isolated iron deficiency. In fact, multiple individuals who reported anemia had no indication of a hemoglobinopathy and instead had "Celiac disease", "platelet dysfunction leading to too much blood loss during menses", "blood loss", or a "Lack of iron absorption and B12 due to gastric ulcer and loss of iron due to heavy menstruation". Of these individuals, some free text responses, such as "G6PD deficiency", demonstrate that not all individuals who reported a hemoglobinopathy diagnosis truly did have a hemoglobinopathy. One response cited an unusual method of discovery coupled with a confusing additional component:

> "I am a long distance runner and grew anemic (iron deficiency) while running. It lasted for 6 years and then one day I decided to take Vitamin D and all of a sudden my iron started going up." -Participant

This response demonstrates an unclear understanding of the effects of vitamin D and source of anemia or iron levels. These responses are significant, especially given the explicit definitions of hemoglobinopathy and anemia provided in the survey. There were also more expected responses aligning with a hemoglobinopathy diagnosis, such as "Thals/Alpha", "thelsemia", and "on separate occasion iron deficiency and hemoglobinopathy" (Table 3B). Notably, a participant grossly misspelled thalassemia which may indicate a shallow understanding of the condition overall, a lack of resources and guidance from the clinic, or inversely an overload of information from the providers and clinics seen. One qualitative study addressing hemoglobinopathy experiences in the Netherlands found that many women

undergoing hemoglobinopathy screening found counseling to be overwhelming and reported that they could not adequately absorb all information (Holtkamp et al., 2018).

The context of participants' hemoglobinopathy diagnoses were similarly variable, although not quite as surprising. There were five individuals whose hemoglobinopathy was identified through a pregnancy-related visit, with two individuals receiving genetic carrier screening during this visit. Another four individuals received genetic carrier screening (but not through a pregnancy-related visit) and four reported receiving a diagnosis through a medical encounter for symptoms; of these groups, one individual reported that during this medical encounter, genetic carrier screening was ordered. Two individuals similarly reported their hemoglobinopathy was discovered through a routine doctor's visit. Interestingly, of the 19 individuals who answered this question, none were diagnosed via newborn screening or through blood donation processes, and two individuals could not remember their diagnosis setting.

None of the participants from the study reported being diagnosed through newborn screening. When the ages of several of the participants and the origins of newborn screening for hemoglobinopathies are considered, it follows that none of the participants would have known about their diagnosis through this early screening. It would be expected that at least some of the participants would have received screening for their hemoglobinopathy through the California Newborn Screening Program, which began screening for hemoglobinopathies in 1990 (Bender et al., 2021). However, hemoglobinopathy screening was not included in the Recommended Uniform Screening Panel until 2006 (Bender et al., 2021). This means that for a participant of this survey to have discovered a hemoglobinopathy through newborn screening, they would have to be born 2006 or later (or after 1990 in California), making them ineligible for the survey at sixteen years old. Even once newborn screening did include hemoglobinopathies as a

recommendation, a majority of states only screened for specific hemoglobinopathies, such as sickle cell disease or beta thalassemia. More recently, as reviewed earlier, many more states are screening for abnormal hemoglobin variants in addition to the more common hemoglobinopathies. California, for example, began screening for alpha and beta thalassemia, beta hemoglobin variants, and hereditary persistence of fetal hemoglobin as early as 1990 (ACMG 2006). Given that we did not assess where participants were born and that a majority of the survey participants were between the ages of 18-35, it is assumed that at least some individuals would have missed the window of time post-2006 when hemoglobinopathy diagnoses could be made at birth.

4.4 Sample Demographics

Participants were largely of European ancestry, female, below the age of 35 years old, and had a relation to healthcare. This ethnic demographic is somewhat consistent with the greater Orange County area, which is 69.7% European (U.S. Census Bureau 2020). Since the survey was released at least partially to the University of California, Irvine's healthcare workforce the fact that the ethnic demographic of the survey matched this area is significant. This survey's ethnic demographic is somewhat representative of the United States (75.8%) in terms of European background as well. However, when looking at sex of survey participants, the survey responses were skewed female, but this makes up only 50.4% of the population in Orange County, California, and the United States (U.S. Census Bureau 2020). Additionally, the majority of the survey participants had some relation to healthcare, which is essential in considering how hemoglobinopathy diagnosis and care may change with accessibility to routine physical check-ups. For example, individuals in the general population who are more regularly examined may be

more likely to receive a CBC test at their appointments. Thus, microcytic anemia that displays as a result of a hemoglobinopathy may be more easily identified and diagnosed in this population.

4.5 Limitations of the Study

This study had several limitations, with the most notable being small sample size. With only 92 participants completing the survey, it left some groups of categories too small to run tests to assess for statistical significance. Additionally, of these 92 participants, only 54 individuals had an anemia diagnosis, and 19 individuals had a hemoglobinopathy. To have enough statistical power to conduct analysis, around 250 participants would have been necessary. Additionally, the study was largely female, European, healthcare-focused, and younger, which is not generalizable to the population of hemoglobinopathy patients in the U.S. For this study to be more applicable to this subset of patients, a more diverse ethnic and educational background is necessary.

This survey also included several terms which could be complicated to an audience unfamiliar with hemoglobinopathies or healthcare. These terms include: hemoglobinopathy, anemia, high performance liquid chromatography, carrier, etc. While these terms were outlined and defined briefly throughout, given the complexity of hemoglobinopathies and anemia, these survey questions could have still provoked confusion in the reader or participants. For this reason, a substantial limitation of the survey is the convoluted nature of hemoglobinopathies.

Specifically, in the knowledge section, answers to Question 12: “A carrier of a hemoglobinopathy is someone who…”, were only considered correct if all options were selected. These included, “has symptoms of a hemoglobinopathy”, “does not have symptoms of a hemoglobinopathy”, and “can pass down a hemoglobinopathy to their children”. However, the resolute wording of these options meant that an individual may be dissuaded from selecting all

answers as correct. For this reason, if an individual selected only “can pass down a hemoglobinopathy to their children”, this should have been marked correct, and is thus a limitation of the study.

An additional related limitation could be the length and layout of the survey. At 47 questions, the survey was not brief and included free-text questions, Likert scales, and select all applicable questions which took additional time to answer. The combination of both the amount and style of questions included in the survey likely contributed to a lower completion rate overall with only 92 of 123 completing the survey.

4.6 Future Study Recommendations

Future studies could build on this data through more focused qualitative research on one type of hemoglobinopathy and patient experience surrounding it. Through this research more nuanced information may be obtained that cannot be generalized in a survey format. For example, the smaller group setting may allow participants to feel more comfortable disclosing clinical experiences and further clarification could be provided from the interviewer regarding definitions of hemoglobinopathies and anemias. Various centers focused on only sickle cell or only alpha or beta thalassemia may provide a more robust platform and specialized group settings for this qualitative research.

The population assessed in this survey largely consisted of individuals who had not received genetic counseling, as documented by the amount of “not applicable” selections in the Likert scale responses. With this information it may be possible to elucidate how genetic counseling, specifically, influences overall participant knowledge scores. Furthermore, this information could provide a better understanding of the role and relevance genetic counseling has within the hemoglobinopathy community. Healthcare providers and specialty clinics could

thus be informed about where to best allocate resources in their clinics more effectively for hemoglobinopathy care and patients.

Some information from this study was very focused on the hemoglobinopathy community. This is especially in terms of how care in the U.S. may differ from countries where carrier prevalence for hemoglobinopathies is more highly concentrated. For this reason, more information on how individuals from outside the U.S. were diagnosed and screened for their hemoglobinopathies could be helpful in adjusting future measures within the U.S. This future research could have direct implications on newborn, preconceptional, and prenatal screening for hemoglobinopathies.

4.7 Conclusion

The results of this study suggest that individuals in the hemoglobinopathy community, whether affected or related to those who are affected, may lack understanding of their condition and management. The free text responses suggest confusion about hemoglobinopathies as well, despite definitions of terms throughout the survey. This is likely, at least in part, due to a shortcoming of standardized hemoglobinopathy care in the U.S. combined with an increasing population of individuals with hemoglobinopathies. Immigrant populations are increasing from areas of the world where hemoglobinopathies are prevalent, so it will become more important for providers to recognize the need to screen some individuals with anemia for hemoglobinopathies, rather than assuming that all anemia is related to an iron deficiency.

This survey's findings suggest that more can be done to broaden the knowledge of the healthcare providers as well as patients in order to ultimately provide higher quality care to all within the hemoglobinopathy community. A majority of individuals who participated in this survey had some relation to healthcare, yet the maximum knowledge score obtained by a

participant still fell below the highest possible score of seven. Additionally, several individuals reported that they had not received care from a genetic counselor, which could contribute to the lower knowledge scores overall. This brings forth the idea that confusion may be inevitable until healthcare providers, including genetic counselors, are readily available and able to provide more sound and standardized care to patients with hemoglobinopathies and their family members.

Individuals with a history of clinical care outside of the U.S. provided valuable insight as to how the current state of hemoglobinopathy care could improve within the U.S. The increasing immigration rates of populations with high hemoglobinopathy carrier status is inevitable as the U.S. population continues to grow. Providing information about hemoglobinopathy care to healthcare providers in-training, especially obstetricians/gynecologists and hematologists, is an ideal foundation to grow a solid knowledge base for the entire community. Thus, hemoglobinopathies, with such a high and ever-increasing global disease burden, will be appropriately understood and care can be better implemented for future patients.

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APPENDIX A: IRB Exempt Letter

University of California, Irvine

Office of Research
160 Aldrich Hall
Irvine, CA 92697-7600

THE EXEMPT SELF DETERMINATION PROCESS

November 2021

To Whom it May Concern:

The Exempt Self-Determination Tool may be used to self-determine certain types of exempt research at UCI, including exempt research conducted through the Undergraduate Research Opportunities Program (UROP). Exceptions do apply. Please refer to the Exempt Self Determination Tool webpage on this topic. The Exempt Self-Determination Tool is initiated through Kuali Research Protocols (KRP**).**

As part the Exempt Self-Determination Tool process, UCI IRB review is not required and will not be provided. For studies that are submitted to the IRB where the Exempt Self-Determination Tool may be used instead, the study will be returned to the researcher to self-determine. In addition, amendments to studies that have undergone the self-determination process are to be maintained independently. No amendments should be submitted in KRP. Do submit an IRB Application if a change to the self-determined protocol results in the study no longer being eligible for self-determination. For exempt or expedited studies that require UCI IRB review, Lead Researchers must submit an IRB Application in KRP.

UROP students using the Exempt Self-Determination Tool in KRP to conduct exempt research should contact UROP for questions related to the use of the tool.

As part of using the Exempt Self-Determination Tool, Lead Researchers and Faculty Sponsors (as applicable) provide their assurance that they will follow relevant Human Research Protection Program (HRPP) policies and procedures, among other criteria. For a copy of the assurance, please review the following page.

If there are any questions, please contact HRPP Staff.

-The UCI HRPP

University of California, Irvine

Office of Research
160 Aldrich Hall
Irvine, CA 92697-7600

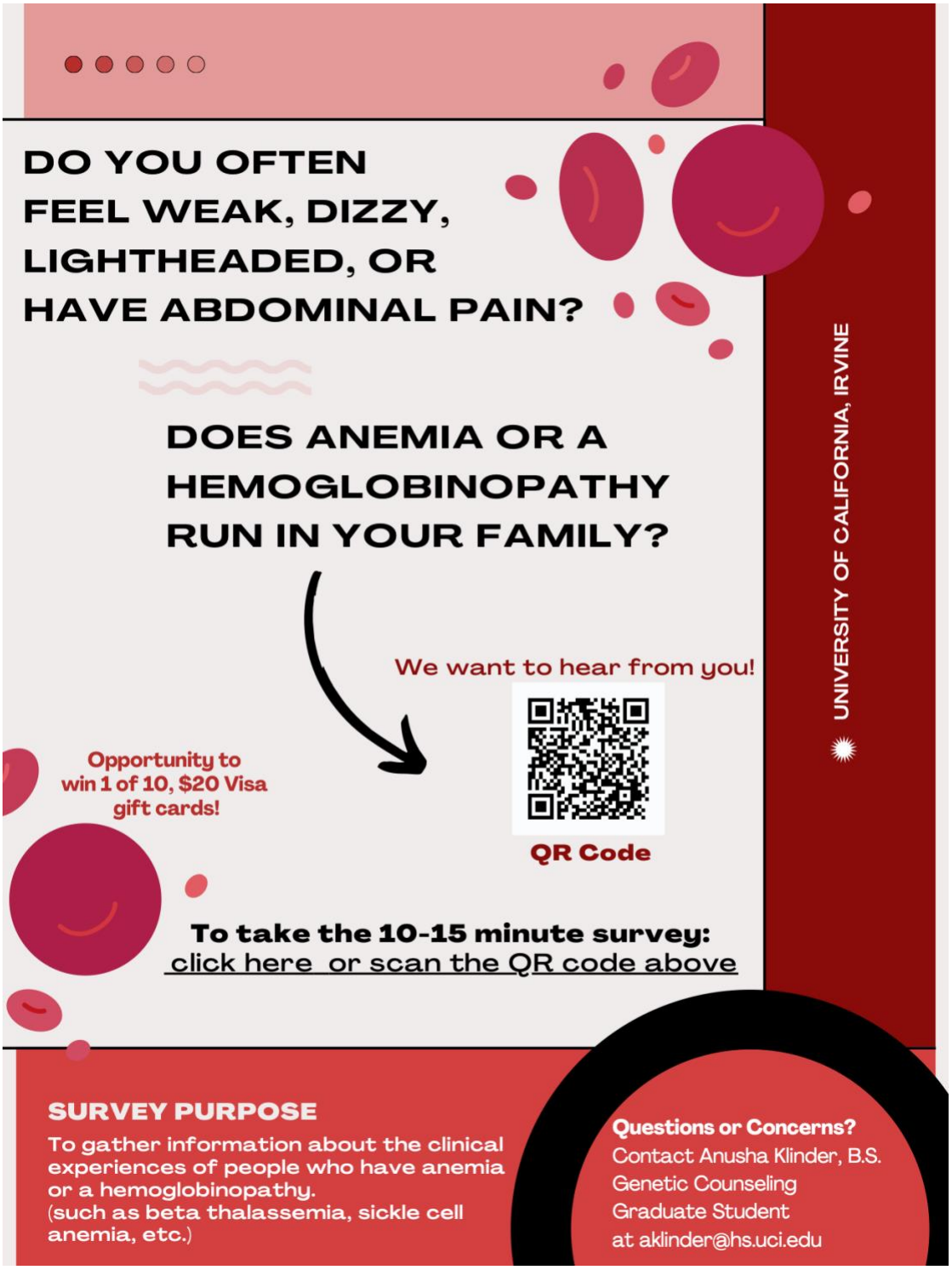
AS PART OF THE EXEMPT SELF DETERMINATION PROCESS AT UCI, THE LEAD RESEARCHER AND FACULTY SPONSOR (AS APPLICABLE) ASSURES THE FOLLOWING:

As Primary Lead Researcher and Faculty Sponsor, we have ultimate responsibility for the performance of this study, the protection of the rights and welfare of the human subjects, and applicable UCI policies, as well as state statutes for research involving human subjects.

I hereby assure the following:

1. The information provided in this application is accurate to the best of my knowledge.
2. The information provided in this application has been discussed and shared with my Department Chair. Any requests for changes based on this discussion are included in this application upon submission.
3. All named individuals on this project have read the procedures outlined in the protocol, are aware of and have reviewed relevant HRPP Policies and Procedures and understand their role on the study.
4. All named individuals on this project have completed the required electronic educational research tutorials and have been made aware of the "Common Rule" (45 CFR Part 46) and acknowledge the importance of the Belmont Principles - Respect for Persons, Beneficence and Justice in conducting research involving human participants. Also UCI has signed the Federalwide Assurance (FWA) that is available for review on the Human Research Protections (HRP) website.
5. Minor changes to the research that do not increase risk to participants, or significantly alter the study aims or procedures, such as the addition or removal of students researchers, do not require additional self-confirmation of exemption or approval from the IRB. Major changes that increase risk or constitute substantive revisions to the research including procedural changes will require a new self-confirmation of exemption or approval from the IRB.
6. When conducting research at a non-UCI location outside of California (but within the United States), Lead Researchers must comply with the requirements and policies of the location and State laws regarding human research procedures.
7. When collaborating with another entity (e.g., another UC, CHOC, CSUF, or a local school district), the collaborators who are engaged in human research activities are responsible for securing their own (non-UCI) IRB exemption/approval.
8. The Exempt Self-Determination, consent documents including recruitment materials and data collection materials will be maintained by the Lead Researcher or Faculty Sponsor for 10 years beyond the completion of the research. If you will cease your affiliation with UCI during this 10 year period and intend to transfer your identifiable data to a new institution, please notify your Faculty Sponsor and Department to determine whether this is permissible.
9. This research study is subject to routine monitoring by the Human Research Protections (HRP) unit of the Office of Research. Through the Education Quality and Improvement Program (EQUIP) program, HRP staff conduct periodic quality improvement monitoring and educational outreach.

APPENDIX B: Survey Flyer



APPENDIX C: Survey

Demographics

University of California, Irvine
Study Information Sheet

Clinical Experiences, Attitudes, and Genetic Knowledge within the Hemoglobinopathy Community

Lead Researcher

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Faculty Sponsor

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Please read the information below and ask questions about anything that you do not understand. A researcher listed above will be available to answer your questions.

Purpose: To gain insight into the experiences, attitudes, and genetic knowledge of individuals who are carriers or affected by hemoglobinopathies. We invite you to complete this anonymous survey regarding your understanding of hemoglobinopathies, your demographic background, and your experiences or attitudes within a clinic setting.

Participation in this anonymous survey is voluntary. You may refuse to participate or discontinue your involvement at any time without penalty or loss of benefits.

- Estimated time to complete the survey: 10-15 minutes

Anyone above the age of 18 and residing in the U.S. is eligible for this study regardless of hemoglobinopathy carrier or affected status.

Possible Risks/Discomforts: Potential reminder of trauma in clinical care previously experienced and potential breach of

confidentiality. To minimize risk, this study has been built to have minimally invasive questions, is intentionally concise, and information will be stored as anonymous and de-identified.

Potential Benefits: There are no direct benefits from participation in the study. However, this study may aid in understanding clinical care gaps for carrier screening and may provide a more comprehensive idea of who/which populations to offer hemoglobinopathy screening to and in which settings. Findings from this survey could help establish or update care guidelines within a genetic counseling setting or for other healthcare personnel.

Participants can voluntarily submit a valid email address to enter a drawing to win one of 10 available $20 Visa electronic gift cards. Your email address will not be connected to your survey response. You may submit your email address here or at the end of the survey. Email addresses will be assigned a number and a random number generator will be used to select the 10 winners. Electronic gift cards will be emailed to winners by June 2022. All email addresses collected will be destroyed after compensation is distributed.

Information Storage: All research data collected will be stored securely and confidentially. Information will be password protected and maintained in an encrypted format on the UCI/Qualtrics server.

Future Research Use: Researchers will use your information to conduct this study. Once the study is done using your information, we may share them with other researchers so they can use them for other studies in the future. We will not share your name or any other private identifiable information that would let the researchers know who you are. We will not ask you for additional permission to share this de-identified information.

Questions? If you have any comments, concerns, or questions regarding this study please contact the researchers listed at the top of this form. (Anusha Klinder: aklinder@hs.uci.edu or Katie Singh: kesingh@hs.uci.edu)

- If you have questions or concerns about your rights as a research participant, you can contact the UCI Institutional Review Board by phone, (949) 824-6662, by e-mail at IRB@research.uci.edu or at 160 Aldrich Hall, Irvine, CA 92697-7600.

What is an IRB? An Institutional Review Board (IRB) is a committee made up of scientists and non-scientists. The IRB's role is to protect the rights and welfare of human subjects involved in research. The IRB also assures that the research complies with applicable regulations, laws, and institutional policies.

If you would like to participate in this study, **are over the age of 18, and residing in the U.S.**, complete the verification below to start the survey.

- ○ I agree

Before continuing, please complete the verification below.

I'm not a robot reCAPTCHA Privacy - Terms

What is your age?

[ ]

Were you born in the U.S.?

- ○ Yes
- ○ No

At what age did you arrive in the U.S.?

[ ]

What is your sex?

- ○ Male
- ○ AMAB (Assigned Male at Birth)
- ○ Female
- ○ AFAB (Assigned Female at Birth)
- ○ Intersex
- ○ Prefer not to say
- ○ [ ] Other

Education level?

Which category/ies best describe your ethnicity?

(SELECT all applicable categories and FILL-IN specific countries of origin)

- ☐ Northern European (Denmark, Finland, Ireland, England, France etc.)
- ☐ Southern European (Albania, Andorra, Greece, Italy Portugal, Spain, etc.)
- ☐ Other European (Canada, Russia, etc.)
- ☐ Hispanic or Latino origin (Mexico or Mexican American, Puerto Rico, Cuba, Salvador, Dominican Republic, etc.)
- ☐ Black or African American (Jamaica, Haitian, Nigerian, Ethiopian, Somalian, etc.)
- ☐ Central or East Asian (China, Phillippines, Vietnam, Korea, Japan, etc.)
- ☐ South Asian (Pakistan, India, Nepal, Afghanistan, Sri Lanka, etc.)
- ☐ American Indian or Alaska Native (Navajo nation, Blackfeet tribe, Mayan, Aztec, Native Village or Barrow Inupiat Traditional Government, Nome Eskimo Community, etc.)
- ☐ Middle Eastern or North African (Lebanon, Iran, Egypt, Syria, Morocco, Algeria, etc.)
- ☐ Native Hawaiian or Other Pacific Islander (Native Hawaiian, Samoa, Chamorro, Tonga, Fiji, etc.)
- ☐ Other

What is your pregnancy history?

- ○ Currently Pregnant
- ○ Previously pregnant
- ○ Never been pregnant
- ○ Not applicable

Are you personally connected with anyone in the healthcare industry?

(yourself, your partner, family/close friend)

- ○ Yes
- ○ No

Who/what is your connection to the healthcare industry?

- ○ Myself
- ○ Family member
- ○ Close friend
- ○ [ ] Other, please specify

Knowledge of Hemoglobinopathies

The following questions are to better determine your understanding of genetic terms and conditions. Please answer to the best of your ability or choose "not sure".

A carrier of a hemoglobinopathy is someone who...
(select all applicable)

- ☐ Has symptoms of a hemoglobinopathy
- ☐ Does not have symptoms of a hemoglobinopathy
- ☐ Can pass down a hemoglobinopathy to their children
- ☐ Not sure

Which is an example of a hemoglobinopathy?
(select all applicable)

- ☐ Sickle Cell Anemia
- ☐ Iron Deficiency
- ☐ Thalassemia
- ☐ Hemoglobin C or D or E Deficiency
- ☐ Not sure
- ☐ None of the Above

Who should be offered testing for a hemoglobinopathy?

(select all applicable)

- [ ] Pregnant individuals
- [ ] Individuals with iron deficiency anemia
- [ ] Individuals with family history of anemia
- [ ] Individuals from high-risk ethnic groups
- [ ] Exclusively females
- [ ] Exclusively males
- [ ] Both males and females
- [ ] Not sure
- [ ] _____ Other

Which of the following is the most effective treatment for a hemoglobinopathy?

- ○ Blood transfusion
- ○ Stem cell transplant
- ○ Medication
- ○ Gene therapy
- ○ None of the above
- ○ Not sure

Which of the following tests are commonly used for a hemoglobinopathy diagnosis: (select all applicable)

- [ ] Magnetic Resonance Imaging (MRI) done at a hospital
- [ ] High Performance Liquid Chromatography (HPLC)
- [ ] Complete Blood Count (CBC)
- [ ] Genetic testing
- [ ] None of the above
- [ ] Not sure

A CBC (Complete Blood Count) is...

- ○ An imaging test using radiation
- ○ A test to determine genetic changes in DNA

- ○ Lab analysis to look at antibodies in blood
- ○ A test to assess several components and features of your blood
- ○ Not sure

Carrier screening is...

- ○ A test that will tell me for certain whether my child will have a condition
- ○ A test to determine genetic changes in DNA
- ○ Lab analysis to look at antibodies in blood
- ○ A test to assess several components and features of your blood
- ○ Not sure

Clinical Experiences

The next question asks about your personal experience with anemia. Anemia is "defined as a low number of red blood cells" or low levels of hemoglobin, where either one would meet the definition. (WebMD) "If you have anemia, your blood does not carry enough oxygen to the rest of your body" (MedlinePlus)

Have you ever been diagnosed with anemia?

- ○ Yes
- ○ No

In what context were you diagnosed with anemia?
(select all applicable)

- ☐ Routine doctor's visit
- ☐ Pregnancy-related visit
- ☐ Genetic carrier screening
- ☐ Medical encounter for symptoms
- ☐ Newborn screening
- ☐ Blood donation
- ☐ Cannot remember
- ☐ [ ] Other

Have you ever received care for your anemia outside of the U.S?

- ○ [ ] Yes (specify country below)
- ○ No

Did you perceive a difference in care inside of the U.S. or outside of the U.S.?

- ○ Yes
- ○ No
- ○ Not sure

How was your care different?

[ ]

Was the underlying cause of the anemia determined?

- ○ Yes
- ○ No
- ○ Not Sure

What was the underlying cause?

- ○ Hemoglobinopathy (beta-thalassemia, sickle cell anemia, trait, etc.)
- ○ Iron deficiency
- ○ Not sure
- ○ [ ] Other

Was further testing done? Please enter type of test if known.

- ○ [ ] Yes
- ○ No

- ○ Not Sure

Did your anemia require treatment?

- ○ Yes
- ○ No

Was an iron supplement prescribed as part of this treatment?

- ○ Yes
- ○ No

Did the prescribed iron resolve your iron deficiency?

- ○ Yes
- ○ No
- ○ Not sure

The next questions ask about a hemoglobinopathy. A hemoglobinopathy is "a group of disorders in which there is abnormal production or structure of the hemoglobin molecule" - MedlinePlus. (i.e. Beta-thalassemia, Alpha-thalassemia, Sickle Cell Anemia, Hemoglobin E deficiency, Delta-thalassemia, etc.)

Have you ever been diagnosed with a hemoglobinopathy or as a carrier of a hemoglobinopathy?

- ○ Yes
- ○ No
- ○ Not Sure

Please explain below why you selected "not sure" for the previous question

(Have you ever been diagnosed with a hemoglobinopathy or as a carrier of a hemoglobinopathy?)

Please select or enter the condition or trait:

- [ ] Beta-thalassemia
- [ ] Alpha-thalassemia
- [ ] Sickle cell anemia
- [ ] _____ Other Condition

When were you diagnosed with a hemoglobinopathy relative to your iron deficiency anemia diagnosis?

- ○ Prior to the iron deficiency diagnosis
- ○ At same time as the iron deficiency diagnosis
- ○ After the iron deficiency diagnosis

In what context were you diagnosed with **the hemoglobinopathy**?
(select all applicable)

- [ ] Routine doctor's visit
- [ ] Pregnancy-related visit
- [ ] Genetic carrier screening
- [ ] Medical encounter for symptoms
- [ ] Newborn screening
- [ ] Blood donation
- [ ] Cannot remember
- [ ] _____ Other

Were you told at any point that your hemoglobin levels or red blood cell counts were low?

- ○ Yes
- ○ No
- ○ Not sure

Do you have a family member who has been diagnosed with a hemoglobinopathy or as a carrier for a hemoglobinopathy?

- ○ Yes
- ○ No
- ○ Not sure

Please explain below why you selected "not sure" for the previous question

(Do you have a family member with a hemoglobinopathy or who is a carrier for a hemoglobinopathy?)

Please enter the condition and number of affected family members:

	Click to write Column 1 # of affected family members with Condition
Condition 1	
Condition 2	
Condition 3	

Are you currently undergoing treatment for your condition?

- ○ Yes
- ○ No
- ○ Not sure

Please select your current treatment(s) below:

- ☐ Hematopoietic Stem Cell Transplant (HSCT)
- ☐ Medication
- ☐ Blood Transfusions
- ☐ Other

How often do/did you receive blood transfusions as part of your treatment?

Would your religion influence your treatment choice?

- ○ Yes
- ○ No
- ○ Not sure
- ○ I do not identify with a religion
- ○ [ ] Other

If you are willing to share, please explain in which ways your religion would influence your treatment.

Rate the following statements regarding your clinical experiences at your **initial diagnosis of a hemoglobinopathy:**

	Agree	Somewhat Agree	Neither Agree nor Disagree	Somewhat Disagree	Disagree	Not Applicable
I understood my condition as it was initially explained to me	○	○	○	○	○	○
I appreciated being seen by a genetic counselor	○	○	○	○	○	○
My experience in clinic was helpful	○	○	○	○	○	○
All of my questions were answered	○	○	○	○	○	○
A plan for treatment of my condition was made clear to me	○	○	○	○	○	○
I understood my condition was not my fault	○	○	○	○	○	○

Rate the following statements regarding your clinical experiences at your **follow-up appointments:**

	Agree	Somewhat Agree	Neither Agree nor Disagree	Somewhat Disagree	Disagree	Not Applicable
I understood my condition as it was explained to me	○	○	○	○	○	○
I appreciated being seen by a genetic counselor	○	○	○	○	○	○
My experience in clinic was helpful	○	○	○	○	○	○
All of my questions were answered	○	○	○	○	○	○
A plan for treatment of my condition was made clear to me	○	○	○	○	○	○
I understood my condition was not my fault	○	○	○	○	○	○

Rate each of the following individuals regarding the quality of care with them for your hemoglobinopathy diagnosis.
Select "Not Applicable" for all individuals NOT involved in your care.

	Excellent	Good	Neutral	Fair	Poor	Not Applicable
Genetic Counselor	○	○	○	○	○	○
General Practitioner	○	○	○	○	○	○
Obstetrician/Gynecologist	○	○	○	○	○	○
Hematologist	○	○	○	○	○	○
Religious Leader	○	○	○	○	○	○
Nurse	○	○	○	○	○	○
Other Provider	○	○	○	○	○	○

How did you learn about this survey?

○ Support group

- ○ Social media
- ○ Healthcare provider/clinic
- ○ _____ Other

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APPENDIX D: Boardman et al., 2019 Survey

THALASSAEMIA SCREENING SURVEY (UK)

A survey of the views of families living with thalassaemia in the UK on the possibility of pre-conception/prenatal genetic screening

Dr. Felicity Boardman and Dr. Rachel Hale
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Thalassaemia Screening Survey (UK)

Welcome to the Thalassaemia Screening Survey (UK). This survey is part of a research project called 'Pre-conception genetic screening for conditions of uncertain or variable prognosis: social and ethical implications' (http://www.warwick.ac.uk/imagining_futures). This survey has been designed to explore the views of people living with thalassaemia (or who have a relative with the condition) towards the possibility of screening the population pre-conceptually (before a pregnancy is conceived) for thalassaemia. 'Screening' refers to the identification of thalassaemia in the whole UK population, not just within families already known to be affected by the condition. A screening programme would mean that people without a family history of thalassaemia would be offered the same opportunities to undergo pre-conception or prenatal genetic screening that are currently only offered to affected families.

Whilst the NHS Sickle Cell and Thalassaemia (SCT) screening programme, which offers genetic screening to all pregnant women and fathers-to-be (where antenatal screening shows the mother is a genetic carrier) was introduced in 2001 and all newborn babies (as part of the newborn blood spot screening programme) are screened in the UK, there is currently no newborn screening programme available to the general population that can detect thalassaemia.

Why is the study being done? At present, very little is known about how families currently living with genetic conditions such as thalassaemia feel about the possibility of a pre-conception or newborn genetic screening programme. This survey is designed to address this gap in understanding. The outcome of this survey will be submitted to any screening policy reviews for thalassaemia screening carried out by the UK National Screening Committee (the advisory body to government on issues related to screening). To develop this survey, 15 in-depth interviews were undertaken with people who either have thalassaemia, or have it in their family. These interviews gave us a picture of the sorts of views people living with thalassaemia have on screening, and these views have been incorporated into the survey.

Why am I being asked to take part? You are being invited to complete this survey if you are aged over 18, live in the UK and have thalassaemia in your family, or have it yourself. We are interested to hear from a range of family members (e.g. aunts/uncles, cousins, siblings, grand-parents, step- and half-relatives) or anyone who considers themselves a 'family member' of someone with thalassaemia, regardless of whether you are biologically related, and regardless of whether your relative with thalassaemia is still living, or has died. People, and family members of those, who have been cured of thalassaemia with a bone marrow transplant are also eligible to take part.

How do I participate? Simply fill in the Thalassaemia Screening Survey (UK) and return it in the pre-paid envelope, or to the address found at the back of this survey. The survey takes about 15-20 minutes to complete. Please complete the survey as an individual, rather than as a couple or family, as everyone feels differently about screening (even within couples and families) and it is important to get an accurate picture of the range of views on this topic. If you prefer, you may complete this survey online at: http://www.warwick.ac.uk/thalassaemiascreeningsurvey (active from 21.05.2018)

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What will happen to my information if I participate? The anonymised summary results of this survey (not individual data) will be published in academic journals, written up as a research report for the UK Thalassaemia Society's newsletter and also used for conference presentations (academic, professional and patient). It will also be submitted as research evidence to any policy review of thalassaemia screening conducted by the UK National Screening Committee. Upon completion of the research project, the anonymised data from this survey will be archived with the UK Data Service (https://www.ukdataservice.ac.uk/) so that in the future, other researchers may make use of the data. ***If you do not want your anonymised survey answers to be archived, please contact us by email or telephone (screeningstudy@warwick.ac.uk / 02476 151291) BEFORE completing the survey.***

What if I change my mind? If you start the survey and decide you do not want to continue for whatever reason, simply do not return it. However, once a completed survey is returned, it will not be possible to withdraw it from the study. This is because the survey is anonymous and therefore it will be impossible to link an individual back to their survey.

Will my taking part be kept confidential? All data collected from this survey will be held anonymously and securely using data encryption software. No data which may identify you (e.g. your name/address) will be asked for, but you will be asked for background information about yourself. This is in order that we can get a clearer understanding of the backgrounds of the people responding. All data will be handled in strict accordance with the Data Protection Act 1998.

Who is conducting the research? This research is being conducted by Dr. Felicity Boardman (Assistant Professor) and Dr. Rachel Hale (Research Fellow), at Warwick Medical School, and is funded by the Wellcome Trust. The research was given a favourable opinion by Warwick's Biomedical and Scientific Research Ethics Committee on 5th April 2018 (REGO-2017-1910 AM04).

Are there any disadvantages to taking part? Some people may find the topic of screening for thalassaemia upsetting. Should the completion of this survey raise any issues for you which you would like support with, or further information on, please contact your GP or the clinician who ordinarily treats your thalassaemia.

What if there's a problem? Any complaint about the way you have been dealt with during this study will be properly addressed by a person who is independent of the study. Please address your complaint to: Deputy Director/ Head of Research Governance, Research & Impact Services, University House, University of Warwick, Coventry CV4 8UW. Or email: researchgovernance@warwick.ac.uk

If you have any comments or queries about the survey, or to request further paper copies, please contact us at screeningstudy@warwick.ac.uk or complete the comments box at the end of the survey. **You may want to tear off and keep the cover page of this survey before returning it in order to retain the project details. Alternatively, email (screeningstudy@warwick.ac.uk) and ask for this information to be posted or emailed to you.**

Thank you!

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THALASSAEMIA SCREENING SURVEY (UK)

Section 1: About You

In this section you will be asked for basic background information about yourself. These questions are being asked in order that the researcher can gain a better understanding of the social backgrounds of people living with thalassaemia in their family.

1. What is your sex?

O Male O Female

2. What is your age?

O 18-25 years O 46-55 years

O 26-34 years O 56-65 years

O 35-45 years O 66+ years

3. What is your highest qualification level?

O No qualifications

O GCSE or O Level

O GCE, A level or similar

O Vocational (BTEC/NVQ/Diploma)

O Degree level or above

O Other (please specify): _____

4. What is your ethnic group?

O White- British

O White- Irish

O White- Gypsy or Traveller

O White- European

O Mixed- White and Black Caribbean

O Mixed- White and Black African

O Mixed- White and Asian

O Asian- Indian

O Asian- Pakistani

O Asian- Bangladeshi

O Asian- Chinese

O Black- African

O Black- Caribbean

O Arab

O Prefer not to say

O Other (please specify): _____

5. Do you have a religious faith?

O Yes O No O Prefer not to say

If yes, how would you describe your religious faith?

O Christian (any denomination)

O Jewish

O Muslim

O Sikh

O Hindu

O Buddhist

O Other (please specify): _____

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Section 2: Thalassaemia: You and Your Family

In this section you will be asked questions about the number of people affected by thalassaemia in your family, any treatment you are currently receiving, as well as your perceptions of your own, and your family members' health and well-being.

6. Do you have any children who have (or used to have) thalassaemia? (This might include step-children, foster children, adopted children or any child for whom you consider yourself to be the parent or legal guardian)

O Yes O No

If yes, how many children do you have? _____

7. What is your relationship to thalassaemia?
(please tick all that apply)

O I have thalassaemia myself

O Someone in my family has, or had, thalassaemia

8. What type of thalassaemia do you have yourself, or do you have in your family? *(please tick all that apply to you and your family)*

O Alpha thalassaemia major / Haemoglobin H Disease

O Beta thalassaemia major

O Beta thalassaemia intermedia

O Delta thalassaemia

O Other (please specify): _____

O Don't know

8A. Have you, or your relative, to the best of your knowledge, ever received contaminated blood in your treatment for thalassaemia?

O Yes O No O Don't know

8B. If yes, please state which conditions were contracted as a result of receiving this contaminated blood (please tick all that apply):

O HIV

O Hepatitis C

O Another condition (please specify): _____

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9. Please list your relationships to family members (to a maximum of 10) who are or has been affected by thalassaemia. This may include extended family members. If your family member(s) have died, please sate their approximate year of death and age at death (if known), e.g. Grandmother, died 1990, aged 80. If no one else in your family has or had thalassaemia, please go on to question 11.

	Your relationship to family members with THALASSAEMIA, their age and date of death (where applicable), e.g. son, died 1990 aged 14
a. Family member 1	
b. Family member 2	
c. Family member 3	
d. Family member 4	
e. Family member 5	
f. Family member 6	
g. Family member 7	
h. Family member 8	
i. Family member 9	
j. Family member 10	

10. Do you currently, or have you at any point in the past, lived in the same household as your family member(s) listed in question 9 (please answer for each family member as listed in the order above)? 'Living in the same household' would include living together on a temporary basis with your family members affected by thalassaemia, e.g. regular holidays or stays of more than two weeks in the same household.

	Currently, or at some point in the past, lived in the same household?	
	Yes	**No**
a. Family member 1	○	○
b. Family member 2	○	○

	Currently, or at some point in the past, lived in the same household?	
	Yes	**No**
c. Family member 3	○	○
d. Family member 4	○	○
e. Family member 5	○	○
f. Family member 6	○	○
g. Family member 7	○	○
h. Family member 8	○	○
i. Family member 9	○	○
j. Family member 10	○	○

11. How would you rate your current health and well-being?

○ Very good ○ Good ○ Fair ○ Bad ○ Very Bad

12. How would you rate the current health and well-being of your family member(s) currently or previously affected by thalassaemia listed in question 9? Please rate in the order you listed them in above. If you have no family members currently or previously affected by thalassaemia, please go on to Section 3.

	Current Health and Well-being of Family Members with THALASSAEMIA						
	Very good	**Good**	**Fair**	**Bad**	**Very Bad**	**Don't know**	**Not applicable** (family member died)
a. Family member 1	○	○	○	○	○	○	○
b. Family member 2	○	○	○	○	○	○	○
c. Family member 3	○	○	○	○	○	○	○
d. Family member 4	○	○	○	○	○	○	○
e. Family member 5	○	○	○	○	○	○	○
f. Family member 6	○	○	○	○	○	○	○
g. Family member 7	○	○	○	○	○	○	○
h. Family member 8	○	○	○	○	○	○	○
i. Family member 9	○	○	○	○	○	○	○
j. Family member 10	○	○	○	○	○	○	○

Section 3: Your Use of Genetic and Screening Technologies

In this section, you will be asked about your previous use of genetic and screening technologies for thalassaemia.

13. Are you, or your partner, currently pregnant or trying to get pregnant?

○ Yes ○ No ○ Prefer not to say

14. In your current, or previous pregnancies, have you, or your partner, ever used any of the following technologies? Please tick all that apply. Please see 'Glossary' at the end of the survey for further explanation of these technologies. (Please go on to Section 4 if you, or your partner, have never been pregnant before)

- ○ CVS or Amniocentesis (diagnostic testing in pregnancy) for thalassaemia
- ○ CVS or Amniocentesis (diagnostic testing in pregnancy) for a condition other than thalassaemia
- ○ Pre-Implantation Genetic Diagnosis (PGD) (creation of embryos using IVF prior to testing) for thalassaemia
- ○ Pre-Implantation Genetic Diagnosis (PGD) (creation of embryos using IVF prior to testing) for a condition other than thalassaemia
- ○ Screening for Down's Syndrome (usually offered as a scan and/or blood test at around 12 weeks of pregnancy)
- ○ Carrier Testing for thalassaemia
- ○ None of the above

15. Have you, or your partner, ever undergone a pregnancy termination (abortion) due to thalassaemia?

○ Yes ○ No ○ Prefer not to say

15a. If yes, please state how many terminations _____

16. Have you, or your partner, ever undergone a pregnancy termination (abortion) due to a prenatal diagnosis of a condition other than thalassaemia?

○ Yes ○ No ○ Prefer not to say

Section 4: Your Views on thalassaemia

In this section, you will be asked about your views about thalassaemia. You will be asked about how far you agree, or disagree, with, a list of statements. These statements were derived from interviews conducted with families living with thalassaemia and represent a wide range of views. This survey will measure how widespread these views are and how strongly they are held by others living with thalassaemia. Please note, there are no right and wrong answers to these questions. Everyone feels differently.

17. Please state how far you agree, or disagree with, the following statements about thalassaemia

	Views About THALASSAEMIA					
	Strongly agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't know**
a. People with thalassaemia can have a good quality of life	○	○	○	○	○	○

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	Views About THALASSAEMIA					
	Strongly agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't know**
b. Having thalassaemia causes those people to suffer	○	○	○	○	○	○
c. People with thalassaemia and their families are well supported by wider society	○	○	○	○	○	○
d. Quality of life with thalassaemia varies greatly depending on severity	○	○	○	○	○	○

Section 5: Your Views on Screening for Thalassaemia

In this section, you will be asked about your views on screening for thalassaemia. You will be asked how far you agree or disagree with a list of statements about thalassaemia, derived from interviews with families living with thalassaemia. These statements represent a wide range of views. This survey will measure how widespread they are, and how strongly they are held by the wider population of families living with thalassaemia. Screening involves the identification of thalassaemia in the UK population either pre-conceptually or in the newborn period. However, it cannot accurately predict the severity of the condition.

Screening for thalassaemia could be done in different ways:

1) **Pre-conception genetic screening** would identify 'carriers' of a thalassaemia gene (people who could transmit thalassaemia to future generations) before they have children or whilst they are planning a pregnancy. This would enable prospective parents to be informed of their risk of having a child with thalassaemia before the baby is even conceived.

2) **Newborn genetic screening** would identify babies with thalassaemia shortly after their birth through a blood test, 'the heel prick test'. While some babies with thalassaemia are already being identified though this test when it is being used to look for other disorders, there is no formal newborn screening programme currently in place in the UK.

You will be asked a general question about screening for thalassaemia, before being asked to agree, or disagree with statements relating to preconception genetic screening and newborn genetic screening outlined above.

Please be reminded that some people may find the topic of screening for thalassaemia distressing. Should the completion of this survey raise any issues for you which you would like support with, or further information on, please contact your GP or treating clinician.

18. These statements relate to pre-conception genetic screening. Please state how far you agree or disagree with them by ticking in the appropriate box. Pre-conception genetic screening would allow people the option to know their carrier status before conceiving a pregnancy, so that they could be made aware from the outset of any future child's chance of being born with thalassaemia.

	Pre-Conception Genetic Screening for THALASSAEMIA					
	Strongly agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't know**
a. Identifying carriers of thalassaemia before a pregnancy is conceived will affect people's choice of reproductive partner (the person you choose to have a baby with)	○	○	○	○	○	○
b. It will be harder for thalassaemia carriers to get married and/or have children once their genetic status is known about	○	○	○	○	○	○
c. Identifying carriers of thalassaemia in the general population will lead to carriers feeling stigmatised or different	○	○	○	○	○	○
d. Identifying carriers of thalassaemia before a pregnancy is established is a good thing, as it will reduce the number of terminations as parents will be aware of the chances beforehand	○	○	○	○	○	○
e. Identifying carriers of thalassaemia in the general population will increase awareness of thalassaemia as a condition	○	○	○	○	○	○
f. People from the general population won't be interested in finding out their carrier status as they won't think it's relevant to them	○	○	○	○	○	○
g. Pre-conception genetic screening is a form of 'social engineering' (a way of controlling the genetic make-up of the population)	○	○	○	○	○	○
h. I would support a pre-conception genetic screening programme for thalassaemia	○	○	○	○	○	○

19. These statements relate to newborn screening for thalassaemia. Please state how far you agree or disagree with them.
This type of screening would identify babies affected by thalassaemia shortly after birth through a blood test. It might also identify some carriers of thalassaemia.

	Newborn Genetic Screening for THALASSAEMIA					
	Strongly agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't know**
a. Identifying thalassaemia at birth would lead to better support and health care for the child and their family	○	○	○	○	○	○
b. Identifying thalassaemia at birth would extend the life expectancy of a child with thalassaemia	○	○	○	○	○	○

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	Newborn Genetic Screening for THALASSAEMIA					
	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Don't know
c. Identifying thalassaemia before a child develops any symptoms prevents the child and their family from enjoying life whilst they are still symptom-free	○	○	○	○	○	○
d. Identifying thalassaemia at birth would help research into cure by enabling more children to be enrolled into clinical trials early on	○	○	○	○	○	○
e. Identifying thalassaemia at birth would interfere with the early bonding process between parent and child	○	○	○	○	○	○
f. Diagnosing thalassaemia at birth would make the diagnosis easier for parents to accept	○	○	○	○	○	○
g. Identifying thalassaemia at birth would spare parents the difficulties associated with finding a diagnosis for the child later on	○	○	○	○	○	○
h. Even though parents would not know for sure how severely affected their new-born baby will be, it's still better that they know about the thalassaemia straight away	○	○	○	○	○	○
i. Identifying thalassaemia at birth is important as it would enable parents to make informed decisions about any future pregnancies	○	○	○	○	○	○
j. I would support a newborn genetic screening programme for thalassaemia	○	○	○	○	○	○

Section 6: Your Wider Views on Termination of Pregnancy (Abortion)

In this section, you will be asked about your wider views on pregnancy termination (abortion). The question in this section is replicated from a 2003 survey, 'Views and Decisions about Prenatal Screening', which was given to pregnant women undergoing screening for Down's Syndrome. This question is being asked to explore whether families living with thalassaemia view termination of pregnancy (abortion) differently to women from the general population in the circumstances listed below.

20. These statements relate to attitudes towards termination of pregnancy (abortion). Please state whether you personally agree with a woman having a termination if...

	Wider Views on Termination of Pregnancy					
	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Don't know
a. The family has a low income and cannot afford any more children	○	○	○	○	○	○
b. The woman decides she does not wish to have a child	○	○	○	○	○	○
c. The child is certain to have a serious mental disability and will never live independently	○	○	○	○	○	○
d. The child is certain to have a serious physical disability and will never live independently	○	○	○	○	○	○

	Wider Views on Termination of Pregnancy					
	Strongly agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't know**
e. The child would live in good health, but would be certain to die in his/her twenties or thirties	○	○	○	○	○	○
f. The child would be healthy but would never grow taller than an eight year old (between 124cm and 132cm on average)	○	○	○	○	○	○

Thank you!

Thank you for completing the Thalassaemia Screening Survey (UK). Please return your survey in the pre-paid envelope, or to the following address:

Thalassaemia Screening Survey (UK)

C/O Natasha Nakariakova,

ITS, CEDAR Bld,

Warwick University

Coventry

CV4 7AL

Some people may find the topic of screening distressing. Should the completion of this survey raise any issues for you which you would like to discuss further, please contact your GP or treating clinician.

Please feel free to pass this survey on to your relatives and/or any friends/acquaintances you know to be affected by thalassaemia. However, please be aware that screening can be a sensitive topic, and the views of others may not be the same as yours.

You can contact us (screeningstudy@warwick.ac.uk) for extra paper copies or use the link to the online version: http://www.warwick.ac.uk/thalassaemiascreeningsurvey (active from 21.05.2018).

You can find out more about the research project by visiting: www.warwick.ac.uk/imagining_futures

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Glossary of Terms

CVS/Amniocentesis - CVS and amniocentesis are diagnostic procedures used in pregnancy which usually involve the insertion of a needle through the abdomen to remove samples to be genetically tested.

Pre-Implantation Genetic Diagnosis - refers to the creation of embryos using IVF procedures. The embryos can then be tested for genetic conditions, such as thalassaemia, before being transferred back to the mother's uterus.

Screening for Down's Syndrome - Down's Syndrome is a chromosomal disorder caused by an extra copy of chromosome 21 which leads to varying degrees of learning difficulty. It is also known to be associated with particular health problems, including heart problems, reduced vision and hearing, as well as early-onset Alzheimer's Disease (a form of senile Dementia). Screening for Down's Syndrome is offered to all pregnant women in the UK and usually involves a blood test and/or a scan (to measure the foetus' nuchal fold- the back of the neck) at around 12 weeks of pregnancy.

APPENDIX E: Supplemental Ethnicities Table

APPENDIX E: BREAKDOWN OF ETHNICITIES		
Category	**Country**	**n=92**
Northern European		**n=31**
	Ireland	14
	England	14
	Germany	13
	France	8
	Scotland	5
	Denmark	2
	Wales	2
	Switzerland	2
	Poland	2
	Unknown	2
Southern European		**n=9**
	Italy	4
	Portugal	2
	Spain	2
	"all countries"	1
Other European		**n=10**
	Poland	4
	Ukraine	2
	Russia	2
	Ashkenazi Jewish	2
	Armenia	1
	"Germany, Denmark, and Netherlands"	1
Hispanic/Latino		**n=12**
	Mexico	4
	Cuba	2
	Hispanic	2
	Brazil	1
	Black	1
	Columbia	1
	Ecuador	1
	El Salvador	1
Black/African American		**n=7**
	Black or African American	6
	Belize	1
Central/East Asian		**n=27**

	China	10
	Philippines	6
	Korea	3
	Japan	3
	Vietnam	2
	Afghanistan	1
South Asian		**n=8**
	Indian	8
Middle East/North African		**n=4**
	Egypt	1
	Iran	1
	Israel	1
	Lebanon	1
Native/Indigenous		**n=1**
	Cherokee	1
Other		**n=3**
	"Caucasian"	1
	"White"	1
	"Southeast Asian"	1