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A Comparison of Perceived Barriers to Healthcare between Malaysian and Californian Patients with Rare Disease

THESIS

submitted in partial satisfaction of the requirements
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MASTER OF SCIENCE

in Genetic Counseling

by

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DEDICATION

To the families of patients who are struggling with finding adequate healthcare,

I would like to say thank you for inspiring me to find a cause worth fighting for.

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ABSTRACT OF THE THESIS

A Comparison of Perceived Barriers to Healthcare between Malaysian and Californian Patients with Rare Disease

By

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Master of Science in Genetic Counseling

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Professor John Jay Gargus, Chair

In the era of personalized and genomic medicine, awareness of patients with rare diseases is increasing as new approaches to diagnosis and treatment are developed. This study examined perceived barriers that families with rare diseases experience and explored possible differences between participants in Malaysia and the US. The study involved n=108 participants recruited in genetics clinic appointments at the University of Malaya Medical Center and three sites in Southern California. Participants completed a survey involving multiple choice and Likert scale items pertaining to perceived barriers in access to healthcare. Results from this study provide evidence of cultural differences in how patients experience potential barriers to receiving healthcare. The most frequently cited largest stressor in Malaysia was the knowledge of inheritance of the condition, while financial concerns were cited most frequently in the US. Similarities between participants in the two countries were also noted, such as the perception that expanding healthcare provider knowledge of rare diseases would be most beneficial. In both locations, it was also noted that travel distance to clinic was not perceived as a large stress factor. Taking these observations together, a healthcare model with a central location of providers well-versed in medical

genetics is suggested. The data support a need for improving healthcare provider knowledge of rare disease and cultural sensitivity regarding genetic counseling of the inheritance of disease. Future studies exploring how these perceived stress factors are impacting families as well as different methods of educating providers are suggested by findings from the study.

I. INTRODUCTION

The most difficult patients to reach in healthcare are those who have fallen between the cracks. These families are the ones who are unreachable, cancel at the last second, and those who were never referred or scheduled in the first place. In an attempt to better understand these patients, this study explores families who have surpassed the obstacles of obtaining and attending a genetics clinic, and the barriers these families encountered along the way. This study involves an international comparison between patients in Malaysia and California who are attending genetics clinic appointments. There are clear differences in the healthcare systems employed by the two sites, such as newborn screening programs and availability of service providers. However, these programs and services may not be perceived as barriers by patients. Physical barriers may have little impact; in contrast, mental or psychological barriers must be overcome before a patient and their family agrees to enter a genetics clinic. [38] This study is designed to explore perceived barriers in these unique sets of populations. Malaysia is a melting pot of Asian cultures, such as Indian, Malay, and Chinese individuals; similarly Southern California is an ethnically diverse area. These sites were chosen based on the high density of ethnicities and cultures, in an attempt to provide a broader understanding of existing commonalities or differences among genetic counseling patients in accessing adequate healthcare. Patients in genetics clinics represent a large portion of those needing continuous care in the healthcare system, and there is value in studying the experiences of these patients and their families.

1.1 Rare diseases

There are many definitions of what constitutes a 'rare disease', from the European Union (EU) defining it as a condition affecting fewer than 1 in 2,000 individuals to the

National Institutes of Health (NIH) defining it as a condition affecting 200,000 or fewer Americans at any given time. [4, 5] While each individual condition is considered a 'rare disease', collectively these make up a large portion of the patient population. The EU estimates that about 6-8% of Europeans are affected by a rare disease, approximately between 27 to 36 million people. [4] In the United States (US) alone, these rare diseases are estimated to affect between 25 to 30 million people, which is more than the entire state population of New York. [5, 12] Currently, about 7,000 rare diseases have been identified and it is estimated that roughly eighty percent are genetic in origin. [5, 8] A vast majority of patients being seen in genetics clinics have rare diseases. One of the most common genetic conditions, Down syndrome, affects about 250,000 families in the US.[9]

This patient population has fought a long, hard battle to spread awareness. Government policies have been put into place that bring attention to these families, and have helped to further research in these areas. With the help of policymakers, many advances have been made with respect to techniques and treatments of these rare diseases.

1.1.1 Rare disease research and incentives

The Orphan Drug Act was passed in 1983 by the Federal Drug Administration (FDA) in the US. [3] Between 1973 and 1983, fewer than ten drugs and biological products were released in the market for rare diseases. [3] After the Orphan Drug Act was passed, more than 400 of these products have been marketed. [3] The Orphan Drug Act includes incentives such as expedited FDA approval, assistance with protocols, tax credits, fee waivers, and orphan drug market exclusivity. [63] These incentives help to propel interest and motivate researchers in the rare disease field. Some examples of advances are enzyme replacement therapies such as imiglucerase, agalsidase beta, and alglucosidase alfa, and substrate reduction therapies

such as eliglustat.[74] A few of the current investigation therapies showing promise include exon skipping drugs for Duchenne muscular dystrophy and gene therapies. Thirty eight orphan drugs received marketing approval specifically for pediatric usage, which constitute 26% of the orphan drugs with marketing approval during that time period.[68] Pediatric drug research is an important field, and more than half of all rare diseases begin to manifest in childhood.[8, 68] Nowadays, it is also known that earlier treatment of some rare diseases, such as Fabry disease, can lead to prevention of later onset complications such as renal failure.[45] Other countries have followed suit and have established laws offering similar incentives, such as Japan, South Korea, Taiwan, and the EU.[67] While this has helped to stimulate research, the current available treatments are limited.

1.1.2 Cost of treatments

There are several pathways of treatment for genetic conditions. For some inborn errors of metabolism (IEM), the options may consist of special diet formulas and restrictions, enzyme replacement therapy (ERT) and substrate reduction therapy, and hematopoietic stem cell transplantation (HSCT). However, even given the progress of genetic medicine and incentives for drug development, enzyme replacement therapy remains an option for only six of the 50 identified lysosomal storage diseases (LSDs) as of 2012.[35]

1.1.2.1 Enzyme replacement therapy

ERT is currently being used as treatment for many conditions, particularly those categorized as IEM. Many IEM conditions are due to a malfunction or deficiency of an enzyme necessary for creating or using energy. By replacing the deficient enzyme, many symptoms of these disorders can be alleviated or even reversed. However, there are several limitations to these treatments. For disorders that have symptoms involving the central

nervous system (CNS), it is difficult to design a delivery method that is able to penetrate the blood brain barrier.[59] For example, about 75% of lysosomal storage diseases impact the CNS, however ERT has not been able to alleviate the CNS manifestations.[28, 59, 75] Another obstacle is due to the cost of these treatments for patients. For example, a patient in the US with Gaucher Disease may spend $200,000 USD per year on imiglucerase infusions alone.[36] In comparison, a rheumatoid arthritis patient may spend approximately $25,000 USD per year on adalimumab.[36] Oftentimes, Gaucher disease patients require lifelong intravenous infusions every other week. The imiglucerase is able to alleviate bone pain and ameliorate hepatosplenomegaly, however the liver and spleen remain abnormally large even five years after beginning treatment.[70] Not only do these treatments cost vast amounts of money, but they also cost these families valuable time. Some lucky families are able to have infusions at home, but others who may not be as fortunate must travel to an infusion center, which may be located hours from their homes. This story is not uncommon among patients with IEM disorders. Other countries have adopted systems that include reimbursements for patients.[67] Taiwan's government provides incentives for research involving genetic conditions, and also provides 70% reimbursement of medical expenses for patients, and a full reimbursement for patients of low-income families.[67] Unfortunately, these health policies are not in place everywhere and patients' families must find other sources to finance their medical expenses.

1.1.2.2 Bone marrow transplant & hematopoietic stem cell transplant

More permanent treatments for IEM disorders include bone marrow transplants (BMT) or hematopoietic stem cell transplants (HSCT). These types of treatments may even be considered cures in some cases, such as in cases where sufficient amounts of enzyme

begin to be produced ameliorating certain IEM disorders. Yet again, there are many limitations. For those disorders that are effectively treated with BMT or HSCT, the median cost is approximately $200,000 USD for the treatments up to 100 days after the initial surgery. [53] Another hindrance is the ability to find an acceptable donor. In developed countries, there are organizations such as the National Marrow Donor Program that have databases of willing donors. [54] However, the individuals donating to these programs are largely Caucasian, who are less likely to be matches for those of Asian ethnicity. [54] In developing countries, it may be more economically feasible for families to opt for BMT or HSCT as treatments as it is not a lifelong treatment; however it is those very countries that are lacking suitable donors. Therefore, this treatment remains as an option only for those wealthy enough to pay for the procedure itself, as well as those with the resources to find a suitable donor if not using a family member.

1.1.2.3 Other therapies & alternative methods

For many patients with genetic conditions, special therapies are needed. Genetic counselors typically ask about the following at every appointment as part of the interval history; occupational therapy, speech therapy, extra help in school, and physical therapy. Many patients' families find it difficult to attend the myriad of therapy appointments required. In some cases, families are able to acquire a therapist willing to make house calls, however this is often not the case for low-income families. It is also a worry that those without the means to obtain the recommended therapies may resort to alternative methods that may be detrimental to the affected individual's healthcare. The possibility that families are using traditional Eastern medicine to treat genetic conditions has been considered, and is not well studied in this population. [77]

1.2 Availability of care

1.2.1 Genetics professionals

The role of a genetic counselor in the United States includes many aspects of healthcare. According to the National Society of Genetic Counselors (NSGC), the scope of practice includes the following:

> *"a) obtain and evaluate individual, family, and medical histories to determine genetic risk for genetic/medical conditions and diseases in a patient, his/her offspring, and other family members;*
>
> *b) discuss the features, natural history, means of diagnosis, genetic and environmental factors, and management of risk for genetic/medical conditions and diseases;*
>
> *c) identify and coordinate genetic laboratory tests and other diagnostic studies as appropriate for the genetic assessment;*
>
> *d) integrate genetic laboratory test results and other diagnostic studies with personal and family medical history to assess and communicate risk factors for genetic/medical conditions and diseases;*
>
> *e) explain the clinical implications of genetic laboratory tests and other diagnostic studies and their results;*
>
> *f) evaluate the client's or family's responses to the condition or risk of recurrence and provide client-centered counseling and anticipatory guidance;*
>
> *g) identify and utilize community resources that provide medical, educational, financial, and psychosocial support and advocacy; and*
>
> *h) provide written documentation of medical, genetic, and counseling information for families and health care professionals."* [19]

The NSGC has worked hard to establish credentials for genetic counselors working in the United States and Canada. In order to practice as a genetic counselor, one must have graduated with a master's degree from an institution accredited by the American Board of Genetic Counselors (ABGC) or American Board of Medical Genetics (ABMG) and also have

passed or be an active candidate for the certification board exam issued by the ABGC/ABMG. [19] Not only are genetic counselors recognized as healthcare providers in hospitals and healthcare systems, but they are also valued team members of genetic testing laboratories. The community is working towards establishing the profession and as technology advances, the role of the genetic counselor is constantly being modified. Currently, genetic counselors are working towards recognition by Medicare (a national social insurance program in the US) as healthcare providers in order to help promote access to services for those of lower socioeconomic standing. [15] The US Bureau of Labor Statistics projects a 29% increase in employment of genetic counselors from 2014 to 2024, while the US genetic counseling training program matriculation has remained relatively stable in the past few years. [10, 58]

In contrast, the Ministry of Health in Malaysia does not recognize 'genetic counselor' as a position in the workforce. A genetic counselor is paid under various other titles, such as 'scientist' or 'social worker'. That being said, the availability of genetic counselors in Malaysia is lacking. As of 2013 there were two associate genetic counselors in Peninsular Malaysia, and nine medical geneticists providing genetics services. [77] The lack of genetic counseling programs in the Southeast Asia region is a contributing factor to this dilemma. California has three genetic counseling training programs, each training six to nine graduates per year. While these genetics specialists are more common in the US, the lack of appropriate genetics education in physicians remains a problem. [49]

1.2.2 Multidisciplinary teams

Multidisciplinary teams are an ideal way to provide genetic services, yet this requires both time and resources.[42] The specialists required may include social workers, nutritionists, medical geneticists, genetic counselors, and registered nurses. Certain disorders also require additional specialists, such as surgeons or cardiologists. The Malaysian workforce is unable to provide these specialists who have specialized training in genetics.[51] In the US, there remains an uneven distribution of specialty clinics. Existing multidisciplinary clinics mainly focus on blood disorders and on cystic fibrosis.[42] Much work is needed in this area to provide quality care to those with rare diseases.

1.3 Potential barriers to accessing healthcare – rare disease patients

1.3.1 Cost of genetic testing

The cost of genetic testing has been proven to be a barrier for many families.[55, 77] Technological improvements have helped to drive the cost of genetic testing down, particularly in the past seven years.[71] With the recent advancements of massively parallel sequencing and high throughput screening allowing several samples to be run at the same time, the cost per raw megabase of DNA sequencing has dropped from about $1000 USD in 2005 to less than 10 cents today. The cost of clinical genetic testing also includes the cost of storage and interpreting the data, which are current limitations of whole exome sequencing and whole genome sequencing.[47]

1.3.2 Insurance policies

One longitudinal study from the Netherlands showed that after the government changed from a public and private healthcare insurance system in 2006 to a mandated universal baseline insurance package, participants were less likely to be worried about

genetic discrimination by insurance companies.[44] The Affordable Care Act of 2010 in the US allowed equal access of all citizens to healthcare, which may have a similar effect, although it has not been studied.[11] Coverage of genetic testing varies between the different providers, and it is well known among health professionals that there are certain insurance plans that deny coverage of most genetic testing. Because genetic testing is relatively new, insurance policies have not yet integrated genetics services and may not be in a position to make an informed decision in each case about the possible benefit. In some fields such as cancer, genetic testing can be seen as a preventative measure with published surveillance and management guidelines. Genetic testing and management guidelines do not exist for the 7,000 identified rare diseases. With limited knowledge of these conditions in the scientific community, it becomes even more difficult to prove the benefit of testing to insurance companies. There are additional services that aid families in acquiring the necessary medical care. In California, low income families are able to access the state funded California Children's Services (CCS), a type of additional medical insurance that covers special diet needs, medical equipment, therapies, among others.[16] CCS is active until the child reaches 21 years of age.[16] In order to apply for CCS, individuals must demonstrate that they are of low income and have significant impairments, and many rare diseases fit the required CCS criteria.[16]

Malaysia uses a two-tiered healthcare system consisting of a government funded public sector and a private sector. The Malaysian government also includes the optional service of an orang kurang upaya (OKU) card for disabled individuals. People with sensory impairments, physical disabilities, learning difficulties, mental illness, or multiple disabilities are eligible to apply.[20] The OKU card is able to facilitate access to services such as healthcare,

education, employment, social, and rehabilitation services.[20] However, funding for genetic testing in Malaysia is mainly through charitable sources or research funds.[55] The out-of pocket cost for these genetic tests can be incredibly high. In order for families to use the charitable sources or research funds, they must be proactive and often advocate for themselves. Oftentimes, the price for a test can be daunting to a Malaysian family. For example, a genetic test that would normally cost $1000 USD to a family with no insurance in the US would cost approximately 4000 ringgits (RM) for a family in Malaysia. Some testing laboratories may offer a compassionate care cost, which can be about a 10% discount. Even with this discount, a Malaysian family would be required to pay 3,600 RM. The median income of a Malaysian household in 2014 was 4,500 RM per month.[2] This would mean that the average Malaysian family would have to spend almost an entire month's worth of salary in order to pay for one genetic test, as many genetic testing labs are located in the US and do not bill insurance companies from other countries. Even though Malaysia is considered a middle-income country, the national healthcare framework is lacking the inclusion of genetic testing services.[55]

1.3.3 Treatment centers

Malaysia had four centers in 2013 offering genetic services, with a few outpatient clinics offered by those centers.[55, 77] There is one medical geneticist for every 3 million people in Malaysia. In contrast, The Children's Hospital of Los Angeles in California currently employs at least seven medical geneticists in its practice, which is more than half the number of geneticists in the entire country of Malaysia. The city of Los Angeles has a population of approximately four million as of 2014, and a single pediatric hospital has a better service ratio than the entire country of Malaysia. This does not include the other hospitals with

genetic professionals that service patients in the area such as the University of California Los Angeles and University of Southern California health systems. [12] This disparity highlights the need for more genetically trained professionals in Malaysia.

1.3.4 Provider knowledge

Genetic conditions are difficult to treat, and most are incurable. Most of these conditions affect multiple systems of the body, requiring patients to see multiple specialists. Oftentimes, if the underlying genetic condition goes unrecognized by each specialist, the patient continues to see several specialists who are not able to diagnose the principal cause. A US study of neurologists and psychiatrists found that a majority of the respondents considered themselves to have a very poor to average knowledge of genetics. [62] Interpreting test results and conveying the information to patients are difficult with a limited understanding of medical genetics. This demonstrates the need for specialists ordering genetic tests to have proper genetics education. [62] Another study examined the barriers preventing appropriate genetics referrals and identified that a large barrier was due to lack of knowledge of the non-genetics health professional. [34] One way to circumvent the lack of referrals is through a program with automatic referrals after red flags are identified, for instance as part of a newborn screening program. However, the resources needed for implementing a large scale screening program have not been met for many developing countries.

Research has shown that primary care providers may not only be lacking in medical genetics education, but that they are also lacking in their understanding of genetic information protection laws. [34, 49, 50] In the past, physicians were concerned about genetic discrimination against their patients, which manifested as reluctance towards the uptake of

genetic services. [52] This was a realistic concern before the Genetic Information Non-Discrimination Act (GINA) was passed in the US, however more recent studies show that many providers are still unaware of the existence of such a protection. [50] A study in 2013 showed that at least half of the family physicians surveyed were not aware of the existence of GINA; and of the physicians who were aware, more than half were unaware of the limitations of life insurance and long-term care insurance. [50] GINA currently does not offer protection against life insurance and long-term care insurance discrimination. [14] The lack of awareness of GINA as well as the lack of protection in other countries remains yet another barrier for patients' who need to access genetic services.[55]

1.3.5 Public awareness

1.3.5.1 Patient support and advocacy groups

Advocacy groups in the US such as the Evanosky Foundation and Hunter's Hope Foundation have played a major role in public policy. The Evanosky Foundation created the Illinois Senate Bill 1761 which was passed in 2011, requiring that Mucopolysaccharidosis I (MPS I), MPS II, and Severe Combined Immunodeficiency (SCID) be added to the newborn screening panel in that state. [33] Illinois, New York, and Missouri currently screen for certain lysosomal storage diseases. [18] The Hunter's Hope Foundation has also advocated for increased newborn screening; they contributed both time and resources to pushing for Krabbe disease to be added to newborn screening in New York. Both of these foundations were born from families with children affected by rare diseases. The Hunter's Hope Foundation was able to garner the public's attention due to the star power of Jim Kelly, a retired National Football League quarterback who was inducted into the Pro Football Hall of Fame in 2002. [13] There are several hundred patient support groups in the US, ranging from

specialized support groups for certain conditions to national organizations such as the National Organization of Rare Diseases (NORD). [5] Malaysia has a similar overarching group, the Malaysian Rare Disease Society (MRDS), however Malaysia is lacking in support groups for specific conditions.[7]

1.3.5.2 Media and pop culture influences

Another example of a public figure directing the general public's attention towards genetic conditions is Angelina Jolie, the internationally famous actress, who underwent genetic testing of the *BRCA1/2* genes. [37] After her public statements of her positive mutation and decision to undergo preventative surgery, many genetic counselors working in the cancer field experienced the "Angelina Jolie effect", where clinics in countries like England and the US were newly flooded with an influx of patients. [37, 46] In these countries, media and pop culture are a large part of society, and these public figures are able to spark movements in public health. [37, 46] Another example of this effect is the public statement by Jenny McCarthy, an actress from the US, who declared on national television in 2008 that her son's autism was caused by vaccination scheduling. [17] After this statement was made, the rates of infant vaccinations decreased, leading to outbreaks of illnesses such as whooping cough, where prevention relies on the concept of herd immunity. [29, 72] The belief that vaccinations are linked to autism is still controversial today. The influence of media and popular figures may lead to an increase in public awareness in some cases, and misinformation in others.

In other countries where culture and beliefs are less influenced by pop culture, it may be more difficult to rally support and attention. In the US, public opinion is largely influenced by mass media, which becomes especially important for healthcare issues. [72] The Malaysian population may relate less to these international movie stars, and may rely more on

information portrayed by the government of their religious circles. Studies have shown that individuals relate better to celebrities with similar demographics, and with a lack of Asian celebrities speaking out about rare diseases, this may contribute to the lack of public awareness in Malaysia of genetics services. [32, 55, 56] Without public awareness, families may view rare diseases negatively, and as a burden to the family. A genetic condition may be seen as shameful to those families, or they may feel disconnected from the other families.[73]

1.3.6 Public acceptance – in and outside the home

Many studies have shown that public awareness of genetics has been increasing, and that more than half of the population believes that more resources should be allocated to developing genetic testing. [44] However, studies have also shown that in ethnic minorities in the US, such as Asian, Latino, and African Americans, the concept of genetic testing is largely unknown.[41]

Many Chinese Americans hold the belief that carriers of genetic conditions should not have children, and that they should not be married. [41, 73] This may largely stem from previous laws instated by the Chinese government in 1995 pertaining to banning the marriage of individuals with family histories of hereditary diseases. [43, 73] The Maternal Health and Infant Law of China originally required that couples undergo a pre-marital medical examination where providers must offer sterilization services or long-term contraception to couples that were found to have 'serious' undiagnosed genetic diseases. [43] The belief still remains in the Asian American community that having a "bad gene" in the family will prevent offspring of that family to be married. [41] These personal beliefs may hinder the acceptance of genetic testing in society.

1.3.7 Religious beliefs

Religious belief can play an important part in making healthcare decisions. Genetic counselors strive to be non-directive, and the decision to pursue genetic testing is often left to the patient and their family. One study found that spiritual individuals regard a diagnosis of rare disease as harmful to a child, which goes against the belief of protecting and preserving the health of a child. [23] In religions with a belief in a god or gods, there is a range of 'freedom'. Some religious beliefs follow the idea that one's entire life is already predetermined, while others follow the idea that humans are in complete control of their lives. The power of genetic information can challenge these beliefs. Some religious communities have promoted the usage of genetic screening, such as Tay-Sachs carrier screening in the Ashkenazi Jewish community. [25] Other religious beliefs have not been well studied in the context of genetic information. Approximately 60% of Malaysians are considered Muslims. [6] It is important to understand the Islamic belief and how it may influence medical decisions. There are Islamic rules concerning adoption, reproductive technology, and termination. [21] For example, adoption is not allowed for those of Islamic faith. [21] These rules would be important to understand when offering options, and it would be best to determine beforehand how strictly the patient follows their beliefs. [21, 24] Each religion has a different set of beliefs regarding medical care, and both the US and Malaysia have populations with several religious beliefs.

1.3.8 Other demographic associations

Different demographic characteristics have been associated with certain perceptions. A study in the Netherlands found that older age and lower education levels are associated with a fear that genetic testing would limit the freedom of individuals. [44] This could play a

role in the decision-making process for both patients considering genetic testing for themselves, as well as parents making decisions for their children. Some perceptions are associated with certain ethnicities, such as distrust of health professionals by the African American community and the belief that carriers of the same genetic condition should not be married in the Ashkenazi Jewish and Asian communities. [26, 41] A study also revealed that Asian women in the US may have some discomfort with Western medicine, as opposed to traditional Eastern medicine. [41] These perceptions need to be addressed in order to assure that patients fully understand the risks and benefits of genetic services.

1.4 Hypothesis

This study aims to explore perceived barriers in access to healthcare for patients with rare disease in California and Malaysia. The lack of studies of perceived burden among genetics patients treated in Malaysia and Southeast Asia demonstrates a need for more research in the area to better tailor the healthcare system. The paucity of research investigating cultural differences, particularly for those of Asian ethnicities, also highlights the need for better understanding as well. Different cultural groups may perceive sources of stress in another way, and knowledge in this area may be able to improve patient well-being. Because the populations of the US and Malaysia differ in several demographic characteristics, as well as different healthcare systems and medical genetics awareness and knowledge, it can be expected that there may be several differences in the types of barriers encountered by patients. Results from this study may be able to guide efforts in improving healthcare access for these patients, as well as their experiences with healthcare as a whole.

It is anticipated that the California and Malaysian patients will differ in their perception of the barriers faced in obtaining healthcare. Because of the lack of genetics

health professionals in Malaysia, it is expected that the respondents will perceive the lack of care centers and the travel time and costs for care to be larger burdens than patients and families in California. It is also expected that there is a larger portion of patients' families in Malaysia choosing to not undergo testing due to cost, stemming from the lack of funding and insurance coverage for genetic tests. Participants in both countries are anticipated to respond similarly when weighing the burden of the knowledge of inheritance of disease, as well as hoping for improvements to healthcare provider knowledge regarding the rare disease occurring in their families. Lastly, it is predicted that respondents who are patients of Asian ethnicities in both Malaysia and California to perceive themselves as a large burden on their families, as well as a larger delay in receiving a diagnosis due to time between noticing first symptoms and receiving medical attention. The goal of this study is to determine what areas of the healthcare system are perceived as needing improvement when specifically targeting patients with rare diseases in genetics clinics.

II. METHODS

This study was reviewed and classified as exempt research by the Institutional Review Board of the University of California, Irvine (HS# 2015-2175)(Appendix A).

2.1 Recruitment

Participants were recruited through the genetics and metabolic outpatient clinics and pediatric inpatient consultations at University Malaya Medical Centre in Kuala Lumpur, Malaysia (UMMC) and from the various genetics, metabolic, and specialty genetics clinics (i.e., Pompe disease) at Long Beach Memorial Medical Center (LBMMC), Children's Hospital of Orange County (CHOC), and University of California Irvine Medical Center (UCIMC) in California, US. Participants were approached during their clinic appointment or consultation visit and asked if they would like to participate in a research study involving a survey investigating barriers in access to healthcare. If interested, the participants were then given a study information sheet with a brief overview of the experiment as well as contact information for the research team. The participants were asked to briefly review the study information sheet before beginning the survey.

2.2 Participants

Participants in this study were required to be at least 18 years of age, and must either have a diagnosis of or be suspected of having a rare disease, or have a family member who fits this description. Participants were required to be attending a genetics or metabolic clinic appointment or consultation visit. The survey was available in English and Malay (Bahasa Melayu). If the participant was blind or unable to read, a member of the research team was available to read the survey questions out loud for the participant. If participants chose to have the survey read out loud in Mandarin, a member of the research team who is a native

speaker was available to read the survey questions out loud for the participant. Therefore the participants were required to understand either English, Malay, or Mandarin. There were no exclusion criteria based on gender, religious beliefs, or educational attainment. The study had a total sample size of 108 (N=108), with 54 participants seen at UMMC in Kuala Lumpur, Malaysia and 54 participants from the various genetics and specialties clinics (Pompe disease and metabolic clinic) at LBMMC (n=19), CHOC (n=9), and UCIMC (n=26), all of which are located in California, US.

2.3 Protection of Participant Privacy

The privacy of the participants was protected throughout the study. No personal identifiers were collected during this study. There were no known harms or discomforts associated with the study beyond those encountered in normal daily life. Research data was collected and stored in a locked box until entered electronically.

2.4 Informed Consent

Informed unwritten consent was obtained using the study information sheet or patient information sheet (Appendices B & C). These two sheets include the same information, but are in slightly different formats based on the standard format used at each data collection site (UCI and UMMC). The patient information sheet was approved by the UCI-IRB as well as the Medical Ethics Committee at UMMC, and was used at the UMMC site. The study information sheet was approved by the UCI-IRB and was used at the sites located in the US. These information sheets reviewed the purpose of the study, the eligibility requirements, possible risks and benefits of the study, contact information for human rights research protection offices and the research team, and the right to withdraw from the study at any time. The possible risks associated with the procedures described in this study

included anxiety, embarrassment, social stigma, and invasion of privacy no more beyond that of normal daily life. The information sheets also explained that no compensation or direct benefits were anticipated from participation in the study; possible community benefits included the potential that results from this study may benefit the rare diseases community as a whole by improving access to healthcare. Participants who wished to continue with the study after reading the information sheet were then provided with the survey.

2.5 Survey

The survey was a paper questionnaire (Appendices D & E) consisting of six demographic questions for the participant, and four demographic questions regarding the patient of the appointment, 17 multiple-choice questions with a subquestion for question 9 resulting in 18 total multiple-choice questions, and 26 Likert scale questions about perceived barriers to healthcare. 10 of the multiple-choice questions (5, 9b, 11, 13a, 13b, 14, 15, 16, 17) also included a free-response section for those who selected "other", or answered "yes" to question 6. Participants also wrote additional comments in the margins, which can be found in Appendix F. The major themes addressed in the survey included medical care received, barriers to receiving genetic services and recommended therapies, stress and burden perceived by the participant, and satisfaction of services received for the care of rare diseases. All questions were created by the researcher and piloted on a total of 15 random participants before data collection began. Participants were able to ask the researcher questions during the questionnaire for clarification.

2.6 Data Entry

Data were entered by the lead researcher into Microsoft Excel during the collection period. The lead researcher also completed double-entry of the complete data set after the conclusion of data collection. Any discrepancies between the two entries were then verified and corrected by checking the original survey for the selected response.

2.7 Survey Scoring and Grouping

The multiple-choice questions were coded as categorical variables. Participants were grouped into two categories based on the location of their clinic appointment or consultation: Malaysia and the US. Participants were further divided into categories based on income level, insurance type, education level, and ethnicity.

The free response answers provided in Malay were translated into English by a native speaker, and then translated back to Malay by a different native speaker and compared with the original answer, to ensure there were no misinterpretations in the translation process. One spelling error was found in the word "mengembangkan", no other errors were identified. While answering the free response portion regarding the genetic condition the patient has been diagnosed with, one participant was unsure of what the appropriate response was; the researcher suggested the participant use the diagnosis that the participant perceived to be correct at the time of the survey. Another participant asked for clarification of question 12 regarding the response of "6+ doctors", and asked if 40 doctors would fall under that response; the researcher replied "yes". Three other participants asked for clarification of "therapies"; the researcher responded with "therapies include services such as physical therapy, speech therapy, and occupational therapy". No other questions were asked by participants during the survey.

Section 1 of the Likert scale questions consisted of the rating of five items regarding burden and amount of stress for the participant's family. The scale ranged from 1 to 5 and included not applicable (1= no burden, 2=low burden, 3=moderate burden, 4=high burden, 5=severe high burden, N/A=not applicable). Section 1 also asked the participant to choose the item from section 1 that is perceived as the largest burden or stress factor for the participant and their family.

Section 2 of the Likert scale questions consisted of the rating of 7 items with respect to the effect on the length of time for receiving a diagnosis. The scale ranged from 1 to 5 and included not applicable (1=no effect, 2=low effect, 3=moderate effect, 4=high effect, 5=severe large effect, N/A=not applicable). Section 2 also includes an item asking participants to choose the item from section 2 that is perceived as the largest factor causing difficulty in receiving a diagnosis.

Section 3 of the Likert scale questions consisted of the rating of 14 items on the effect on satisfactory healthcare. The scale ranged from 1 to 5 and included not applicable (1=negative effect, 2=slight negative effect, 3=no effect, 4=slight positive effect, 5= positive effect, N/A=not applicable).

2.8 Survey Analysis

Descriptive statistics consisted of providing counts for categorical variables (multiple choice questions) and means and standard deviations of the Likert Scale variables (Sections 1 through 3). Responses with low counts were grouped with similar responses (i.e., Catholicism and Christianity) in order to increase the statistical power of tests, as well as to fulfill assumptions required for performing statistical tests. Specific groupings for each analysis are detailed in the results. Analyses of the categorical variables were performed

using a two-tailed Pearson chi-squared (X^2) test with a significance level of $p<0.05$ to determine a statistical difference of responses between groups. If expected counts were fewer than 5 after grouping, a Fisher's exact test was performed for contingency table analysis.

Survey analysis of the Likert Scale variables was performed using independent samples T-tests to determine if there was a statistically significant difference in the mean value between two groups, using a significance level of $p<0.05$. One-way analysis of variance (ANOVA) was used for analysis of the Likert Scale variables when determining if there was a statistically significant difference in the mean values between more than two groups, using a significance level of $p<0.05$. If significance was detected, a Tukey post-hoc test was then performed to determine which comparisons between groups contributed to the significance. All *p*-values reported are nominal *p*-values and have not been corrected for multiple comparisons. These tests were conducted using the statistical software, IBM Statistical Package for Social Sciences 23 (IBM, Armonk, NY).

III. RESULTS

3.1 Participant characteristics and demographics

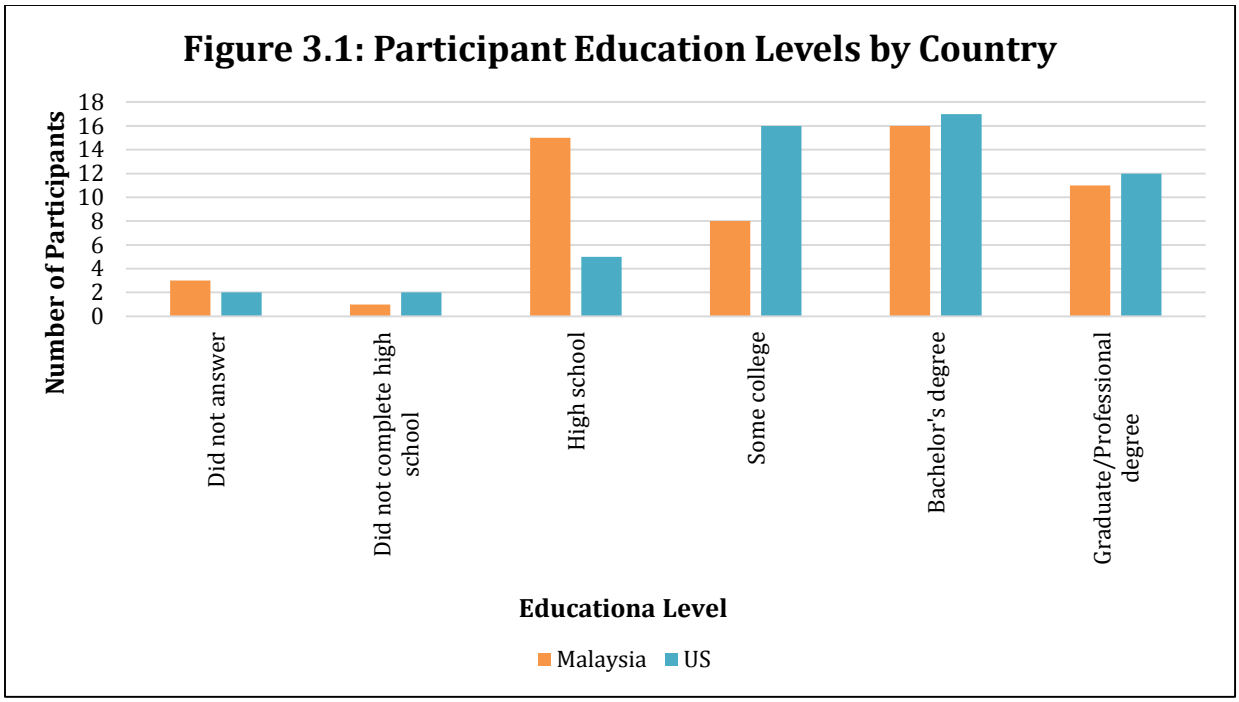
111 study participants began the survey, all of whom were eligible to participate based on age and attendance at a genetics or specialty genetics clinic appointment. 55 of the participants were recruited in Malaysia and 56 of the participants were recruited in California. Of these participants, 108 participants completed more than half the survey, with 54 participants from each country. Three participants were unable to complete more than half the survey due to time constraints. The following demographic characteristics of participants are displayed in Table 3.1; participant age, hospital site of recruitment, gender, country, participant's role of patient or caretaker, educational background, income level, ethnicity, and religion. The age group that was most represented by participants was the 25-34 year age group, with 39 (42%) respondents.

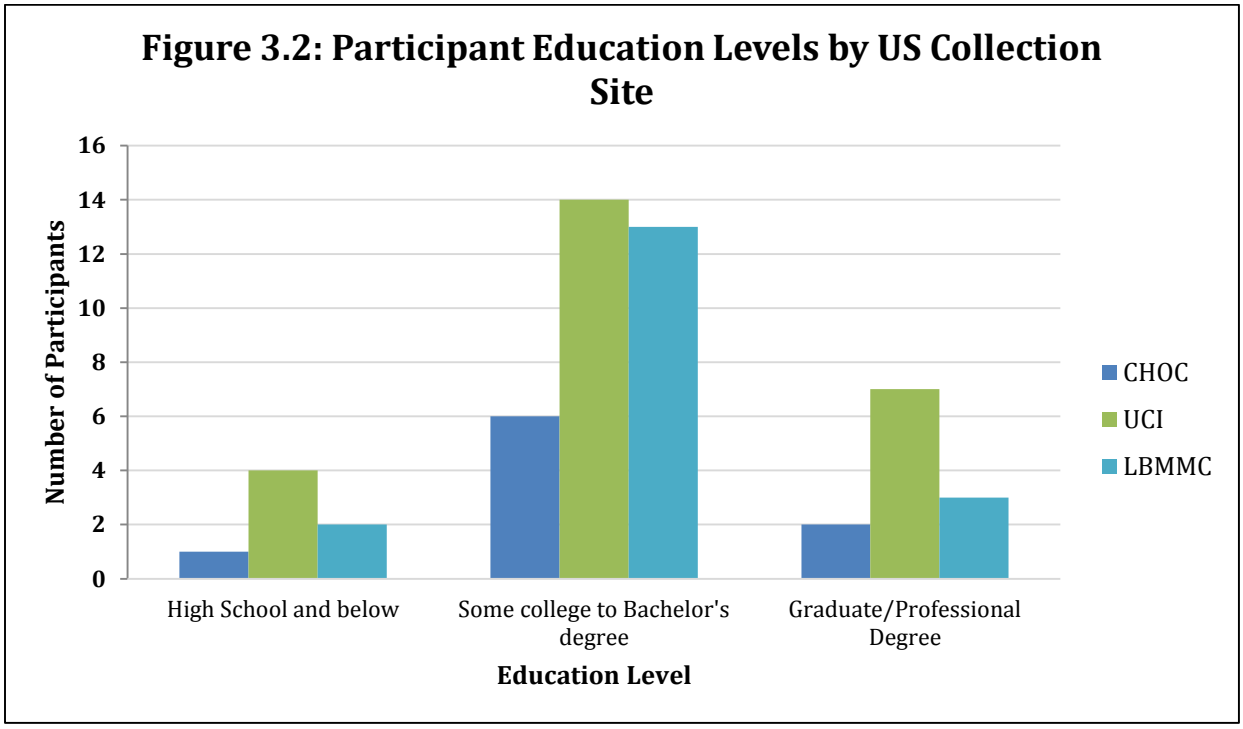
Of the 21 patient participants, 4 were recruited in Malaysia and 17 were recruited in California. Of the 87 caretaker participants, 50 were recruited in Malaysia and 37 were recruited in the US. The mean age of patient participants was 51.5 years, with a range between 18-77 years. The mean age of caretaker participants was 31 years, with a range between 22-82 years. The mean age of patients reported from the caretaker participants was 8.18 years.

Table 3.1: Demographic Characteristics of all Participants	Malaysia	US	Total	
	n	n	n	%
Age (n=94)				
18-24	1	3	4	4
25-34	25	14	39	42
35-44	12	14	26	28
45-54	5	7	12	13
55-64	1	8	9	10
65+	0	3	3	3
Hospital site (n=108)				
University of Malaya Medical Center	54	0	54	50
University of California Irvine	0	26	26	24
Long Beach Memorial Medical Center	0	19	19	18
Children's Hospital of Orange County	0	9	9	8
Gender (n=107)				
Female	35	34	69	65
Male	18	20	38	35
Country (n=108)				
Malaysia	54	0	54	50
United States	0	54	54	50
Patient status (n=108)				
Patient	4	17	21	19
Caretaker	50	37	87	81
Educational background (n=103)				
Did not complete high school	1	2	3	3
High school	15	5	20	19
Some college	8	16	24	23
Bachelor's degree	16	17	33	32
Graduate/professional degree	11	12	23	22
Income level (n=104)				
Low income (<$30,000/year)	20	20	40	39
Middle income ($30,000-$60,000/year)	25	10	35	34
High income (>$60,000/year)	8	21	29	28
Ethnicity (n=108)				
Asian (Malaysian)	23	0	23	21
Asian (Chinese)	20	0	20	19
Asian (Indian)	9	0	9	8
Asian (Other/Pacific Islander)	0	5	5	5
White	0	28	28	26
Black	1	2	3	3
Hispanic	0	12	12	11
Two or more ethnicities	1	7	8	7
Religion (n=98)				
Buddhism	16	1	17	17
Catholicism	1	10	11	11
Christianity	8	18	26	27
Hinduism	8	0	8	8
Islam	19	1	20	20
Judaism	0	1	1	1
None	2	9	11	11
Other	0	4	4	4

Of the 107 participants who reported their sex, 69 (65%) were female and 38 (35%) were male. This remained consistent when comparing participants recruited in Malaysia and participants recruited in the US, X^2 (1 df, N = 107) = 0.110, p=.740. Of the 53 participants who responded in Malaysia, 35 (66%) were female and 18 (34%) were male. Of the 54 participants who responded in the US, 34 (63%) were female and 20 (37%) were male.

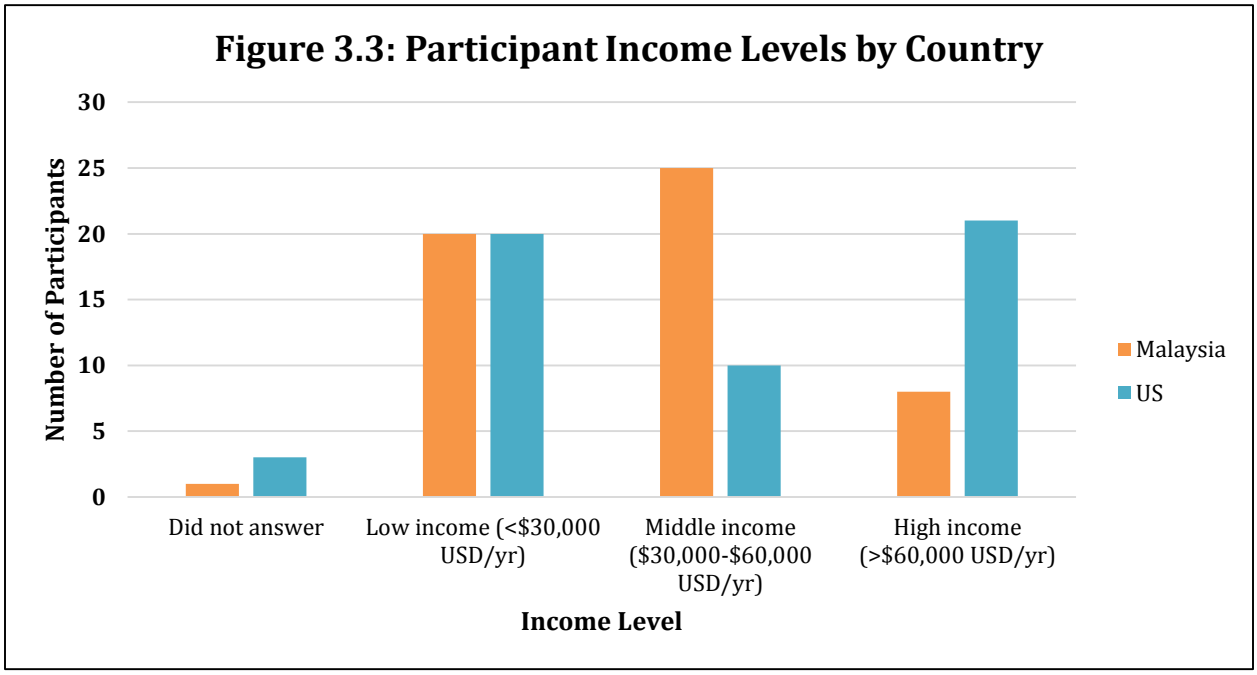
Of the 103 participants who reported their education level, 56 (54%) reported having completed at least a bachelor's degree. See Table 3.1 for reported education levels, Figure 3.1 for comparisons of education levels of respondents in Malaysia and the US and Figure 3.2 for comparisons of education levels of respondents within the US collection sites. Education levels were then grouped into "Up to high school", "Some college of bachelor's degree", and "graduate/professional degree" for analysis. There was no statistical difference observed in education levels reported by participants in the two countries, X^2 (2 df, N = 103) = 4.977, p=.083, however it was noted that there were more Malaysian participants reporting up to high school education than US participants.

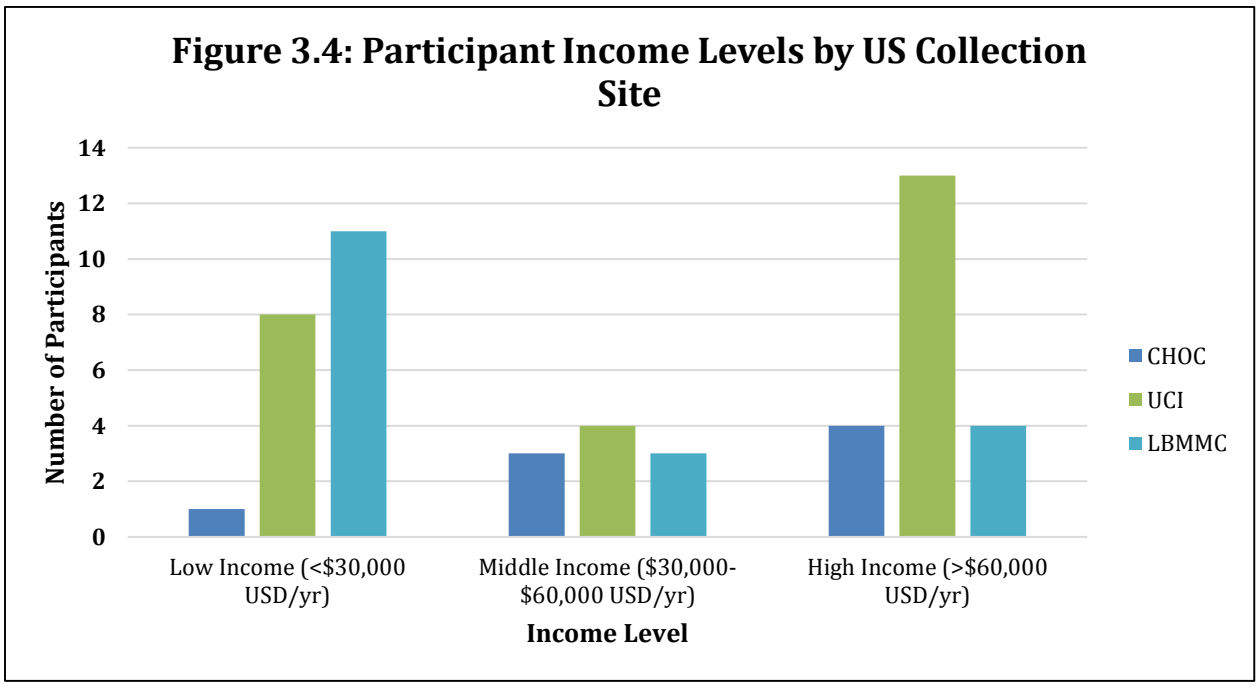




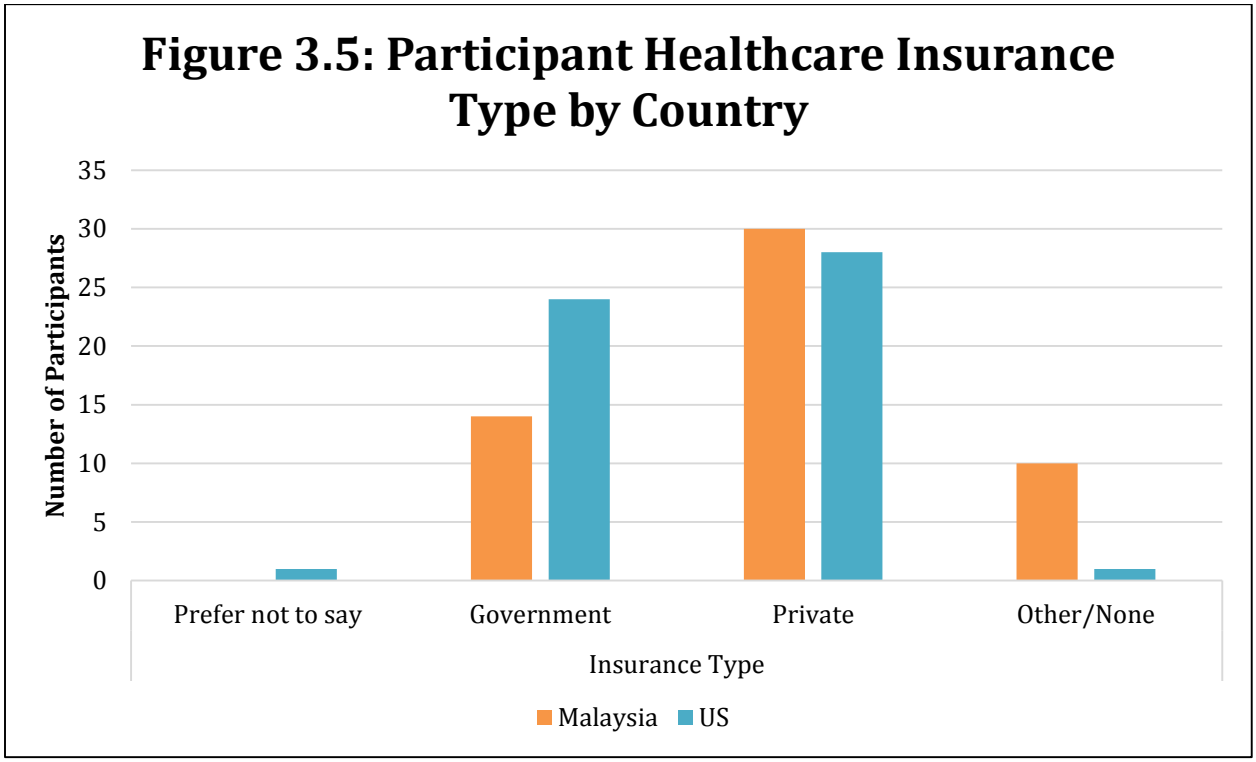
There was an observed difference in reported income levels; more Malaysian participants reported middle income levels and more US participants reported high income levels, X^2, (2 df, N = 104) = 12.222, p=.002. These differences are displayed in Figure 3.3.

There was no observed difference when comparing reported income levels between the US collection sites (p=.089) when using a two-tailed Fisher's exact test, however it was noted that more UCI participants reported high income levels in comparison to LBMMC and CHOC participants. The reported income levels of the US collection sites are shown in Figure 3.4.





Of the participants in Malaysia (n=54), a majority reported having private health insurance (n=30, 56%), with the remaining split between government health insurance (n=14, 26%) and other/no health insurance (n=10, 19%). A majority of the participants in the US (n=54) reported having private health insurance as well (n=28, 52%), however a larger percentage reported having government health insurance (n=24, 44%), and only one participant reported having other/no health insurance (n=1, 2%). There was an observed difference between the reported insurances, with more Malaysian participants reporting "other" and more US participants reporting "government" insurance, X^2, (2 df, N = 107) = 10.056, p=.007.



The participants in Malaysia identified themselves as being Asian Indian, Malaysian, and Chinese, as well as one Black participant. All participants disclosed their ethnicity. There were no participants of mixed ethnicities. The participants in the US identified

themselves as being "Asian (Other/Pacific Islander)", "White", "Black", "Hispanic", as well as mixed ethnicities. 13% (n=7) participants were of mixed ethnicities. . See Table 1 for complete demographic information and Figure 3.6 for reported patient ethnicity by country.

Figure 3.6: Reported Ethnicity of Patient by Country

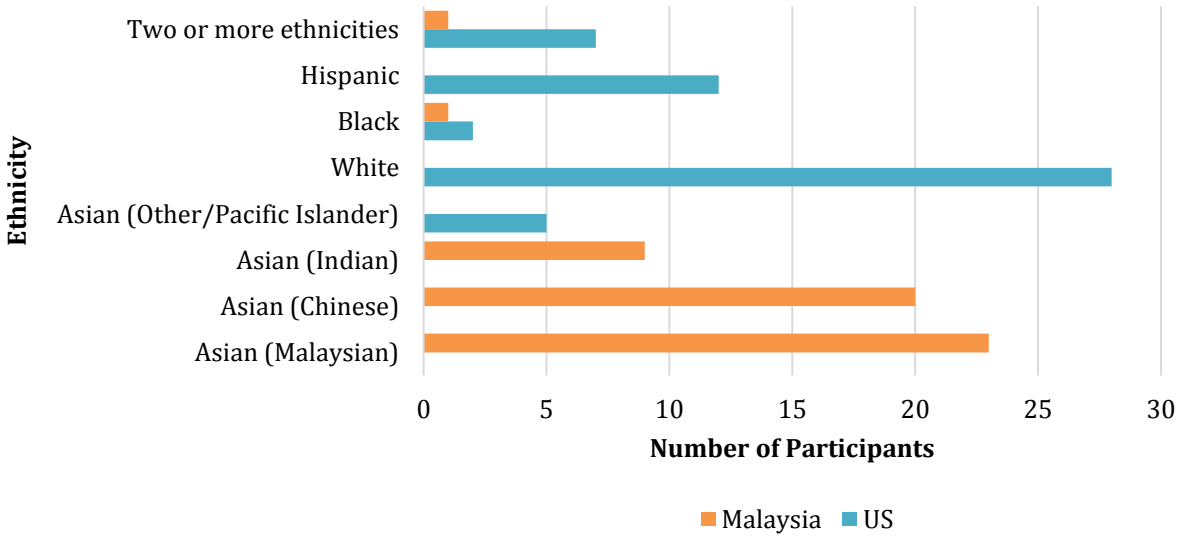
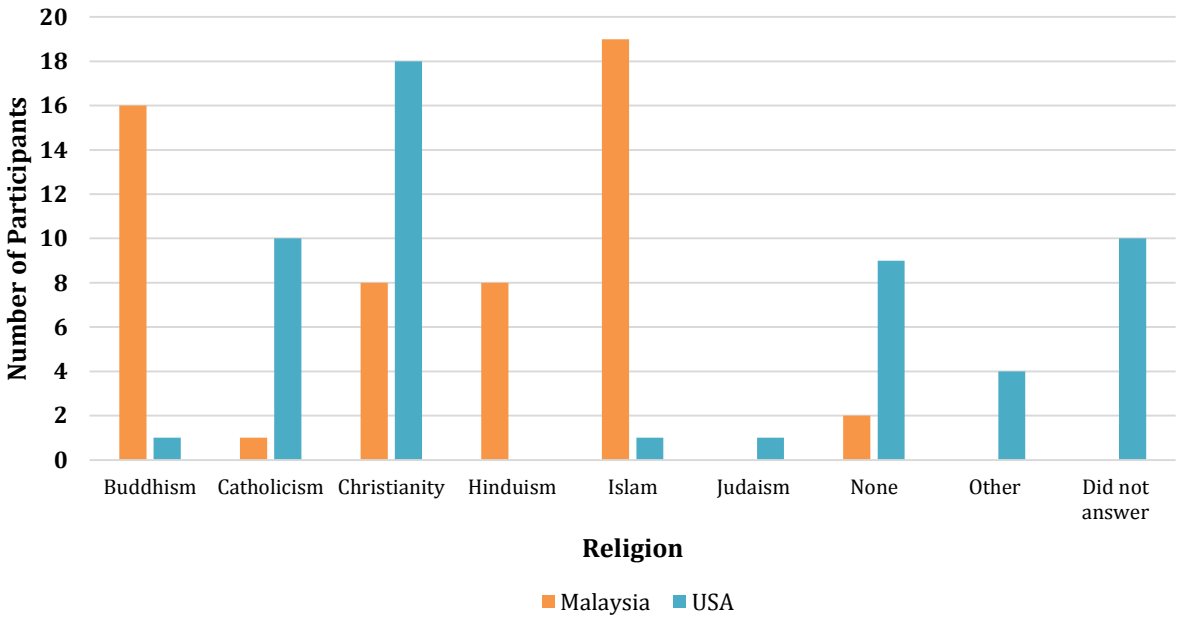


Figure 3.7: Reported Religion of Patient by Country



The participants in Malaysia identified as being of Buddhist, Islamic, Catholic, and Christian religions as well as non-religious participants. All participants in Malaysia disclosed their religious faith. The participants in the US identified as being of Buddhist, Catholic, Christian, Islamic, Jewish religions as well as non-religious individuals and individuals who identified with "other" religions. 10 participants in the US declined to disclose their religious faith.

57 (53%) participants reported that the patient was born in a government or publicly owned hospital, 49 (45%) participants reported that the patient was born in a privately owned hospital, and 2 (2%) participants declined to respond. The distribution remained similar between both countries, X^2 (1 df, N = 106) = 0.631, p=.427.

3.2 Genetic Conditions Diagnosed

Participants were asked whether the patient had been diagnosed with a genetic condition (question 6). Of the 108 participants who answered the question, 49% (n=53) responded "yes, the condition is –" and 51% (n=55) responded "No". The complete list of conditions that were written in the free response portion of this question are listed in Table 3.2. The conditions are listed exactly as the participant wrote on the survey, including spelling, capitalization, and punctuation; the list is unedited, to avoid making any assumptions about the participants' intention. Of the 53 participants who answered "yes", 6 participants did not complete the free response portion of the question.

Table 3.2 Unedited "Genetic disorders" Reported by Participants	
Malaysia (n=20)	**US (n=27)**
3MCTA	beckwith wiedemann
beckwidth wiedemann	Abnormality
cardio diapathy	achondroplasia
Cornelia de lange syndrome	alpha thalassemia, CNS lupus
Down syndrome	Brain
Goldenharr syndrome	chromosomal 13 – autism
Leigh Syndrome	CMT
Morquio syndrome MPS IVa	complex 2 mito disorder + CVID
MPS type IIIa	Ehlers Danlos hypermobile type
neurofibromatosis 1	Ehlers Danlos syndrome
Neurotransmitter	G6PD
NICCD (citrin deficiency)	GSD type 1a
Noonan	intellectual disability
osteogenesis imperfecta	microduplication
pompe but negative/partial pompe	mitochondrial myopathy
septo-optic dysplasia	mitochondrial
Stickler syndrome	Neuropathy
trisomy 21	NF1
tuberous sclerosis	Pompe (n=6)
VACTERL syndrome	primary immunodeficiency, mast cell disease, neutropenia
	trisomy 21
	Vascular Ehlers Danlos

3.3 Genetic Testing Status

Participants were asked to identify whether the patient had genetic testing for the genetic condition (question 7), whether they had told family members of the genetic implications of the condition (question 8), and whether other members of the family besides the patient have had genetic testing for the condition (question 9a). A majority of the participants recruited in Malaysia answered that family members had not had genetic testing for the condition in question (n=43, 80%). Table 3.3 provides a breakdown of the responses given for these three questions by country, and Figures 3.8a, 3.8b, and 3.8c provide comparisons of the responses given by country of site collection. A majority of the participants recruited in the US also answered that family members did not have genetic testing for the condition in question (n=36, 67%). There was no observed statistical difference in responses between the two countries for question 7 (p=0.094), question 8 (X^2 (2 df, N = 107) = 1.387, p=.500), and question 9a (p=0.139). A Fisher's exact test was used for questions 7 and 9.

Table 3.3: Genetic Testing Status and Disclosure	**Malaysia**				**US**			
	Yes	No	I don't know	Total	Yes	No	I don't know	Total
	n (%)	**n (%)**	**n (%)**	**n**	**n (%)**	**n (%)**	**n (%)**	**n**
Question 7: Has the patient had genetic testing for the genetic condition?	30 (56)	19 (35)	5 (9)	54	34 (64)	20 (37)	0 (0)	54
Question 8: Have you told family members of the genetic implications of the condition?	31 (59)	10 (19)	12 (23)	53	33 (61)	6 (11)	15 (28)	54
Question 9a: Have other family members had genetic testing for this condition?	6 (11)	43 (80)	5 (9)	54	14 (26)	36 (67)	4 (7)	54

Figure 3.8a: Question 7 - Has the patient had genetic testing for the genetic condition?

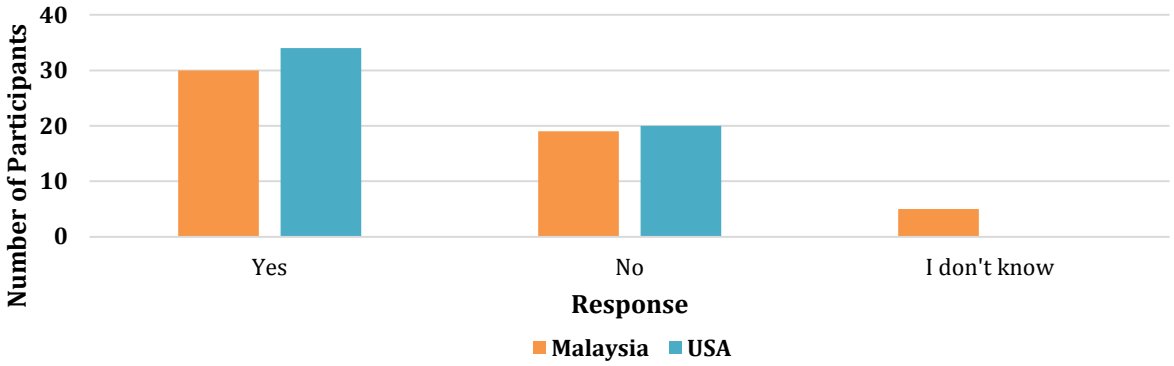


Figure 3.8b: Question 8 - Have you told family members of the genetic implications of the condition?

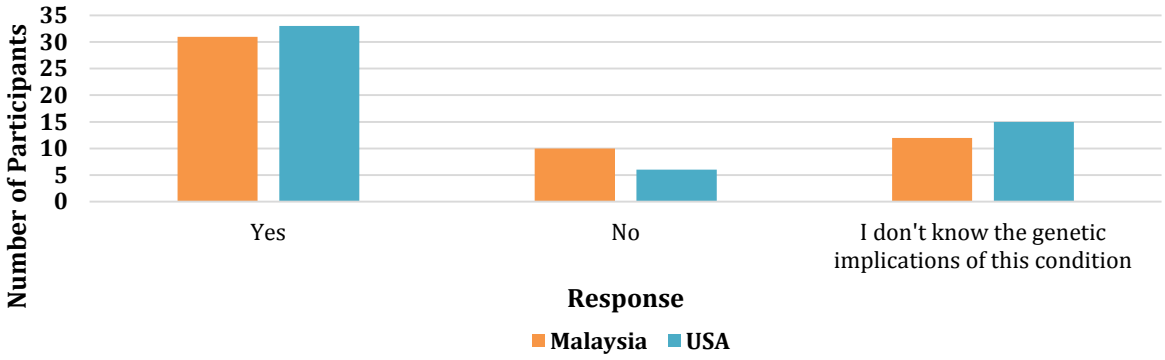
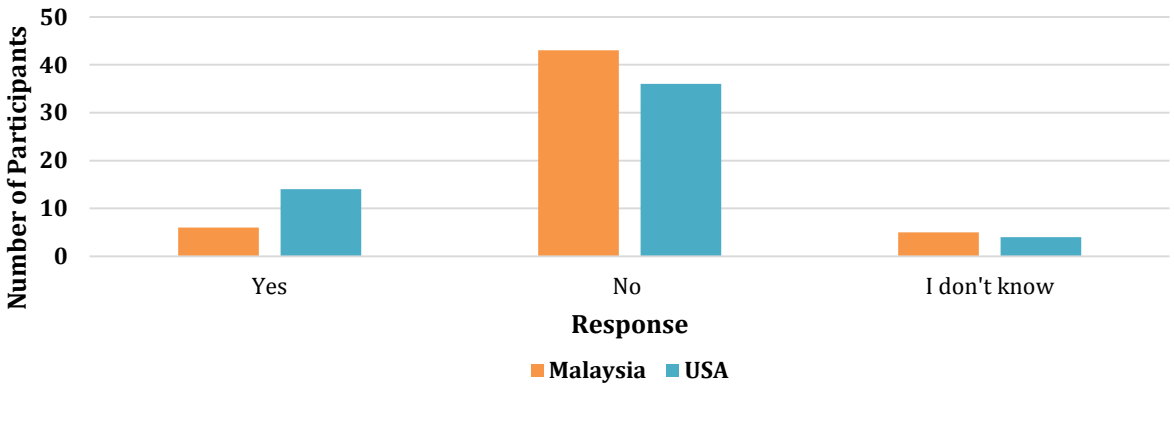


Figure 3.8c: Question 9a - Have other family members had genetic testing for this condition?



Participants whose family members have not had genetic testing were then asked to choose from a list explaining why other members of the family have not received genetic testing (question 9b), the responses are shown in Table 3.4. Those who answered "other:" were able to complete a free response, of which the responses are listed in Table 3.4a.

Table 3.4: Question 9b - Explanations for Family Members not Receiving Genetic Testing	**Country**		**Total**	
	Malaysia	**US**		
	n (%)	**n (%)**	**n**	**%**
It was not offered	21 (45)	7 (19)	28	34
Patient has not received genetic testing	11 (23)	13 (36)	24	29
Burden to family	2 (4)	0 (0)	2	2
Have not told family of condition yet	3 (6)	3 (8)	6	7
Not enough money	2 (4)	3 (8)	5	6
Personal or religious beliefs of family member	2 (4)	2 (6)	4	5
Schedule conflicts	1 (2)	1 (3)	2	2
Other	5 (11)	7 (19)	12	15
p=0.193			88	100

Table 3.4a: Free Response for Question 9b
"Did not feel necessary"
"ignorant"
"testing was negative"
"not diagnosed"
"N/A"
"non-related family"
"they don't have any symptoms"
"also in foster system"

For analyses, "not enough money" and "schedule conflicts" were grouped together as "Money/time". There was no observed difference (p=0.193) between country of collection and responses given as reasons for other family members not having genetic testing when using a Fisher's exact test. It is noted that two participants in Malaysia reported "burden to

family" as the explanation for family members not receiving genetic testing, while no participants in the US chose this response.

3.4 Onset of Symptoms and Receiving a Diagnosis

Table 3.5: Question 10 - At what age were the first symptoms noticed in the patient?	**Country**		**Total**	
	Malaysia	**US**		
	n (%)	**n (%)**	**n**	**%**
Infancy (under 1 year)	29 (54)	13 (25)	42	39
Early childhood (1-2 years)	11 (20)	9 (17)	20	19
Childhood (3-13 years)	14 (26)	14 (26)	28	26
Adolescence (14-19 years)	0 (0)	5 (9)	5	5
Adulthood (over 19 years)	0 (0)	12 (23)	12	11
			107	100

Table 3.6a: Question 11- Who was the person to first notice symptoms?	**Country**		**Total**	
	Malaysia	**US**		
	n (%)	**n (%)**	**n**	**%**
Medical Professional	28 (53)	13 (25)	41	39
Patient	2 (4)	17 (33)	19	18
Parent/Caretaker	20 (38)	19 (37)	39	37
Other	3 (6)	3 (6)	6	6
p<.001*			105	100

Table 3.6b: Question 11- Who was the person to first notice symptoms? (Pediatric and Adult)	**Pediatric**	**Adult**	**Total**	
	n (%)	**n (%)**	**n**	**%**
Medical Professional	37 (48)	4 (14)	41	39
Patient	3 (4)	16 (57)	19	18
Parent/Caretaker	33 (43)	6 (21)	39	37
Other	4 (5)	2 (7)	6	6
p<.001*			105	100

Participants were asked at what age were the first symptoms noticed in the patient (question 10) as well as who the first person to notice symptoms was (question 11), the frequencies of responses to these questions are in Tables 3.5 and 3.6a. Participants who

answered "other:-" in question 11 were able to complete a free response to indicate the first person to notice symptoms in the patient. Responses of the six who answered "other" included "teacher" (n=2), "social worker" (n=1), "friend", (n=1), as well as other family members (n=1).

A difference was observed when using a two-sided Fisher's exact test (p<.001) in response to question 11, where most participants recruited in Malaysia responding with "Medical professional" (n=28) as the first to notice symptoms in the patient, and most participants recruited in the US responding with "Parent/Caretaker" (n=19) or "Patient" (n=17) as the first to notice symptoms in the patient. However, when comparing patient status as pediatric or adult with responses chosen (Table 3.6b) as the first to notice symptoms, a two-sided Fisher's exact test (p<.001) also revealed significance with most participants with adult patient status as responding with "Patient" (n=16) as the first to notice symptoms. This may be explained through there being n=4 adult status patients recruited in Malaysia and n=25 adult status patients recruited in the US, therefore the US participants may be responding with "Patient" due to a later onset of symptoms in the participants recruited, as self-awareness increases with age.

Table 3.7: Question 12 - How many doctors did the patient see between the first onset of symptoms and now?	**Country**		**Total**	
	Malaysia	**US**		
	n (%)	**n (%)**	**n**	**%**
1-2 doctors	15 (28)	12 (23)	27	26
3-4 doctors	10 (19)	25 (47)	35	33
5-6 doctors	10 (19)	3 (6)	13	12
6+ doctors	18 (34)	12 (23)	30	29
p*=.008			105	100

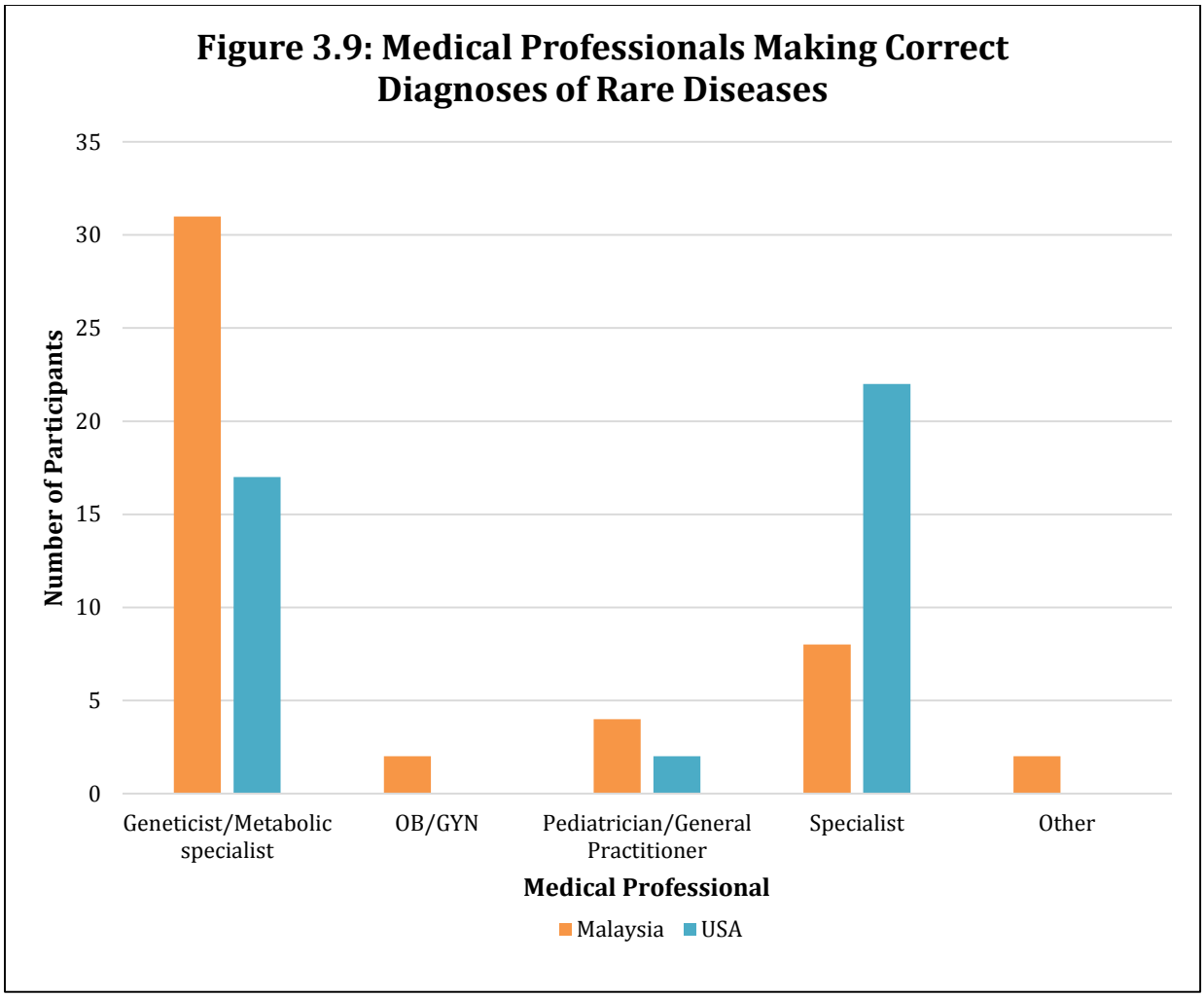
Participants were asked how many doctors the patient has seen since the first onset of symptoms until a diagnosis was made, or if there was still no diagnosis how many doctors

the patient had seen by the time of the survey (question 12) and the responses are shown in Table 3.7. Additionally, patients wrote in additional comments such as "40+ doctors!" and "Approx. 20-60+ doctors". A difference was observed (X^2 (3 df, N = 105) = 11.723, p=.008) between the proportions of responses chosen for number of doctors seen by participants recruited in Malaysia and the US.

Table 3.8a: Question 13a - Which medical professional made the correct diagnosis?	**Country**		**Total**	
	Malaysia	**US**		
	n (%)	**n (%)**	**n**	**%**
Geneticist/Metabolic specialist	31 (66)	17 (41)	48	55
OB/GYN	2 (4)	0 (0)	2	2
Pediatrician/General Practitioner	4 (9)	2 (49)	6	7
Specialist	8 (17)	22 (54)	30	34
Other	2 (4)	0 (0)	2	2
p*=0.001			88	100

Participants were asked to specify which type of medical professional made the correct diagnosis of the condition in the patient (question 13a) and the responses are shown in Table 3.8a. Participants who answered "other:-" were able to complete a free response to specify which type of medical professional made the correct diagnosis of the condition in the patient. Free responses to question 13a included "psychiatric doctor" and "Regional Center".

Of those with diagnoses (n=88), a difference was observed when using a two-sided Fisher's exact test (p=0.001) where participants recruited in Malaysia largely had correct diagnoses made by geneticists or metabolic specialists (n=31) while a majority of the participants recruited in the US reported that specialists (n=22) made correct diagnoses, closely followed by geneticists or metabolic specialists (n=17).



Participants were then asked to specify which type of medical professionals made an incorrect diagnosis, if any (question 13b) and the results are displayed in Table 3.8b, There was a total of n=48 responses with a misdiagnosis, and n=60 responses with no misdiagnoses made. The most frequent responses were specialists (31%, n=15) and pediatricians or general practitioners (31%, n=15) identified as medical professionals making misdiagnoses. Participants who answered "other:-" were able to complete a free response to specify which type of medical professional made an incorrect diagnosis of the patient. Only one of the n=7 who chose "other" completed the free response, and identified a "midwife" as the medical professional who made a misdiagnosis.

Table 3.8b: Question 13b - Which medical professional made an incorrect diagnosis?	Country		Total	
	Malaysia	US		
	n (%)	n (%)	n	%
Geneticist/Metabolic specialist	3 (12)	2 (9)	5	10.5
Nurse	1 (4)	0 (0)	1	2
OB/GYN	4 (16)	1 (4)	5	10.5
Pediatrician/General Practitioner	5 (20)	10 (43)	15	31
Specialist	7 (28)	8 (35)	15	31
Other	5 (20)	2 (9)	7	15
p=.289			48	100

"Nurse" was grouped into "other", and "OB/GYN" was grouped into "Specialist" for analyses. There was no observed difference using the Fisher's exact test (*p*=.289) between the proportions of responses chosen by participants recruited in Malaysia and the US in regards to medical professionals giving misdiagnoses.

3.5 Transportation

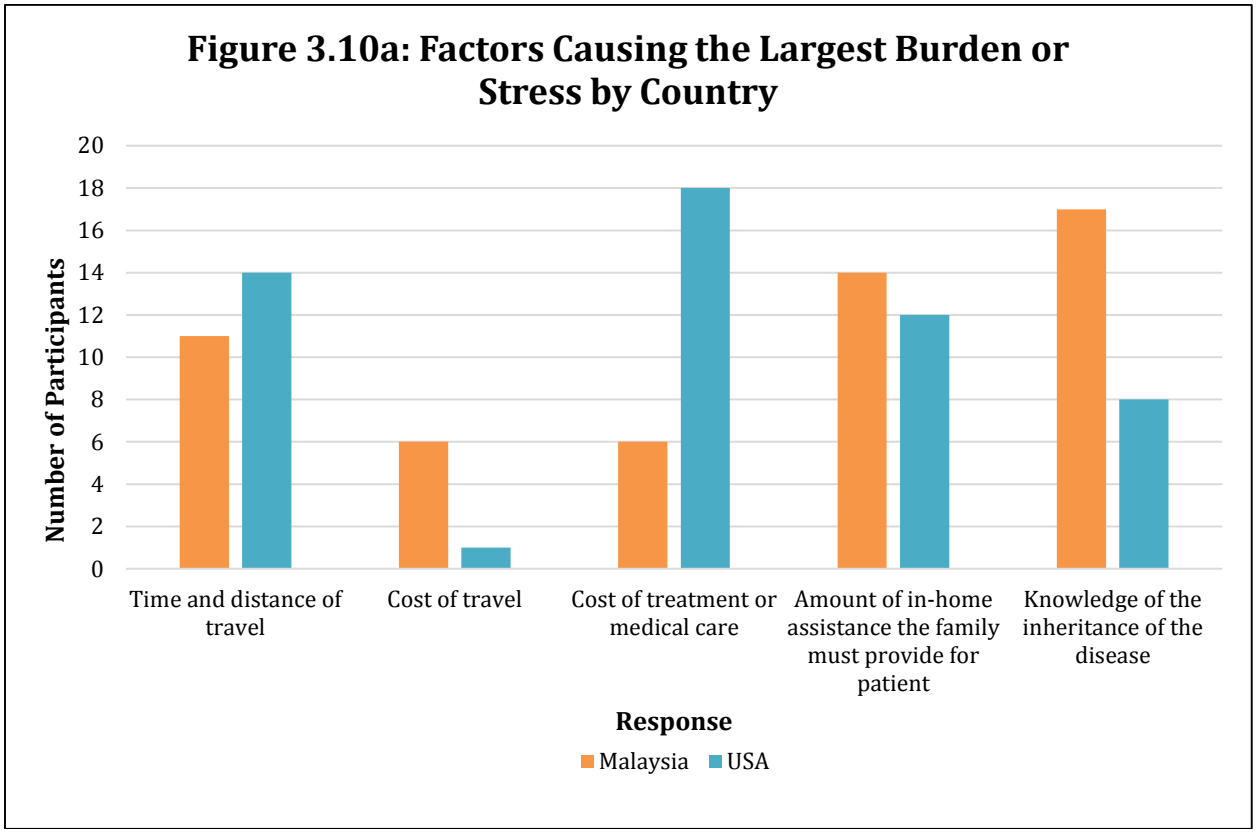
Participants were asked what type of transportation the patient usually uses to go to the hospital (question 15) and the responses are shown in Table 3.9. Participants who answered "other:-" were able to complete a free response to specify which type of transportation the patient uses more frequently. Free responses provided were "ambulance" and "van". There was no observed difference using the Fisher's exact test (*p*=0.421) between the proportions of responses chosen by participants recruited in Malaysia and the US with 91% (n=97) participants selected "car/motorcycle" as the type of transportation used by the patient to go to the hospital.

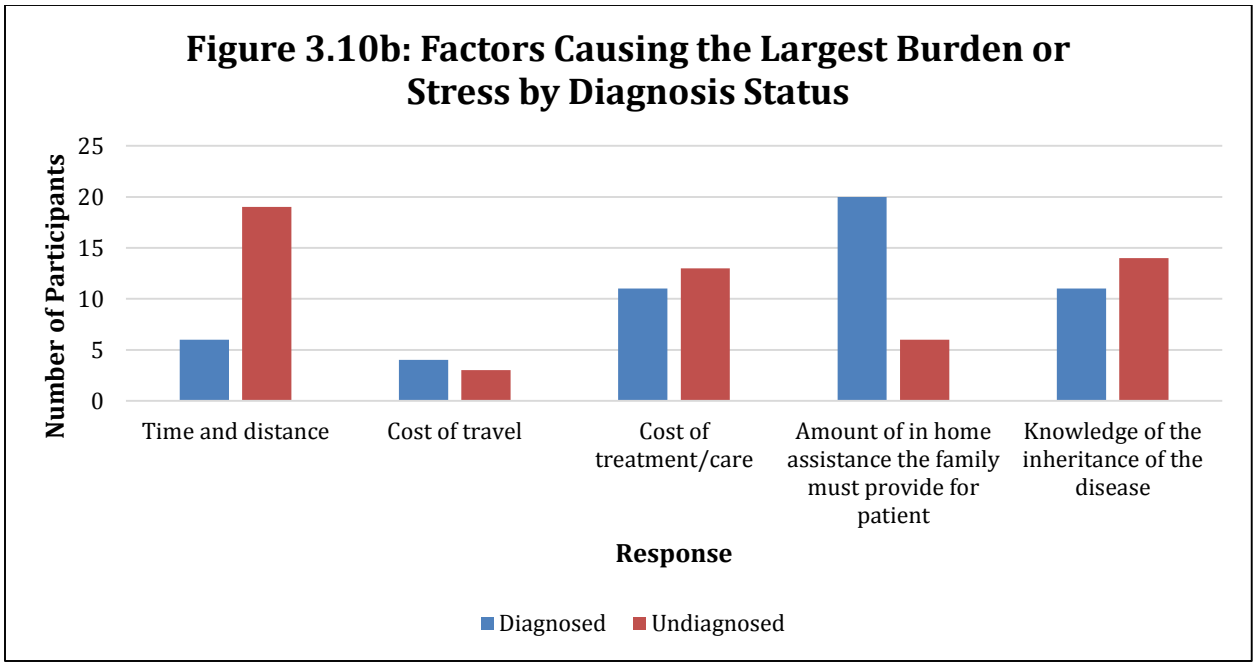
Table 3.9: What type of transportation does the patient use to go to the hospital?	Country		Total	
	Malaysia	US		
	n (%)	n (%)	n	%
Bus	2 (4)	2 (4)	4	4
Car/Motorcycle	47 (89)	50 (93)	97	91
Taxi/Hired car service	3 (6)	0 (0)	3	3
Train	0 (0)	1 (2)	1	0.9
Other	1 (2)	1 (2)	2	2
			107	100

3.6 Burden and Stress Factors on the Family

Participants were asked using Likert scale questions to weigh the burden or amount of stress on the family (section II). Factors included were "time and distance to travel to the hospital or care center", "cost of travel to the hospital or care center", "cost of treatment/medical care for the patient", "amount of in home assistance the family must provide for the patient", and "knowledge of the inheritance of the disease". After rating the burden associated with each factor, participants were then asked to choose the factor that caused the largest burden or stress. Responses are displayed in Table 3.10 and Figure 3.10a, and the results of the independent samples t-test are displayed in Table 3.11. When using a Fisher's exact test, there was a significant difference (p=0.009) in the factor causing the most burden as chosen by participants recruited in Malaysia and the US, with a majority of the participants recruited in Malaysia selecting "knowledge of the inheritance of the disease" and with a majority of the participants recruited in the US selecting "cost of treatment or medical care". Table 3.11 also displays the means of the Likert scale ratings of these stress and burden factors.

Table 3.10: Factor Causing Most Burden or Stress	Country		Total	
	Malaysia	US		
	n (%)	n (%)	n	%
Time and distance of travel	11 (20)	14 (26)	25	23.5
Cost of travel	6 (11)	1 (2)	7	7
Cost of treatment or medical care	6 (11)	18 (34)	24	22
Amount of in-home assistance the family must provide for patient	14 (26)	12 (23)	26	24
Knowledge of the inheritance of the disease	17 (31)	8 (15)	25	23.5
p*=0.009			107	100





There was an observed difference (p=0.004) between the largest stress factor for families with diagnoses and those without diagnoses shown in Figure 3.10b. Most families that have a diagnosed genetic condition selected the "amount of in home assistance the family must provide for the patient" (n=20) as being the largest stress factor, while most families without diagnosed genetic conditions selected "Time and distance to travel to the hospital or care center" (n=19) as the largest stress factor and burden for their families.

When using a Fisher's exact test, there was no observed association between the factor causing the most stress for participants and their families and income level (p=0.279), insurance type (p=0.917), participant sex (p=0.544), participant education level (p=0.954), or participants' patient or caretaker status (p=0.327).

Table 3.11: Independent Samples T-test of Stress Factors and Country of Collection

	Country						95% CI for Mean Difference		
	Malaysia			US					
	M	SD	n	M	SD	n		F(df)	*p*
Time and distance of travel	2.81	1.3	54	2.37	.98	51	-.01, .89	4.289 (103)	.055
Cost of travel	2.78	1.3	54	2.00	.90	50	.35, 1.2	8.229 (102)	**<.001***
Cost of treatment or medical care	2.80	1.4	51	2.58	1.2	50	-.31, .76	3.516 (99)	.406
Amount of in-home assistance the family must provide for patient	3.08	1.2	51	2.36	1.4	45	.20, 1.2	2.296 (94)	**.007***
Knowledge of the inheritance of the disease	3.28	1.2	47	2.71	1.2	45	.09, 1.0	.009 (90)	**.021***

3.7 Length of Time to Diagnosis

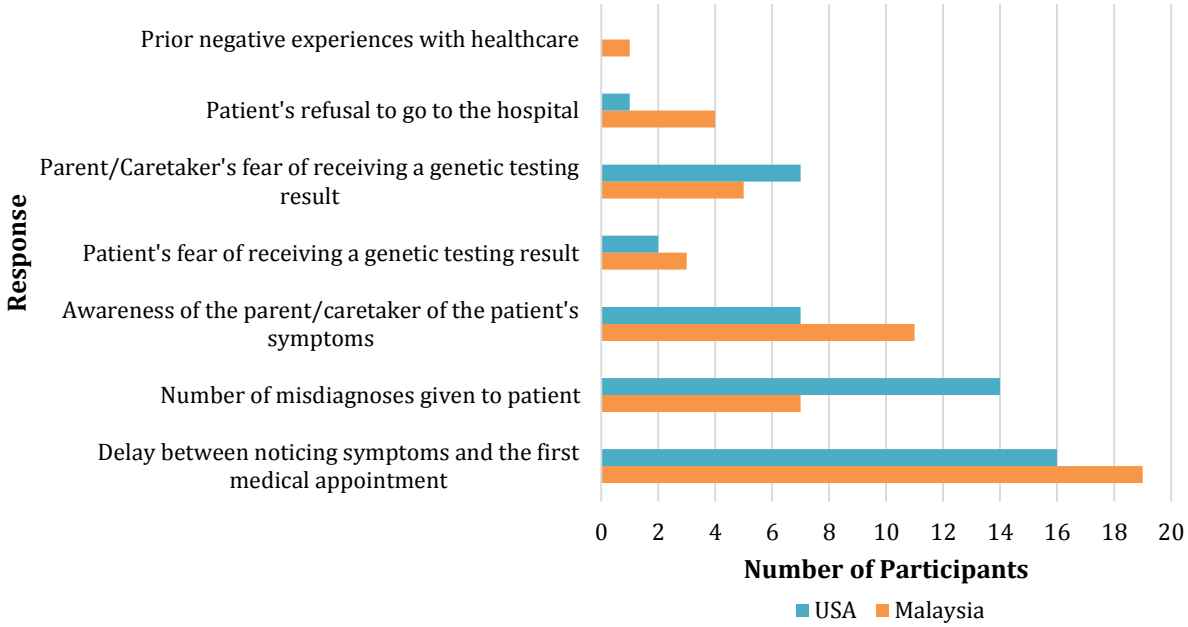
Participants were asked using Likert scale questions to rate the effect of certain factors on the length of time to receive a diagnosis for the patient (section III). Factors included were "the delay between noticing symptoms and the first medical appointment", "the number of misdiagnoses given to the patient", "the awareness of the parent/caretaker of the patient's symptoms", "the patient's fear of receiving a genetic testing result", "the parent/caretaker's fear of receiving a genetic testing result", "the patient's refusal to go to the hospital", and "the family's prior negative experiences with healthcare". Participants were then asked to choose the factor that had the largest effect on the length of time to receive a diagnosis and the responses are shown in Table 3.12. A majority of participants (36%, n=35) indicated that the response "the delay between noticing symptoms and the first medical appointment" had the largest effect on the time it took to receive a diagnosis.

Patient's fear and parent/caretaker's fear of receiving a genetic testing result were grouped and "patient's refusal to go to the hospital" and "prior negative experiences with healthcare" were grouped for analyses. There was no observed association using the

Fisher's exact test (p=0.204) between the proportions of responses chosen by participants recruited in Malaysia and the US in regards to the factor that had the largest effect on the length of time to receive a diagnosis.

Table 3.12: Factors Causing Greatest Delay in Diagnosis	**Country**		**Total**	
	Malaysia	**US**		
	n (%)	**n (%)**	**n**	**%**
Delay between noticing symptoms and the first medical appointment	19 (39)	16 (34)	35	36
Number of misdiagnoses given to patient	7 (14)	14 (30)	21	22
Awareness of the parent/caretaker of the patient's symptoms	11 (22)	7 (15)	18	19
Patient's fear of receiving a genetic testing result	3 (6)	2 (4)	5	5
Parent/Caretaker's fear of receiving a genetic testing result	5 (10)	7 (15)	12	12
Patient's refusal to go to the hospital	4 (8)	1 (2)	5	5
Prior negative experiences with healthcare	1 (2)	0 (0)	1	1
p=0.204			97	100

Figure 3.11: Factors Causing Greatest Delay in Diagnosis



There were no observed associations using the Fisher's exact test between the response chosen indicated as causing the greatest difficulty to receiving a diagnosis and the following demographic characteristics; insurance type (p=0.930), income level (p=0.666), education level (p=0.292), participant sex (p=0.962), or participants' patient or caretaker status (p=0.098).

Table 3.13: Independent Samples T-test for Factors Causing Delay in Diagnosis and Country

	Country						95% CI for Mean Difference	F(df)	*p*
	Malaysia			US					
	M	SD	n	M	SD	n			
Delay between noticing symptoms and first medical appointment	3.04	1.1	51	2.74	1.4	47	-.22, .81	6.569 (96)	.260
Number of misdiagnoses given to the patient	2.61	1.1	44	2.70	1.3	40	-.61, .43	1.704 (82)	.741
Awareness of the parent/caretaker of the patient's symptoms	3.02	1.2	47	2.21	1.1	42	.33, 1.3	.245 (87)	**.001***
Patient's fear of receiving a genetic testing result	2.49	1.3	41	1.78	1.1	41	.18, 1.2	3.521 (80)	**.010***
Parent/caretaker's fear of receiving a genetic testing result	2.52	1.4	44	1.98	1.0	44	-.03, 1.1	7.505 (86)	**.039***
Patient's refusal to go to the hospital	1.85	1.2	41	1.41	.99	39	-.05, 0.93	5.077 (78)	.076
Family's prior negative experiences with healthcare	2.30	1.3	44	1.73	.87	41	.08, 1.0	8.283 (83)	**.022***

When comparing means, this study found that participants in Malaysia rated the awareness of the parent/caretaker of the patient's symptoms as having a larger effect on the length of time to receive a diagnosis (3.02 ± 1.2) compared to participants in the US (2.21 ± 1.1), $t(87) = .245$, p=0.001; participants in Malaysia rated the patient's fear of receiving a

genetic testing result as having a larger effect on the length of time to receive a diagnosis (2.49 ± 1.3) compared to participants in the US (1.78 ± 1.1), $t(80) = 3.521$, $p=0.010$; participants in Malaysia rated the parent/caretaker's fear of receiving a genetic testing result as having a larger effect on the length of time to receive a diagnosis (2.52 ± 1.4) compared to participants in the US (1.98 ± 1.0), $t(86) = 7.505$, $p=0.039$; and that participants in Malaysia rate the family's prior negative experiences with healthcare as having a larger effect on the length of time to receive a diagnosis (2.30 ± 1.3) compared to participants in the US (1.73 ± 0.99), $t(83) = 8.283$, $p=0.022$. The results of the independent samples t-test comparing the means between the two countries are displayed in Table 3.13.

3.8 Satisfaction with Healthcare

Participants were asked using Likert scale questions to indicate the effect of certain factors on the satisfaction with the patient's healthcare ranging from negative to positive effects (section IV), the results of the independent samples t-test performed for the means of healthcare satisfaction by the country of collection are shown in Table 3.14. The exact format of the survey questions can be found in Appendices D and E.

Table 3.14: Independent Samples T-test for Healthcare Satisfaction by Country

	Country						95% CI for Mean Difference		
	Malaysia			US					
	M	SD	n	M	SD	n		F(df)	*p*
Time spent travelling	2.96	1.2	50	3.04	1.3	47	-.57, .41	.231 (95)	.738
Condition being missed at birth	2.76	1.4	45	2.18	1.0	33	-.01, 1.2	3.140 (76)	.053
Cost of treatment/medical care	3.00	1.2	49	2.43	1.2	44	.08, 1.1	.007 (91)	**.024***
Cost of transportation	2.88	1.2	49	2.64	.99	44	-.22, .70	1.249 (91)	.297
Ethnicity of patient/family	2.98	1.2	47	2.90	.94	41	-.37, .53	3.576 (86)	.737
Explanation of inheritance	3.48	1.3	48	3.91	1.1	43	-.93, .07	2.299 (89)	.092
Use of genetic counselor	3.92	1.1	38	4.24	.89	41	-.76, .11	.071 (77)	.143
General public's attitude towards genetics	2.90	1.2	48	3.17	.79	42	-.71, .17	8.183 (88)	.224
Number of sites for patient's healthcare	3.33	1.1	49	3.18	1.1	44	-.32, .61	.249 (91)	.541
Patient/family's mistrust of healthcare	3.10	1.2	49	2.86	.72	36	-.20, .68	8.337 (83)	.281
Patient's perception of being a burden	2.87	1.1	39	2.54	.96	37	-.13, .79	.026 (74)	.157
Primary care provider's knowledge	3.33	1.2	42	3.26	1.5	47	-.49, .65	3.172 (87)	.786
Referral to genetics/metabolics	3.72	1.0	50	4.16	1.0	45	-.85, -.02	.946 (93)	**.042***
Religious beliefs of patient/family	3.85	1.0	47	3.34	.73	35	.10, .92	13.219 (80)	**.016***

This study revealed that participants in Malaysia rated the cost of treatment and medical care as having no effect on their perception of satisfactory healthcare (3.00 ± 1.2) compared to participants in the US as rating it having a slightly negative effect (2.43 ± 1.2), $t(91) = 2.30$, $p=.024$. It also revealed that participants in Malaysia rate the referral to a genetics or metabolics clinic as having less of a positive effect on their perception of satisfactory healthcare (3.72 ± 1.0) compared to participants in the US (4.16 ± 1.0), $t(93) = -2.065$, $p=.042$. Lastly, it revealed that participants in Malaysia rate religious beliefs as having

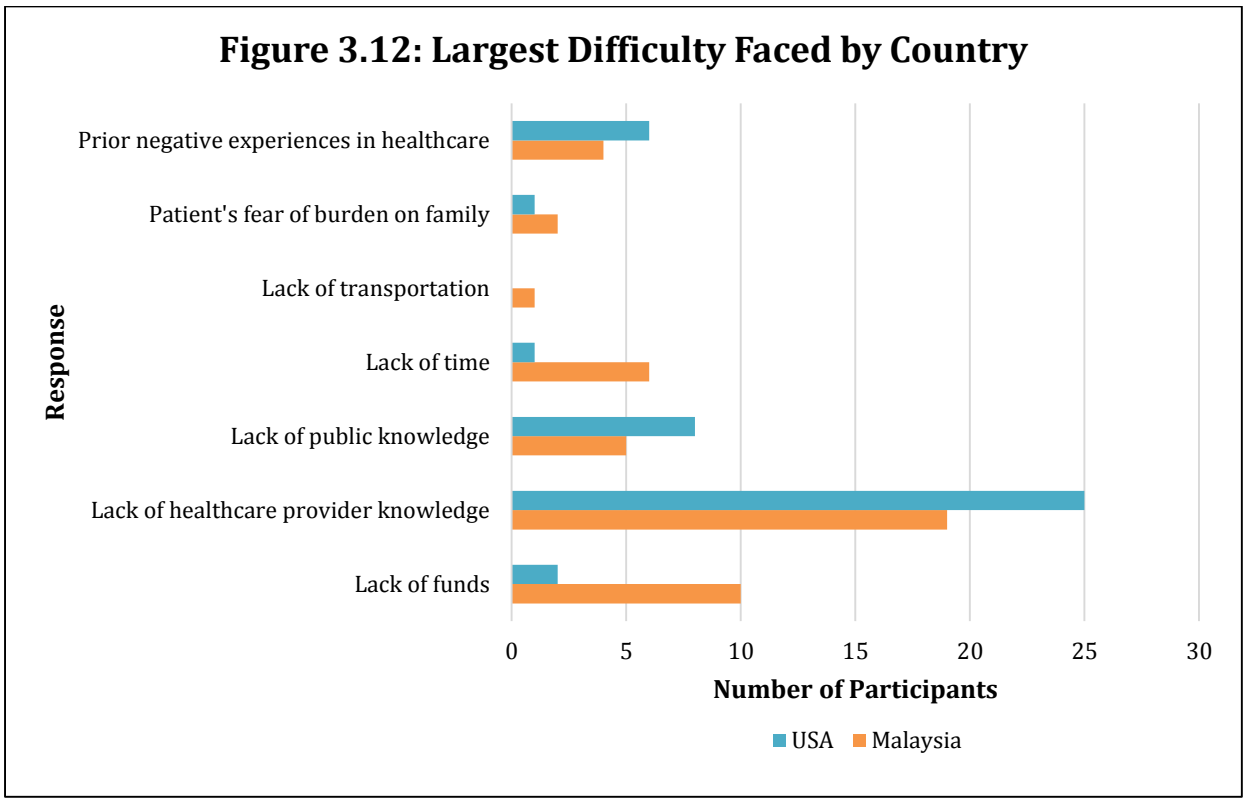
a more positive effect on their perception of satisfactory healthcare (3.85 ± 1.0) compared to participants in the US (3.34 ± 0.73), $t(79.7) = 2.602$, $p=.011$. When comparing participants of different religious faiths and their rating of effect of religious belief upon healthcare satisfaction, those of Islamic faith (n=19) rated it as most positive (4.11 ± 1.1) while those of Catholic faith (n=9) rated it as having a slight positive effect (3.22 ± 0.44). For further values, refer to Table 3.14a. "Catholicism" was grouped into "Christianity" for the one-way ANOVA. There was a statistically significant difference between groups as determined by the one-way ANOVA ($F(4,70) = 2.774$, $p=.034$). A Tukey post-hoc revealed that those of Islamic faith (4.11 ± 1.1) rated the effect of religion more positively than those who do not identify with a religion (3.00 ± 0.0).

Table 3.14a: Religious Belief and Rating of Effect on Healthcare Satisfaction

Religion	M	SD	n	95% CI for Mean Difference
Buddhism	3.59	1.1	17	3.01, 4.16
Catholicism	3.22	0.44	9	2.88, 3.56
Christianity	3.44	0.71	18	3.09, 3.79
Hinduism	3.60	0.99	5	2.49, 4.71
Islam	4.11	1.1	19	3.57, 4.64
None	3.00	0.0	7	3.00, 3.00

Participants were asked to choose the largest difficulty faced to receive satisfactory healthcare for the patient's condition (question 18), which are displayed in Table 3.15 and Figure 3.12. There was an observed difference ($p=0.042$) using the Fisher's exact test between the proportions of responses chosen by participants recruited in Malaysia and the US. A majority of participants in Malaysia selected "lack of healthcare provider knowledge" and "lack of funds" as the largest difficulty faced, while participants in the US selected "lack of healthcare provider knowledge" and "lack of public knowledge" as the largest difficulties.

Table 3.15: Largest Difficulty Faced to Receive Satisfactory Healthcare	Country		Total	
	Malaysia	US		
	n (%)	n (%)	n	%
Lack of funds	10 (22)	2 (5)	12	13
Lack of healthcare provider knowledge	19 (40)	25 (58)	44	49
Lack of public knowledge	5 (11)	8 (19)	13	14
Lack of time	6 (13)	1 (2)	7	8
Lack of transportation	1 (2)	0 (0)	1	1
Patient's fear of burden on family	2 (4)	1 (2)	3	3
Prior negative experiences in healthcare	4 (9)	6 (14)	10	11
p*=0.042			90	100



There were no observed associations between the response chosen indicated as the largest difficulty being faced to receiving satisfactory healthcare and the following demographic characteristics; family insurance type (p=0.228), family income level (p=0.231), participant education level (p=0.502), participant sex (p=0.157), or participants' patient or caretaker status (p=0.123).

3.9 Barriers to Receiving Treatment or Therapies

If the patient is not receiving treatment or therapies, the participant was asked to select a reason for why the patient is not receiving treatment or therapies (question 16 and question 17, respectively), and the results for treatments are shown in Table 3.16 with the results for therapies shown in Table 3.17. Free responses (n=6) of participants who selected "other" for question 16 are shown in Table 3.16a. A Fisher's exact test revealed that there was no observed significance (p=0.118) when comparing the proportions of responses chosen by participants in Malaysia and the US in regards to why patients are not receiving treatments. Out of the 108 total number of participants, 30% (n=32) are receiving treatments, with n=12 responding from Malaysia and n=20 responding from the US.

Table 3.16: Question 16 - Reasons Given for those Not Receiving Treatment	**Country**		**Total**	
	Malaysia	**US**		
	n (%)	**n (%)**	**n**	**%**
Not enough money	4 (10)	0 (0)	4	5
No transportation	2 (5)	0 (0)	2	3
No caretaker	1 (2)	0 (0)	1	4
No time for care	3 (7)	0 (0)	3	74
No treatment available	27 (64)	29 (85)	56	3
Using alternative treatment methods	1 (2)	1 (3)	2	10
Other	4 (10)	4 (12)	8	1
p=0.118			76	100

Table 3.16a: Free Response Portion of Question 16	
Malaysia (n=4)	**US (n=4)**
"n/a"	"waiting"
"unsure of diagnosis"	"not ordered"
	"no known problems"
	"insurance"

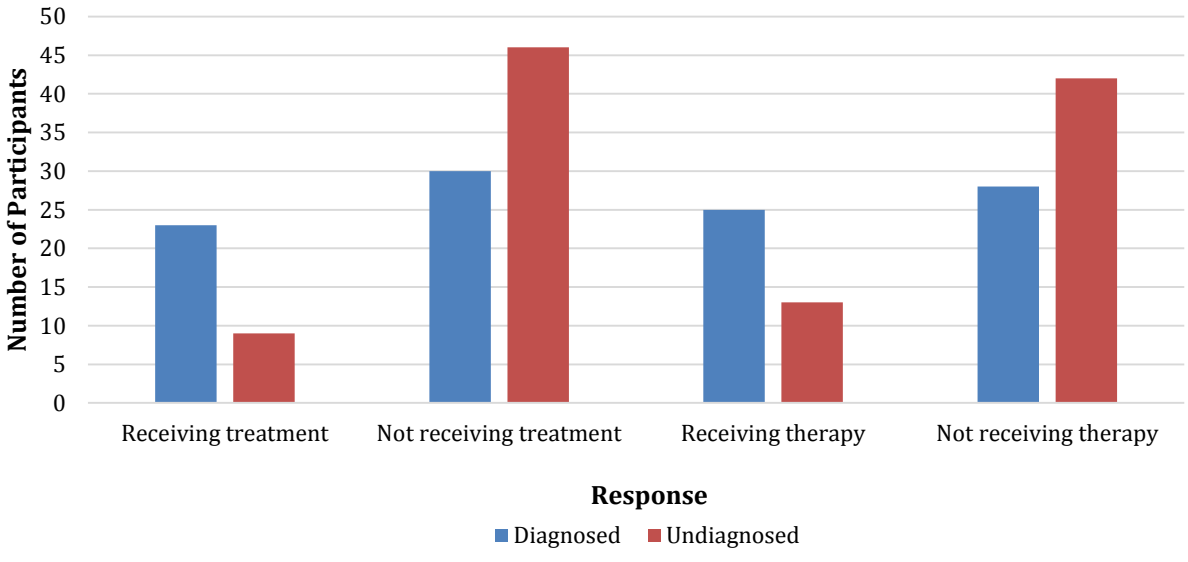
Free responses (n=5) of participants who selected "other" for question 17 are shown in Table 3.17a. A Fisher's exact test revealed that there was an observed different (p=0.003) when comparing the proportions of responses chosen by participants in Malaysia and the US in regards to why patients are not receiving therapies. Participants in Malaysia provided varied responses for reasons why the patient was unable to receive therapy, whereas 73% (n=22) of the participants in the US selected the reason as "no therapies needed". Out of the 108 total number of participants, 35% (n=38) are receiving therapies, with n=14 responding from Malaysia and n=24 responding from the US. A statistically significant difference was observed when comparing whether participants in the two countries were receiving therapies, where more respondents in the US reported receiving therapies, X^2 (1 df, N = 108) = 4.060, p=.044.

Table 3.17: Question 17 - Reasons Given for those Not Receiving Therapy	**Country**		**Total**	
	Malaysia	**US**		
	n (%)	**n (%)**	**n**	**%**
Not enough money	5 (13)	1 (3)	6	9
No caretaker	1 (2)	0 (0)	1	1
No time for care	7 (18)	1 (3)	8	11
No therapies needed	15 (38)	22 (73)	37	53
Mistrust of therapy	2 (5)	0 (0)	2	3
Using alternative therapeutic methods	6 (15)	0 (0)	2	9
Personal/religious beliefs	1 (2)	0 (0)	1	1
Other	3 (7)	6 (20)	9	13
p*=0.003			70	100

Table 3.17a: Free Response Portion of Question 17	
Malaysia (n=3)	**US (n=9)**
“n/a”	"waiting"
	“not ordered”
	“N/A”
	“regional center is not giving him a therapist”

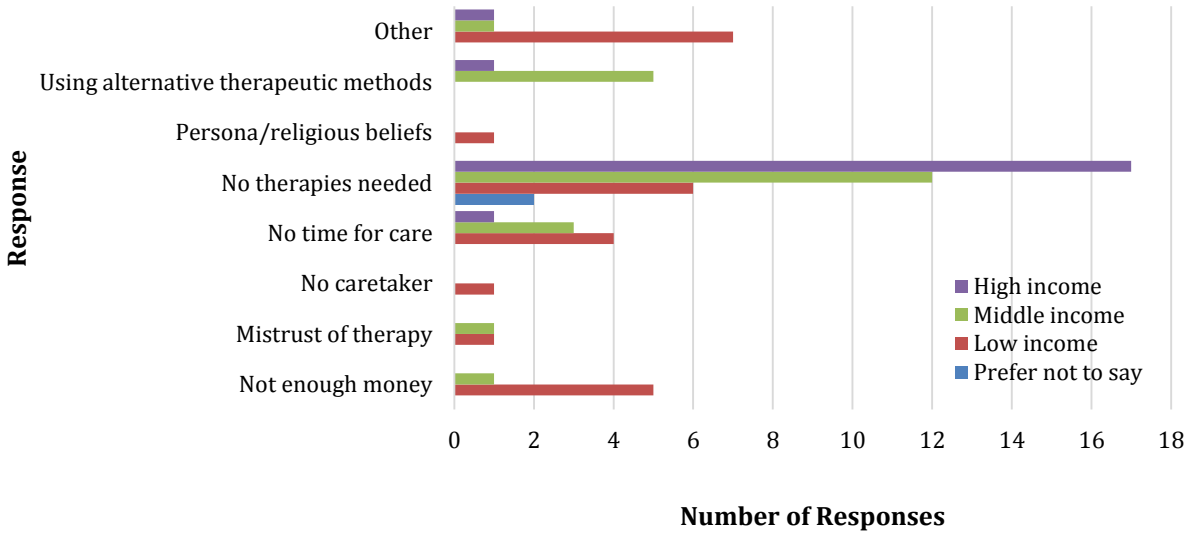
Of the 53 participants with diagnoses of genetic conditions in their families, 47% (n=25) are receiving therapies, compared to the 24% (n=13) of the 55 participants without diagnoses. 43% (n=23) of participants with diagnoses are also receiving treatments, compared to 16% (n=9) of participants without diagnoses. The differences of diagnosis status on treatment and therapy status are displayed in Figure 3.13. For therapies, there was an observed difference (p=.008) among different income levels and reasons for not having therapies.

Figure 3.13: Diagnosis Status and Treatment or Therapy Services



There were no observed associations between the response chosen reasons for not having received treatment and the following demographic characteristics; family insurance type (p=0.126), family income level (p=0.201), participant education levels (p=0.095), participant sex (p=0.264), or participants' patient or caretaker status (p=0.688). There were no observed associations between the response chosen reasons for not having therapies and the following demographic characteristics; family insurance type (p=0.580), participant education level (p=0.271), participant sex (p=0.390), or participants' patient or caretaker status (p=1.000) when using a Fisher's exact test. There was an observed difference (p=0.002) when comparing participant income levels and responses chosen in regards to reasons why patients are not receiving therapies, the differences are displayed in Figure 3.14. It is noted that those of middle or high income level did not select "not enough money" while those of low income did not select "using alternative therapeutic methods".

Figure 3.14: Income Level Differences Among Responses for Not Receiving Therapies



3.10 Most and Least Beneficial for Patients

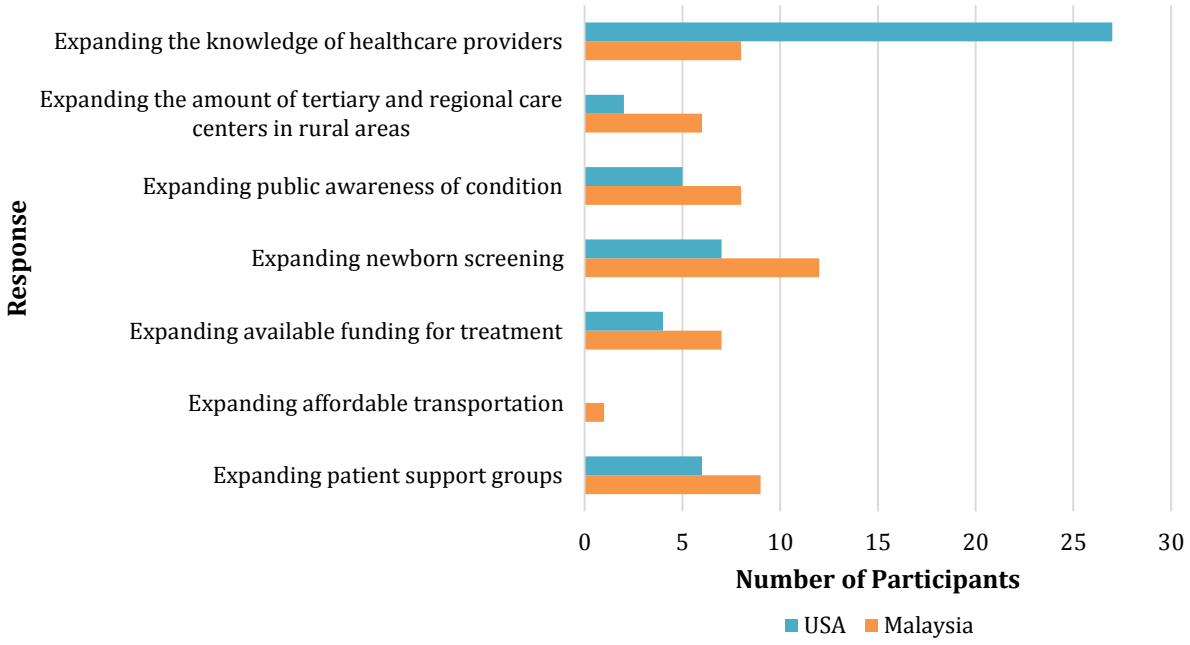
Participants were asked to select what they believed would be the *most* helpful for people with the diagnosed genetic condition and what they believed would be the least helpful (question 19 and question 20, respectively), of which the results are displayed in Tables 3.18 and 3.18a as well as Figures 3.16. The selections with the most responses as being the most beneficial were 34% (n=35) answering "expanding the knowledge of healthcare providers", 19% (n=19) answering "expanding new born screening program (checking babies at birth for this condition)", and 15% (n=15) answering "expanding patient support groups". Participants in Malaysia had a wider spread of responses, with the most being centered on newborn screening, support groups, healthcare provider knowledge and public awareness of the rare disease.

The selections with the most responses as being the *least* helpful were 44% (n=42) answering "expanding affordable transportation" and 19% (n=18) answering "expanding the amount of tertiary and regional centers in rural areas".

Table 3.18: Tools Selected as Most Beneficial for those with Rare Diseases	**Country**		**Total**	
	Malaysia	**US**		
	n (%)	**n (%)**	**n**	**%**
Expanding patient support groups	9 (18)	6 (12)	15	15
Expanding affordable transportation	1 (2)	0 (0)	1	1
Expanding available funding for treatment	7 (14)	4 (8)	11	11
Expanding newborn screening	12 (24)	7 (14)	19	19
Expanding public awareness of condition	8 (16)	5 (10)	13	13
Expanding the amount of tertiary and regional care centers in rural areas	6 (12)	2 (4)	8	8
Expanding the knowledge of healthcare providers	8 (16)	27 (53)	35	34
p*=0.006			102	100

Table 3.18a: Tools Selected as Least Beneficial for those with Rare Diseases	Country				Total	
	Malaysia		US			
	n (%)		n (%)		n	%
Expanding patient support groups	3	(6)	5	(11)	8	8
Expanding affordable transportation	20	(41)	22	(47)	42	44
Expanding available funding for treatment	4	(8)	1	(21)	5	5
Expanding newborn screening	5	(10)	5	(11)	10	11
Expanding public awareness of condition	4	(8)	4	(9)	8	8
Expanding the amount of tertiary and regional care centers in rural areas	12	(24)	6	(13)	18	19
Expanding the knowledge of healthcare providers	1	(2)	4	(9)	5	5
p=0.445					96	100

Figure 3.15: Tools Selected as Most Beneficial for Patients with Rare Disease



There was a significant difference (p=0.006) when comparing participants in Malaysia and the US and responses chosen as being the most helpful for those with the diagnosed genetic condition using a Fisher's exact test. There were no observed associations

between the response chosen as the most helpful for people with the diagnosed genetic condition and the following demographic characteristics; family insurance type (p=0.426), family income level (p=0.320), participant education level (p=0.220), participant sex (p=0.195), or participants' patient or caretaker status (p=0.230). There was no observed difference in those with or without diagnoses of genetic conditions (p=0.087) or with the number of doctors the patient has seen (p=0.389).

There was no observed difference (p=0.445) when comparing between the two countries for the responses chosen as the least helpful when using a Fisher's exact test. There were no observed associations when using a Fisher's exact test between the response chosen as the *least* helpful for people with the diagnosed genetic condition and the following demographic characteristics; family insurance type (p=0.121), family income level (p=0.301), participant education level (p=.098), participant sex (p=0.242), or participants' patient or caretaker status (p=0.992). There was no observed difference in those with or without diagnoses of genetic conditions (p=0.869) or with the number of doctors the patient has seen (p=0.755).

IV. Discussion

Rare disease patients make up approximately 6-8% of currently ill European patients and about 10% of current American patient population.[4, 5, 9, 12] There is currently no working definition of "rare disease" in Malaysia, therefore there is no estimate of the rare disease patient population. These patients are an important part of the current healthcare system, as healthcare has begun to move towards "precision medicine" and integrating genetic and genomic medicine into medical care. As healthcare is improving around the world, developed countries have moved their focus away from infectious diseases and towards chronic illness and preventative care. Many of these rare diseases are chronic conditions, and therefore have become the current target for healthcare improvement. Insurance policies in the US are recognizing this movement and have begun implementing measures to ensure that patients are able to have the most beneficial services for their needs, such as requiring genetic counseling prior to genetic testing.[1] An estimated 80% of all rare diseases are genetic in origin, therefore many rare disease patients require genetic evaluations by medical geneticists and genetic counselors.[5, 8] Not only do the insurance policy changes help patients to interact with the appropriate providers, but they also help the healthcare system by limiting the number of unnecessary genetic tests being ordered. The importance of this study is to explore the barriers being perceived by these patients when accessing genetic services, and to determine whether these perceived barriers differ based on patient characteristics. By including international patients in this study, cultural sensitivities between patients may also be uncovered. A better understanding of these factors may direct appropriate actions and interventions on improving access and satisfaction of these services.

The priorities of the healthcare system and the priorities of patients and their families are not always aligned. Ideally, improvements to healthcare would be made that would benefit both parties, and both parties would prioritize the same areas needing improvement. However, in practice this is not necessarily the case due to limited funding and the lengthy process of implementing healthcare system changes on the national level.

The purpose of this study was to broadly assess the perceptions of patients and their caretakers when being asked about barriers in access to healthcare. By better understanding the wants and needs of patients, intervention programs and systemic changes may be implemented specifically and better focused for those dealing with rare diseases, as this population goes largely unnoticed when healthcare policies are implemented on a large scale. While large-scale programs may take time to be put into motion, the hope is that this study will be able to provide evidence that there are aspects that may be improved upon that may not require large-scale programs. This study was conducted by collecting anonymous surveys responses from the sample population at genetics and metabolics clinics. This study analyzed the total sample population of participants for differences in perceived barriers and stress factors based on location, age, sex, educational background, ethnicity, religion, insurance type, diagnosis status, and income levels.

4.1 Travel time and clinic accessibility

Participants largely did not consider travel time and travel costs to be an important factor of stress and burden for the family. For a few participants, travel time and costs were considered to have higher amounts of stress for their families. This was particularly true for caretakers with more severely affected patients, lower income, and farther distances to travel. Patients arriving at the University of Malaya Medical Center (UMMC) clinic may have

traveled from down the street, or may have traveled from a different state, which could take several hours. Most patients travelled by car in both countries. Those who use public transportation rated travel times and costs as higher stress factors for their families.

One of the hypotheses in this study was that the participants in Malaysia would perceive the lack of care centers and the travel time and costs for care to be larger burdens than the participants in California. It was found that both Malaysian and Californian participants did not perceive the lack of care centers to be a priority for patients. In fact, increasing the number of care centers was chosen more often as being the least beneficial for patients with rare diseases. The responses of the participants in Malaysia regarding the question of the most beneficial tool for those with rare disease were spread across many responses, such as expanding newborn screening and increasing patient support groups. This is most likely due to the limited newborn screening in Malaysia, lack of specific patient support groups, among other factors that differ from the resources available in the US.

The aspect of healthcare perceived as causing the greatest difficulty and requiring the most improvement for rare disease patients at both collection sites pointed towards improving healthcare provider knowledge of genetic conditions. This can be interpreted as patients wanting to increase knowledge of the existing providers, rather than have more available providers in their area. This was ascertained by asking what the participant perceived to be the greatest difficulty experienced during their experience with healthcare, as well as what improvement of the healthcare system would be the most beneficial. This could be interpreted as a need for more geneticists and genetic counselors, or for increased knowledge among specialists, general practitioners, and other physicians utilizing genetic testing. Oftentimes, geneticists and genetic counselors educate other medical providers

during residency programs, grand rounds, and continuing medical education conferences.[27, 48] Again, this points towards a need for more geneticists and genetic counselors.

In the United States, genetic counseling training programs are increasing enrollment numbers, however there are limitations due to the need for clinical training sites.[58, 61] US based genetic counseling program directors consider clinical training site availability the main barrier to expanding the size of genetic counseling programs.[58, 61] In Malaysia, although there are significantly fewer genetics clinics,[51, 77] the patients traveling to these clinics also preferred to increase provider knowledge as opposed to increasing the amount of clinics available. Without an established genetic counseling training program in the country, and very few in the entire region of Southeast Asia as well as lack of government positions for genetic counselors, increasing the number of genetic counselors quickly may not be currently feasible in the region. While it may be possible to increase the number of medical geneticists, another possible route is to integrate a more comprehensive genetics and genomic medicine course into medical education. In this way, physicians will have increased knowledge and will also be more accessible to patients. In both the US and Malaysia, genetics clinics often have long wait lists, where patients possibly wait for months before an opening is available. One way to reduce the genetics clinic wait list is to help other physicians become more comfortable and knowledgeable with ordering genetic testing, as well as helping educate providers when a referral is inappropriate.

4.2 Healthcare provider knowledge regarding rare diseases

The field of medical genetics is constantly growing and is propelled by advances in technology and medicine, which are linked. In this digital age, as more information is shared through databases, more is understood about these rare and "ultra-rare" diseases. Since each condition is rare and unique, it is understandable that most physicians are not experts on each and every rare condition imaginable, however a basic understanding of genetics would be practical. Medical genetics expertise requires a comprehensive understanding of the basics of genetics. If a physician is not well versed with a particular condition, the option of a referral to a genetics clinic remains. If genetic diagnoses are being made by inexperienced physicians utilizing genetic testing outside of the genetics clinic, problems may arise. Several specialists have begun to incorporate genetic testing into their practices, such as neurologists and cardiologists. [62, 69] A recent study found that although neurologists and psychiatrists are ordering genetic tests, a majority do not have a geneticist or genetic counselor to whom to refer patients.[62]

This study found a statistically significant difference between the proportions of responses given by participants in Malaysia compared to participants in the US for the question asking which type of medical professional made the correct diagnosis for the patient. In Malaysia, a majority of the participants reported having the correct diagnosis made by a geneticist or metabolic specialist, while in the US a majority of correct diagnoses are being made by other specialists, closely followed by geneticists. In the US, genetic tests are being ordered frequently by specialists outside of the genetics clinic. However, these specialists may not understand how to interpret the subsequent test results, or may not be knowledgeable about the rare condition that would be revealed by the testing results. [62] For

example, a neurologist may order a genetic test for a child with seizures, however if the result returns for a condition that has many symptoms besides just seizures, a geneticist may be able to more confidently recommend screening and treatment methods for the other symptoms of the condition. It is possible that as genetic testing becomes more widely available, specialists in Malaysia may also begin to utilize these diagnostic tools more often. However, in order to effectively and efficiently use genetic testing to benefit patients, it appears that participants in both countries would like to see improvement of healthcare provider knowledge of these rare conditions. Guidelines regarding genetic testing are being published and are beginning to become accepted among several organizations. One example is the recent guidelines regarding clinical exome sequencing which have been accepted by the American Academy of Neurology.[39]

There are many approaches that can be used to expand healthcare provider knowledge of rare diseases today. For example, this could be achieved through the encouragement of using physician friendly resources that are approved of in the genetics community, such as GeneReviews and the Online Mendelian Inheritance in Man database, which are curated by the National Center for Biotechnology Information. If information seeking and data mining are appropriately directed, accurate information can be provided.

Medical school students are required to take a medical genetics course, which varies in coverage of topics between institutions. Improvement and standardization of these courses and core competencies could be another outlet for improving education. In 2001 in the US, the American Society of Human Genetics and the Association of Professors in Human and Medical Genetics issued a statement regarding integration of medical genetics education into medical school curriculum known as the “Medical School Core Curriculum in Genetics”.

[22] It was around this time that more coursework in medical genetics began to be required in medical school. However, the coursework is highly variable. For example, a medical genetics course in Thailand could be anywhere from a week to a month long. [64] At the growing pace of the utilization of genetic testing services, medical school curricula around the world are being pushed to expand and include proper education regarding genetic and genomic medicine. [60, 66] The group "Inter-Society Coordinating Committee for Practitioner Education in Genomics" has been formed by the National Human Genome Institute, which is charged with determining how to integrate adequate education of medical genetics into the medical school curricula.[40]

4.3 Factors influencing delay in diagnosis

Patients with rare disease often embark on the long and arduous journey referred to as the "diagnostic odyssey". While this study found a statistically significant difference in responses from Malaysia and the US in regards to the first person to notice symptoms, further analysis revealed that this may largely be due to the differences in genetic conditions represented by the two populations. The patients in the US included some with later onset diseases that may begin to manifest in adolescence and adulthood, while all patients recruited in Malaysia were presenting with symptoms before 18 years. Therefore, it cannot be concluded that there is a true difference in first person to notice symptoms between the two populations.

Similarly, the difference in age at which first symptoms were noticed was also found to be statistically significant, with earlier ages in Malaysia and later ages in the US. However, age is heavily confounded by the inclusion of several adult onset conditions of participants in the US and the lack of these conditions in the participants in Malaysia.

As mentioned before, the current waitlists for genetics clinics are very long. This study found that patients and their families perceive the delay between noticing symptoms and the first medical appointment as having the largest impact on delay in diagnosis, which reflects the lengthy wait times. Many patients are scheduled months in advance, and some patients have even taken it upon themselves to push for earlier appointments through other clinics that may not be as well equipped to handle patients with complex rare conditions; this may cause further delay. Many participants perceived that misdiagnoses also had a large impact on the time to receive a diagnosis. The approaches discussed above for improving healthcare provider education will also be beneficial in reducing the likelihood of a misdiagnosis.

Another important factor that some participants selected as delaying a diagnosis was the fear of receiving a genetic testing result. Even though only 18% (n=17) of participants selected this as the factor causing the greatest delay in diagnosis, it is important to address. Some possible explanations may be concerns about genetic discrimination and stigmatization. In the US, the Genetic Information Non-discrimination Act (GINA) protects patients from healthcare discrimination as well as employer discrimination, but does not currently extend to life insurance or long-term care.[14] Participants entering genetics clinics are typically offered information on GINA, and it is often a part of informed consent for genetic testing. However in Malaysia and much of Southeast Asia, there are no such protections. This may be impacting the uptake of genetic testing services; this has also been confirmed by other studies.[30, 51, 76] However this remains to be further studied outside of the cancer genetics setting.

4.4 Factors influencing stress and burden on families

This study revealed that participants in Malaysia found that knowledge of inheritance of the genetic condition caused the largest burden or stress on the family, whereas the participants in the US found the cost of medical care and treatment to be the largest burden or stress. This may stem from the difference in healthcare insurance policies for the two countries, as well as the different services available for those with disabilities. Those in the US with a preferred provider organization (PPO) health insurance plan often pay a percentage of their healthcare costs until a deductible and out of pocket payment has been met for the year, which may range from a few hundred USD to several thousand USD depending on the plan. It can also be difficult to obtain coverage for genetic testing due to insurance policies considering several types of genetic testing as "investigational" and "experimental". In Malaysia, the universal healthcare system is in place, however genetic testing is more difficult to obtain because most laboratories are based outside of the country and require out of pocket payments. Visits to government-designated physicians and hospitals are generally covered, however the wait lists may be several months long, and enzyme replacement treatments are largely funded by government funds and supplemented by charities. Again, genetic testing services are often not included in the public and private sectors of Malaysian healthcare insurance policies.[51]

Another possible explanation of the participants in Malaysia selecting the knowledge of inheritance as the greatest stress factor could be cultural differences between the two participant populations. All but one participant recruited in Malaysia identified themselves as being of an Asian ethnicity, with very few participants in the US. Asian culture differs from Western philosophy in that the family functions as one, and each member contributes to the

unity and bettering of the whole family.[65] Asian women in particular have strong feelings of self-blame and shame incorporated into their cultural values, and low feelings of self-worth may occur if a woman feels that her duty to her family is to bear healthy children, yet has a child with a rare disease.[57, 65] The family model for many Southeast Asian cultures emphasize the value of a large number of healthy children, because these healthy children will in turn provide support for their parents in the future.[57, 65] If these children are not healthy and the parents are expected to care for them throughout their lifetime, it may be perceived as shameful and burdensome. This has been found in other studies as well, particularly the burden of carrier status.[30, 57, 76] Carrier status has been cited frequently as a barrier to receiving genetic testing in the cancer setting in Southeast Asia, but has yet to be examined in the context of autosomal recessive conditions.[30, 76] This study was able to compare responses between participants in Southeast Asia and the US, some of which who identified autosomal recessive conditions in their families. The differences in responses of the largest stress factor provide further evidence that cultural differences should be considered when providing genetic counseling to patients' families, particularly on the subject of inheritance.

This study also found that most patients' families have not had familial testing because it was either not offered, or the patient has not had genetic testing. This survey was unable to ascertain reasons why the patient may not have had genetic testing. Other responses chosen included cost concerns, the family being unaware of the condition, and burden to family. There was no statistical difference among the responses chosen by participants in the two countries, however it was noted that two participants in Malaysia chose burden to family as the main reason why familial testing was not performed, whereas no participants in the US chose that response. This may also be associated with the burden

of the knowledge of inheritance of the genetic disease. While most viewed the explanation of the genetic inheritance of a condition as having a positive effect on healthcare satisfaction, it may also be causing stress and burden for patients and their families. This could be due to stress of knowing their genetic disease status for adult onset conditions, or the reproductive possibilities associated with being a carrier of a genetic condition. It is unknown how familial testing causes burden for the families of these patients, although studies have shown there is a psychological component where familial genetic testing is concerned, and have identified possible barriers such as fear of carrier status. [38, 76] Further exploration of this topic could provide insight as to what the source of stress and burden is in regards to the inheritance of the condition.

This study found that as a whole, participants who identified with a religious faith rated their faith as having a positive effect on their satisfaction with healthcare. Those of Islamic faith had the highest mean rating, while those of Catholic faith had the lowest mean rating, however still in the positive effect range of above 3.00. Studies have shown that patients use religious belief as a coping mechanism at times, and the religious community is also available as a support system. [31] It may be important to identify those who are perhaps not religious or spiritual, and may be using other methods of coping and support systems.

4.5 Factors influencing amount of time spent to obtain diagnoses

The search for a diagnosis can be a lengthy and mentally draining on patients and their families. When comparing those with diagnoses and those without diagnoses, a larger percentage of those with diagnoses were receiving treatment. In some instances, having a diagnosis may facilitate obtaining the necessary treatments and therapies needed for an individual. Another benefit of a diagnosis is that it may guide treatment and therapy

decisions as well. Even though the search for a diagnosis is arduous, the benefit of a diagnosis is without a doubt. The factors perceived by participants as having the largest impact on amount of time spent to obtain diagnoses included the number of misdiagnoses and the wait list time for a clinic appointment. Again, improvements in these areas may begin with increasing the genetics proficiency of healthcare providers.

4.6 Limitations of the study

While this study was aimed at collecting data regarding barriers in access to healthcare in the population attending genetics clinics, it was unable to reach those patients who have been lost to care or were unable to surpass these barriers to receive adequate healthcare. The participants surveyed in this study were only those who were able to successfully surpass barriers in access to healthcare, which largely included those with health insurance. This could mean that barriers that are most problematic for families were not ascertained, since these may have precluded the family from ever coming to the clinic.

This survey was not available to Spanish speaking individuals, and therefore was unable to accommodate a majority of the Hispanic population. It was also unavailable to individuals who do not understand English, Malay, or Chinese Mandarin. Therefore, other populations were also lacking such as Middle Easterners and Asians who are not of Chinese, Malay, or Asian Indian background. The collection sites included one clinic in Kuala Lumpur, Malaysia and three sites in Southern California. Populations of patients at other clinics in Malaysia and at other sites in the US were not surveyed. This means that the population surveyed is not representative of all patients in the US and all patients in Malaysia.

The higher positive effect of a genetic counselor on a participant's satisfaction with healthcare may largely be due to the study design, in which participants were recruited to

the study by a genetic counselor or genetic counseling student. This may have impacted the participants' views of genetic counselors. They may have also felt pressured to rate a higher score, and may not accurately represent their true perception of the effect of a genetic counselor on satisfactory healthcare.

While this survey assessed the perception of travel time and costs of travel and the level of burden on the family it incurred, it did not use an absolute measure of travel time and costs. Therefore, there is no evidence to link the perception of burden incurred by travel time and costs to the true travel time of the participant. For example, if most participants' travel times were between five to ten minutes, then the perception of low burden may be due to low travel times. Likewise, if most participants' travel times were over two hours, then the perception of low burden even in the face of large amounts of time spent traveling may have more meaning. This study was unable to make these types of comparisons, and relied heavily on participants' perceptions.

This survey was also designed to broadly assess participant perceptions of hindrances to obtaining satisfactory healthcare, however there may be barriers that were not assessed in this study. Some of the questions did not allow free response answers, and therefore may have required participants to choose responses that did not fit with their true perceptions. There is also the chance that for questions that asked participants to choose only one answer, they may have wanted to choose several but were limited to one.

This study was unable to recruit the number of participants needed to provide an analysis of differences between participants of Asian ethnicity living in different countries, since there were only five participants of Asian ethnicity from the US. There was not enough statistical power to reliably analyze the differences between the two groups.

4.7 Future studies

The field of medical genetics is growing and the number of available genetic tests is increasing, not only through physician orders but also through direct-to-consumer testing. Therefore, it has become increasingly necessary to educate both patients and the public about the risks and benefits of genetic testing. While this study did not find that the general public's knowledge of genetics was the largest barrier being perceived by patients and their caretakers, it is still an aspect that remains to be further studied. The general public's knowledge of genetics may be influencing stigmatization of genetic carrier status, which remains to be further assessed outside of the clinical setting.[30, 76]

Further studies could involve implementing intervention programs that would look more deeply into the barriers that these participants are experiencing, such as blame and guilt. Family dynamics and how these play a role as an obstacle to achieving satisfactory healthcare should also be further studied. The relationship between the patients' and the caretakers' views and beliefs could also be further studied. This will require a study design in which both patients and caretakers participate; the majority of the participants in this study identified as the patient's caretaker.

While one aim of this study was to compare perceptions of Asians from Asian countries to Asian Americans, there were not enough Asian Americans recruited to reliably make a comparison. Future studies would expand to further populations outside of Southern California in order to compare responses across the US as well.

4.8 Conclusion

This study examined the barriers to healthcare perceived by patients and their caretakers in genetics and metabolics clinics in both Southern California and Malaysia. The

study sample consisted of 104 participants, 54 from each country. The purpose of this study was to have a better understanding of what hardships the patients and their caretakers are experiencing that are perceived as most burdensome and what aspects of improvement to healthcare they believe would be most beneficial to those with rare diseases. Differences in perceptions of participants in Malaysia and the US were also able to be explored.

The majority of participants believed that expanding healthcare provider knowledge would be the most beneficial for these with rare conditions. Most participants in Malaysia did not perceive travel times and costs of travel or treatment to be the largest obstacles blocking adequate access to satisfactory healthcare. Participants in Malaysia also found the knowledge of inheritance of the disease to be most burdensome while participants in the US perceived cost of treatment and medical care as a key stress and burden factor for the patient's family. This could be due to cultural differences as well as differences in the healthcare systems of both countries. These results suggest that improvements are needed in healthcare provider education of medical genetics knowledge, as well as different interventions and counseling approaches may be needed to alleviate stress and burden for patients' families in the two countries.

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APPENDIX A

CONFIRMATION OF EXEMPT RESEARCH REGISTRATION

September 17, 2015

EMILY QIAN
PEDIATRICS

RE: HS# 2015-2175 *A Comparison of Perceived Barriers to Healthcare between Malaysian and Californian Rare Disease Patients*

The human subjects research project referenced above has been registered with the UC Irvine Institutional Review Board (UCI IRB) as Exempt from Federal regulations in accordance with 45 CFR 46.101. This exemption is limited to the described activities in the registered UCI IRB Protocol Narrative and extends to the performance of such activities at the sites identified in your UCI IRB Protocol Application. Informed consent from subjects must be obtained unless otherwise indicated below. UCI IRB conditions for the conduct of this research are included on the attached sheet.

Information provided to prospective subjects to obtain their informed consent should, at a minimum, consists of the following information: the subject is being asked to participate in research, what his/her participation will involve, all foreseeable risks and benefits, the extent to which privacy and confidentiality will be protected, that participation in research is voluntary and the subject may refuse to participate or withdraw at any time without prejudice.

Questions concerning registration of this study may be directed to the UC Irvine Office of Research, 5171 California Avenue, Suite 150, Irvine CA 92697-7600; 949-824-6068 or 949-824-2125 (biomedical committee) or 949-824-6662 (social-behavioral committee).

Level of Review: Exempt Review, Category 2

Tahseen Mozaffar, MD
Chair, Institutional Review Board

Registration valid from 09/17/2015 to 09/16/2018
UCI (FWA) 00004071, Approved: January 31, 2003

Informed Consent Requirements:
1. Signed Informed Consent Not Required
    a. Study Information Sheet Required

UCI IRB CONDITIONS FOR ALL UCI HUMAN RESEARCH PROTOCOLS

UCI RESEARCH POLICIES:
All individuals engaged in human-subjects research are responsible for compliance with all applicable UCI Research Policies (http://www.research.uci.edu/compliance/human-research-protections/hrp-policy-library/hrppPolicies.htm). The Lead Researcher of the study is ultimately responsible for assuring all study team members adhere to applicable policies for the conduct of human-subjects research.

LEAD RESEARCHER RECORDKEEPING RESPONSIBILITIES:
Lead Researchers are responsible for the retention of protocol–related records. The following web pages should be reviewed for more information about the Lead Researcher's recordkeeping responsibilities for the preparation and maintenance of research files: http://www.research.uci.edu/compliance/human-research-protections/researchers/lead-researcher-recordkeeping-responsibilities.html
and http://www.research.uci.edu/compliance/human-research-protections/researchers/preparation-maintenance-research-audit-file.html.

PROTOCOL EXPIRATION:
The UCI IRB expiration date is provided on the exempt registration letter. **All exempt protocols are registered for a maximum period of 3 years**. If the study will continue beyond 3 years, a new Application for IRB review is required. No annual continuing renewals are required.

MODIFICATIONS & AMENDMENTS:
No changes are to be made to the registered protocol or the approved, stamped consent form without the prior review and approval of the UCI IRB. All changes (e.g., a change in procedure, number of subjects, personnel, study locations, new recruitment materials, study instruments, etc.) must be prospectively reviewed and confirmed by the IRB before they are implemented.

APPROVED VERSIONS OF CONSENT DOCUMENTS, INCLUDING STUDY INFORMATION SHEETS:
Unless a waiver of informed consent is granted by the IRB, the consent documents (consent form; study information sheet) with the UCI IRB approval stamp must be used for consenting all human subjects entered into this study. Only the current approved version of the consent documents may be used to consent subjects. **Approved consent documents are not to be used beyond their expiration date**.

ADVERSE EVENT & UNANTICIPATED PROBLEMS REPORTING:
All unanticipated problem involving risk to subjects or others or serious adverse events must be reported to the UCI IRB in accordance with Federal regulations and UCI policy. See http://www.research.uci.edu/compliance/human-research-protections/researchers/reporting-of-adverse-events-unanticipated-problems-and-violations.html for complete details.

CHANGES IN FINANCIAL INTEREST:
Any changes in the financial relationship between the study sponsor and any of the investigators on the study and/or any new potential conflicts of interest must be reported immediately to the UCI Conflict of Interest Oversight Committee (COIOC). If these changes affect the conduct of the study or result in a change in the required wording of the approved informed consent document, then these changes must also be reported to the UCI IRB via a modification request.

CLOSING REPORT:
An electronic closing report should be filed with the UCI IRB when the research concludes. See http://www.research.uci.edu/compliance/human-research-protections/researchers/closing-a-protocol.html for complete details.

October 20, 2015

EMILY QIAN
PEDIATRICS

RE: HS# 2015-2175 *A Comparison of Perceived Barriers to Healthcare between Malaysian and Californian Rare Disease Patients*

Electronic Modification Request # 17825

The following modification(s) for the human subjects research protocol referenced above has/have been reviewed and approved by Human Research Protections Staff, on behalf of the UC Irvine Institutional Review Board (UCI IRB). Below is a summary of the approved changes requested via e-modification request number 17825**:

Add/Remove Research Procedures:

Remove: Surveys/Questionnaires/Interviews/Oral Histories
Reason: I have a revised version of the survey that I would like to use that includes participant age in years as well as participant's sex.

Add: Surveys/Questionnaires/Interviews/Oral Histories
Reason: This is the revised survey I would like to use with the participant's age in years and sex.

**Changes to approved protocols may not be made without prior approval. All changes proposed in the e-modification request may not have been approved. Review the above summary of approved changes and the approved documents released with this letter. If a requested change does not appear in the summary above or in the revised documents, the change was not approved. Please consult with an IRB Administrator for further information.

Note: If the approved modification(s) includes changes to the informed consent document, the approved stamped consent document will be released with this letter. Please discontinue use of any previous versions of the informed consent document and use only the most updated version for enrollment of all new subjects. Questions concerning registration of this study or approval of this modification request may be directed to the UC Irvine Office of Research, 5171 California Avenue, Suite 150, Irvine CA 92697-7600; 949-824-6068 or 949-824-2125 (biomedical committee) or 949-824-6662 (social-behavioral committee).

Level of Review: Exempt Review

Le'Quan Jackson
IRB Senior Analyst

Approval Issued: 10/20/2015
Expiration Date: 09/16/2018
UCI (FWA) 00004071, Approved: January 31, 2003

APPENDIX B

UNIVERSITY OF CALIFORNIA, IRVINE
Study Information Sheet

A Comparison of Perceived Barriers to Healthcare between Malaysian and Californian Rare Disease Patients

Lead Researcher
Emily Qian, Graduate Student in Genetic Counseling
Department of Pediatrics, UCI
+1-714-456-5837 or qiane@uci.edu

Faculty Sponsor
John Jay Gargus, MD, Ph.D, Director of Center for Autism Research and Treatment
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Co-Researchers
Meow Keong Thong, MD, Head of Genetics & Metabolism Unit
Department of Paediatrics, UMMC
+60-37-949-2065 or thongmk@ummc.edu.my

You are being asked to participate in a research study. The purpose of this research study is *to explore the barriers that are encountered in the process of getting a diagnosis of a rare genetic disease to understand what areas of healthcare need improvement in regards to these patients*. You are eligible to participate in this study if you or a family member have/are being suspected of having a rare genetic disease, and if you are **18 years of age or older**. The study involves taking a **5-10 minute survey**.

There are no known harms or discomforts associated with this study beyond those encountered in normal daily life, such as anxiety, embarrassment, social stigma, and invasion of privacy. All research data collected will be stored securely and confidentially in a locked box, until it is electronically transferred. Research data will be stored electronically on a laptop computer that is password protected.

You will not directly benefit from participation in this study. However, the results from this study will benefit the rare diseases community as a whole by improving access to healthcare. You will not be compensated for your participation in this research study.

The research team, authorized UCI and UMMC personnel, and regulatory entities such as the Office of Human Research Protections (OHRP), may have access to your study records to protect your safety and welfare. Any information derived from this research project that personally identifies you will not be voluntarily released or disclosed by these entities without your separate consent, except as specifically required by law. Study records provided to authorized, non-UCI or non-UM entities will not contain identifiable information about you; nor will any publications and/or presentations without your separate consent.

If you have **any comments, concerns, or questions** regarding the conduct of this research, please contact the research team listed at the top of this form. Please contact UCI's Office of Research by phone, (949) 824-6662, by e-mail at IRB@research.uci.edu or at 5171 California Avenue, Suite 150, Irvine, CA 92697, if you are unable to reach the researchers listed at the top of the form and have general questions; have concerns or complaints about the research; have questions about your rights as a research subject; or have general comments or suggestions.

Participation in this study is voluntary. There is no cost to you for participating. You may choose to skip a question. You may refuse to participate or discontinue your involvement at any time without penalty. Your decision will NOT affect your future relationship with UMMC, UCI, CHOC or your quality of care at UMMC, CHOC, or UCIMC. You are free to withdraw from this study at any time. **If you decide to withdraw from this study you should notify the research team immediately**.

APPENDIX C

MEDICAL ETHICS COMMITTEE
UNIVERSITY MALAYA MEDICAL CENTRE

PATIENT INFORMATION SHEET

Please read the following information carefully, do not hesitate to discuss any questions you may have with your doctor.

You are invited to take part in a research study.

Study Title: *A Comparison of Perceived Barriers to Healthcare between Malaysian and Californian Rare Disease Patients*

1. Introduction (Scientific basis of the study)
Rare disease patients require medical care and follow up, and often times they are not able to get all the care they need. This study is to determine how to better improve access to healthcare for these patients.

2. What is the purpose of this study?
The purpose of this research study is to explore the barriers that are encountered in the process of getting a diagnosis of a rare genetic disease to understand what areas of healthcare need improvement in regards to these patients.

3. What are the procedures to be to be carried out?
The study involves taking a 5-10 minute survey.

4. Who should and should not enter the study? (Inclusion and exclusion criteria)
You are eligible to participate in this study if you or a family member have/are being suspected of having a rare genetic disease, and if you are 18 years of age or older.

5. What will be the benefits of the study:
(a) to the subject?
You will not directly benefit from participation in this study.
(b) to the investigator?
The results from this study will benefit the rare diseases community as a whole by improving access to healthcare.

6. What are the possible drawbacks? (side effects,etc.)
There are no known harms or discomforts associated with this study beyond those encountered in normal daily life, such as anxiety, embarrassment, social stigma, and invasion of privacy. All research data collected will be stored securely and confidentially in a locked box, until it is electronically transferred.

7. What payments or reimbursement will research subjects receive?
You will not be compensated for your participation in this research study.

8. Can I refuse to take part in this study?
Participation in this study is voluntary. You may choose to skip a question. You may refuse to participate or discontinue your involvement at any time without penalty. Your decision will NOT affect your future relationship with UMMC, UCI, CHOC or your quality of care at UMMC, CHOC, or UCIMC. You are free to withdraw from this study at any time. If you decide to withdraw from this study you should notify the research team immediately.

9. Who should I contact if I have additional questions during the course of the study?
If you have any comments, concerns, or questions regarding the conduct of this research, please contact Emily Qian via email at qiane@uci.edu, or Dr. Meow Keong Thong, MD, at 603-7949-2065 or thongmk@ummc.edu.my.

10. Who should I contact if I have concerns about the conduct of this study?
Please contact UCI's Office of Research by phone, +1-(949) 824-6662, by e-mail at IRB@research.uci.edu or at 5171 California Avenue, Suite 150, Irvine, CA 92697, if you are unable to reach the researchers listed at the top of the form and have general questions; have concerns or complaints about the research; have questions about your rights as a research subject; or have general comments or suggestions. You may also contact the UMMC medical ethics committee at 603-7956-4422, or email at ummc@ummc.edu.my.

BK-MIS-1116-E02

APPENDIX D

ID Number:

You are (circle one): Patient / Caretaker Your age: Your sex: M / F

Parent/Family Info:

1. Insurance (choose all that apply):
   - ☐ Government
   - ☐ Private
   - ☐ Other

2. Please choose your income level:
   - ☐ Less than $30,000 (RM 35,000)/year
   - ☐ $30,000 - $60,000 (RM 35,000-70,000)/year
   - ☐ Over $60,000 (RM 75,000)/year

3. Choose your highest education level:
   - ☐ Did Not Complete High School / No school or primary education
   - ☐ High School/ GED / Secondary School
   - ☐ Some College / Some Tertiary Education
   - ☐ Bachelor's Degree / Completed Tertiary Education
   - ☐ Graduate / Professional Degree

Patient Info (all questions from here are about the patient):

1. Current Age: _____ 2. Sex: M / F

3.Ethnicity:
- ☐ Asian (Malaysian)
- ☐ Asian (Chinese)
- ☐ Asian (Indian)
- ☐ Asian (Other/Pacific Islander)
- ☐ White
- ☐ Black
- ☐ Hispanic
- ☐ Native American

4.Religion:
- ☐ Buddhism
- ☐ Catholicism
- ☐ Christianity
- ☐ Hinduism
- ☐ Islam
- ☐ Judaism
- ☐ None
- ☐ Other

5.Birthplace (circle one): Government/Public hospital Private Hospital Home Other: _____

6.Have you been diagnosed with a genetic condition?
- ☐ Yes, the condition is: _____
- ☐ No

7.Have you had genetic testing (ex: DNA, chromosomes) for this condition?
- ☐ Yes
- ☐ No
- ☐ I don't know

8.Have you told family members of the genetic implications of this condition?
- ☐ Yes, I have told my family.
- ☐ No, I have not told my family.
- ☐ I don't know the genetic implications of this condition.

9a.Have other members of your family had genetic testing for this condition?
- ☐ Yes
- ☐ No
- ☐ I don't know

9b.If not, please choose ONE of the following as the main reason:
- ☐ Burden to family
- ☐ Have not told family of condition yet
- ☐ Not enough money
- ☐ It was not offered
- ☐ Patient has not received genetic testing
- ☐ Personal or religious beliefs of family member
- ☐ Schedule conflicts
- ☐ Other: _____

10.Approximately at what age were the first symptoms noticed?

- Infancy (under 1 year)
- Early Childhood (1-2 years)
- Childhood (3-13 years)
- Adolescence (14 – 19 years)
- Adulthood (19 years or more)

11.Who was the person to first notice symptoms?

- Medical Professional
- Patient
- Parent/Caretaker
- Other:_____

12.How many doctors did the patient see between the first onset of symptoms and diagnosis? (If waiting for diagnosis, how many doctors did the patient see so far?)

- 1-2 doctors
- 3-4 doctors
- 5-6 doctors
- 6+ doctors

13a.Please specify which type of medical professional made the correct diagnosis of the condition:

- Geneticist / Metabolic Specialist
- Nurse
- OB/GYN
- Pediatrician (or General Practitioner if adult patient)
- Specialist (eg., Neurologist, Cardiologist, etc.)
- Other: _____

13b.Please specify which type of medical professional(s) made a diagnosis that was **NOT** correct (if any):

- Geneticist / Metabolic Specialist
- Nurse
- OB/GYN
- Pediatrician (or General Practitioner if adult patient)
- Specialist (eg., Neurologist, Cardiologist, etc.)
- Other: _____

14.Where is the condition chiefly being looked after:

- Government Hospital / Public Hospital
- Private Hospital
- Not being looked after
- Other:_____

15.What transportation does the patient usually use to go to the hospital (choose one)?

- Bus
- Car / Motorcycle
- LRT / Subway
- Taxi / Hired car or van / Taxi Service (eg., Uber, Lyft)
- Train
- Other:_____

16.If patient is NOT receiving treatment, please answer why by choosing ONE of the following:

- Not enough money
- Mistrust of treatment
- No caretaker
- No time for care
- No treatment available
- No transportation
- Patient's fear of burden on family
- Personal / Religious beliefs
- Using alternative treatment methods
- Other: _____

17.If patient is NOT receiving therapies (eg., occupational therapy, speech therapy, physical therapy, etc.), please answer why by choosing ONE of the following:

- Not enough money
- Mistrust of therapy
- No caretaker
- No time for care
- No therapies needed
- No transportation
- Patient's fear of burden on family
- Personal / Religious beliefs
- Using alternative therapeutic methods
- Other:_____

18.Please choose the **largest** difficulty you faced to receiving satisfactory healthcare for your condition.

- Lack of funds
- Lack of healthcare provider knowledge
- Lack of public knowledge
- Lack of time
- Lack of transportation
- Patient's fear of burden on family
- Prior negative experiences in healthcare

19.Please choose ONE from below that you consider would be the **most helpful** for people with this condition:

- Expanding patient support groups
- Expanding affordable transportation
- Expanding available funding for treatment
- Expanding newborn screening program (checking babies at birth for this condition)
- Expanding public awareness of condition
- Expanding the amount of tertiary and regional centers in rural areas
- Expanding the knowledge of healthcare providers

20.Please choose ONE from below that you consider would be the **least helpful** for people with this condition:

- Expanding patient support groups
- Expanding affordable transportation
- Expanding available funding for treatment
- Expanding newborn screening program(checking babies at birth for this condition)
- Expanding public awareness of condition
- Expanding the amount of tertiary and regional centers in rural areas
- Expanding the knowledge of healthcare providers

Please weigh the **burden/amount of stress** of the following **on the family**:

	None (No burden)	Low	Moderate	High	Severe (High Burden)	Not Applicable
1. The time and distance to travel to the hospital or care center.	1	2	3	4	5	N/A
2. The cost of travel to the hospital or care center.....	1	2	3	4	5	N/A
3. The cost of treatment/medical care for the patient.....	1	2	3	4	5	N/A
4. The amount of in home assistance the family must provide for the patient.....	1	2	3	4	5	N/A
5. The knowledge of the inheritance of the disease.....	1	2	3	4	5	N/A

Please choose from the above (numbers 1-5) the largest burden or the factor which caused the most stress on the family: _____

Please rate the effect of the following on the **length of time to receive the patient's diagnosis**:

	None (No effect)	Low	Moderate	High	Severe (Large effect)	Not Applicable
1. The delay between noticing symptoms and the first medical appointment.....	1	2	3	4	5	N/A
2. The number of misdiagnoses given to the patient.....	1	2	3	4	5	N/A
3. The awareness of the parent/caretaker of the patient's symptoms.....	1	2	3	4	5	N/A
4. The patient's fear of receiving a genetic testing result.....	1	2	3	4	5	N/A
5. The parent/caretaker's fear of receiving a genetic testing result.....	1	2	3	4	5	N/A
6. The patient's refusal to go to the hospital.....	1	2	3	4	5	N/A
7. The family's prior negative experiences with healthcare.....	1	2	3	4	5	N/A

Please choose from the above (numbers 1-7) the factor that caused the greatest difficulty to receive a diagnosis: _____

Please indicate the effect of the following **on your satisfaction with the patient's healthcare**:	Negative	Slight Negative	No Effect	Slight Positive	Positive	Not Applicable
1. The amount of time spent traveling to receive healthcare services and therapies	1	2	3	4	5	N/A
2. The condition being missed at birth	1	2	3	4	5	N/A
3. The cost of treatment/medical care for the patient	1	2	3	4	5	N/A
4. The cost of transportation to receive healthcare services and therapies	1	2	3	4	5	N/A
5. The ethnicity of the patient and/or family	1	2	3	4	5	N/A
6. The explanation of the genetic inheritance of the condition by a healthcare provider	1	2	3	4	5	N/A
7. The use of a genetic counselor	1	2	3	4	5	N/A
8. The general public's attitude towards genetics	1	2	3	4	5	N/A
9. The number of sites where the patient receives healthcare services	1	2	3	4	5	N/A
10. The patient/family's mistrust of the hospital/medical professionals	1	2	3	4	5	N/A
11. The patient's perception of being a burden on the family	1	2	3	4	5	N/A
12. The primary care provider's knowledge of the condition	1	2	3	4	5	N/A
13. The referral to a genetics/metabolics clinic	1	2	3	4	5	N/A
14. The religious beliefs of the patient and/or family	1	2	3	4	5	N/A

APPENDIX E

Nombor ID:
Anda adalah (bulatkan satu): pesakit / penjaga **Umur:** **Jantina: L / P**

Maklumat Ibu-bapa/Keluarga:

1. Insurans (tandakan yang berkenaan):
   - ☐ Kerajaan
   - ☐ Swasta
   - ☐ Lain-lain

2. Pilih tahap pendapatan anda:
   - ☐ Kurang daripada RM 35,000 setahun
   - ☐ RM 35,000 - RM 70,000 setahun
   - ☐ Lebih daripada RM 70,000 setahun

3. Pilih tahap pendidikan anda yang tertinggi:
   - ☐ Tidak tamat sekolah menengah
   - ☐ Sekolah menengah
   - ☐ Kolej
   - ☐ Universiti
   - ☐ Graduan/Ijazah profesional

Informasi Pesakit:

1. Umur: _____ 2. Jantina: L / P

3. Golongan Etnik:
   - ☐ Asia (Melayu)
   - ☐ Asia (Cina)
   - ☐ Asia (India)
   - ☐ Asia (Lain-lain)
   - ☐ Amerika
   - ☐ Afrika-Amerika
   - ☐ Hispanik
   - ☐ Amerika Asli

4. Agama:
   - ☐ Buddha
   - ☐ Katolik
   - ☐ Kristian
   - ☐ Hindu
   - ☐ Islam
   - ☐ Judaism
   - ☐ Tiada agama
   - ☐ Lain-lain

5. Tempat lahir (bulatkan satu): Hospital kerajaan Hospital swasta Rumah Lain-lain: _____

6. Adakah anda pernah didiagnos dengan penyakit genetik?
   - ☐ Ya, penyakitnya ialah _____
   - ☐ Tidak

7. Pernahkah anda diuji untuk penyakit genetik tersebut (contoh: DNA, kromosom)?
   - ☐ Ya
   - ☐ Tidak
   - ☐ Tidak tahu

8. Sudahkah anda memaklumkan ahli keluarga anda tentang implikasi genetik keadaan genetic ini?
   - ☐ Ya, saya sudah memberitahu mereka.
   - ☐ Tidak, saya tidak memberitahu mereka.
   - ☐ Saya tidak tahu implikasi penyakit ini kepada genetik mereka.

9 a. Adakah ahli keluarga anda menjalani ujian untuk penyakit genetik tersebut?
   - ☐ Ya
   - ☐ Tidak
   - ☐ Tidak tahu

9 b. Jika tidak, pilih SATU sebab sebagai sebab utama keluarga anda tidak mengambil ujian tersebut:
   - ☐ Membebankan keluarga
   - ☐ Keluarga tidak sedar tentang penyakit anda
   - ☐ Kekurangan wang
   - ☐ Tidak diberitahu tentang ujian tersebut
   - ☐ Pesakit tidak pernah menerima ujian genetik
   - ☐ Kepercayaan sendiri ahli keluarga
   - ☐ Konflik dalam jadual harian
   - ☐ Lain-lain: _____

10.Berapakah umur pesakit apabila simptom penyakit mula muncul?

- ☐ Kurang daripada satu tahun
- ☐ 1-2 tahun
- ☐ 3-13 tahun
- ☐ 14-19 tahun
- ☐ lebih daripada 19 tahun

11.Siapakah orang pertama yang menyedari gejala pesakit?

- ☐ Pakar perubatan
- ☐ Pesakit
- ☐ Ibu bapa/Penjaga
- ☐ Lain-lain:_____

12.Berapa banyak doktor yang telah dijumpai oleh pesakit antara kemunculan simptom dan diagnosis? (Jika sedang menunggu diagnosis, berapa banyak doktor yang telah dijumpai pesakit setakat ini?)

- ☐ 1-2 doktor
- ☐ 3-4 doktor
- ☐ 5-6 doktor
- ☐ 6 + doktor

13 a.Sila nyatakan pakar perubatan manakah yang membuat diagnosis secara tepat:

- ☐ Pakar genetik / Pakar metabolik
- ☐ Jururawat
- ☐ Pakar obstetrik / Pakar sakit puan
- ☐ Pediatrik (GP jika dewasa)
- ☐ Pakar dalam bidang lain (Pakar jantung, dll.)
- ☐ Lain-lain: _____

13 b.Sila nyatakan pakar perubatan manakah yang membuat diagnosis **yang salah**:

- ☐ Pakar genetik / Pakar metabolik
- ☐ Jururawat
- ☐ Pakar obstetrik / Pakar sakit puan
- ☐ Pediatrik (GP jika dewasa)
- ☐ Pakar dalam bidang lain (Pakar jantung, dll.)
- ☐ Lain-lain: _____

14.Di manakah penyakit ini sedang dirawat?

- ☐ Hospital kerajaan
- ☐ Hospital swasta
- ☐ Tidak dirawat
- ☐ Lain-lain: _____

15.Apakah jenis pengangkutan yang diambil oleh pesakit untuk pergi ke tempat rawatan?

- ☐ Bas
- ☐ Kereta / Motosikal
- ☐ LRT / MRT
- ☐ Teksi atau servis yang berkaitan / Kereta sewa
- ☐ Tren
- ☐ Lain-lain: _____

16.Jika pesakit tidak menerima rawatan, sila pilih satu sebab mengapa:

- ☐ Kekurangan wang
- ☐ Tidak yakin dengan rawatan
- ☐ Tiada penjaga
- ☐ Tiada masa
- ☐ Tiada rawatan yang boleh diambil
- ☐ Tiada pengangkutan
- ☐ Pesakit bimbang rawatan akan membebankan keluarga
- ☐ Kepercayaan sendiri / keagamaan
- ☐ Mengunakan rawatan alternatif
- ☐ Lain-lain: _____

17. Jika pesakit TIDAK menerima terapi (cth., terapi Carakerja, terapi pertuturan, lain-lain), sila pilih satu sebab mengapa:
- ☐ Kekurangan wang
- ☐ Tidak yakin dengan terapi
- ☐ Tiada penjaga
- ☐ Tiada masa
- ☐ Tiada rawatan yang boleh diambil
- ☐ Tiada pengangkutan
- ☐ Pesakit bimbang rawatan akan membebankan keluarga
- ☐ Kepercayaan sendiri / keagamaan
- ☐ Mengunakan rawatan alternatif
- ☐ Lain-lain: _____

18. Sila pilih cabaran **terbesar** dalam mendapatkan penjagaan memuaskan untuk keadaan genetik:
- ☐ Kekurangan wang
- ☐ Kekurangan informasi tentang pakar kesihatan
- ☐ Kekurangan ilmu
- ☐ Kekurangan masa
- ☐ Tiada pengangkutan
- ☐ Pesakit bimbang rawatan akan membebankan keluarga
- ☐ Pengalaman negatif dengan rawatan sebelum ini

19. Sila pilih satu yang anda rasa **terbesar membantu** untuk keadaan ini:
- ☐ Mengembangkan kumpulan sokongan
- ☐ Pengangkutan yang murah dan senang didapati
- ☐ Biayaan untuk perubatan
- ☐ Ujian untuk bayi baru lahir
- ☐ Pengetahuan am masyarakat tentang kondisi genetik tersebut
- ☐ Membina lebih banyak klinik di kawasan pedalaman
- ☐ Mengembangkan ilmu pakar perubatan

20. Sila pilih satu yang anda rasa **kurang membantu** untuk keadaan ini:
- ☐ Mengembangkan kumpulan sokongan
- ☐ Pengangkutan yang murah dan senang didapati
- ☐ Biayaan untuk perubatan
- ☐ Ujian untuk bayi baru lahir
- ☐ Pengetahuan am masyarakat tentang kondisi genetik tersebut
- ☐ Membina lebih banyak klinik di kawasan pedalaman
- ☐ Mengembangkan ilmu pakar perubatan

Sila pilih nombor yang menyatakan jumlah **beban / tekanan** kepada keluarga:	Tiada beban	Rendah	Sederhana	Tinggi	Beban yang sangat tinggi	_
1. Masa dan jarak untuk pergi ke tempat perubatan.....	1	2	3	4	5	N/A
2. Kos untuk pergi ke tempat perubatan.....	1	2	3	4	5	N/A
3. Kos perubatan/penjagaan untuk pesakit.....	1	2	3	4	5	N/A
4. Jumlah penjagaan di rumah yang perlu diberi untuk keluarga.....	1	2	3	4	5	N/A
5. Pengetahuan tentang kondisi genetik kepada keluarga…….....	1	2	3	4	5	N/A

Sila pilih daripada soalan di atas (1-5), yang manakah merupakan beban / tekanan terbesar: _____

Sila nilajkan kesan berikut tentang **jangka masa untuk pesakit menerima diagnosis:**	Tiada ada kesan	Rendah	Sederhana	Tinggi	Kesan yang sangat tinggi	_
1. Masa antara kemunculan simptom dan perjumpaan doctor yang pertama.....	1	2	3	4	5	N/A
2. Jumlah diagnosis salah.....	1	2	3	4	5	N/A
3. Pengetahuan ibu bapa/penjaga tentang simptom pesakit.....	1	2	3	4	5	N/A
4. Ketakutan pesakit untuk menerima keputusan ujian genetik.....	1	2	3	4	5	N/A
5. Phobio ibu bapa/penjaga untuk mengambil ujian genetik.....	1	2	3	4	5	N/A
6. Pesakit enggan pergi ke hospital.....	1	2	3	4	5	N/A
7. Pengalaman negatif keluarga pesakit dengan pakar perubatan....	1	2	3	4	5	

Sila pilih daripada atas (1-7), untuk faktor yang menyebabkan kesukaran terbesar untuk menerima diagnosis: _____

Sila nyatakan **impak** berikut kepada **penjagaan pesakit**:	Negatif	Negatif sedikit	Tidak ada kesan	Positif sedikit	Positif	
1. Masa yang diambil apabila pergi ke tempat therapi/perubatan.....	1	2	3	4	5	N/A
2. Kondisi tidak diketahui pada masa lahir.....	1	2	3	4	5	N/A
3. Kos perubatan / penjagaan pesakit.....	1	2	3	4	5	N/A
4. Kos pengangkutan ke tempat perubatan.....	1	2	3	4	5	N/A
5. Golongan etnik pesakit dan/atau keluarga pesakit.....	1	2	3	4	5	N/A
6. Penerangan risiko penyakit genetik ini kepada ahli keluarga oleh pakar perubatan.....	1	2	3	4	5	N/A
7. Penggunaan perkhidmatan kaunselor genetik.....	1	2	3	4	5	N/A
8. Sikap masyarakat terhadap genetik.....	1	2	3	4	5	N/A
9. Jumlah tempat yang dikunjungi pesakit untuk menerima rawatan.....	1	2	3	4	5	N/A
10. Rasa was-was pesakit / keluarga pesakit kepada staf perubatan.....	1	2	3	4	5	N/A
11. Persepsi pesakit bahawa dia membebankan keluarga.....	1	2	3	4	5	N/A
12. Pengetahuan penjaga tentang kondisi tersebut.....	1	2	3	4	5	N/A
13. Rujukan kepada klinik genetik/metabolik.....	1	2	3	4	5	N/A
14. Kepercayaan agama pesakit/keluarga pesakit.....	1	2	3	4	5	N/A

APPENDIX F

Additional comments written in margins throughout survey:

"insurance denial to pay for genetic testing lead to me paying out of pocket to avoid further delays"

"First geneticist was wrong"

"40+ doctors!!!!!!!!!!!!!!!!!!!!!"

"!!!!!!!!!!!!!!!!"

"Approximately 20-60+ doctors"

"doctors did not want to give diagnosis of autism"

"PPUM"

"gov. servant"

"after Prof Thong"

"irrelevant"

"tiada"

"loss of balance"