Finding Utility for Genetic Diagnostics in the Developing World

By

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The idea behind this thesis was born in 2006 when I was working for a big pharmaceutical company and reading about the progress in genetics. I found myself spending more time thinking about the advances and challenges in the personalized medicine space than the immediate tasks and challenges in my employment. Since then, it has been a pleasure to move slowly but surely towards aligning my personal interests with my academic and professional pursuits. I would like to thank my classmates in school, my wonderful professors and my friends and family for brainstorming with me, encouraging me, answering endless questions about very personal genetic choices and offering unwavering support in this journey.

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ABSTRACT

Genetic testing companies have come under fire lately for an array of reasons. Many direct-to-consumer outfits are being challenged by the federal regulatory authorities, by the physicians' community and by the public itself. The desire to derive utility from the existing mass of genetic research is only outpaced by the sheer amount of new information being added to our understanding daily.

These genetic testing companies are simultaneously trying to apply the existing knowledge, build a base for further study and be credible, going concerns from a business perspective. It is a worthy but difficult objective. The direct-to-consumer genetic initiatives face resistance from physicians who are the traditional intermediaries between medical insight and application of this insight. The companies also face a strong adversary in a government that wants to protect its constituents from fraudulent marketing claims and misinformation. Recent, informal studies have also exposed flaws in the product offerings and delivery of information by these companies. Finally, these are all for-profit entities which are struggling to become profitable.

The objective of this thesis is to identify an attractive consumer base and opportunity that would allow for successful deployment of genetic diagnostic capability. I postulate that the success of a direct-to-consumer company would depend on finding a customer that values the genetic insight deeply and is able to take action from such insight. Based on those two fundamental criteria—perceived value and actionable utility—I build a profile of place, person and disease to test my hypothesis.

Driven by the findings of my research, I anchored my hypothesis around an Indian consumer who pays for health care out-of-pocket, is vulnerable to certain genetic diseases due to narrow, endogamous customs and has grown up in a culture of arranged marriages. If this individual's religious and moral code forbids early termination of pregnancy *or* if financial and logistical circumstances make abortion impossible, I posit the desire for this cohort to use pre-marital genetic testing will increase.

My research showed that people born in India and people who had considered arranged marriage as a viable option (the two groups overlapped but not completely) did display a greater likelihood of using genetic tests at the pre-marital and pre-natal stage to make informed decisions about family planning. These groups also showed a greater inclination towards early termination of pregnancy as well as reconsidering partner choice based on the outcome of genetic testing. However, the data also showed that those groups that did not believe in abortion still did not preferentially want a pre-marital genetic test.

STATEMENT OF PURPOSE & GOALS

In June of 2010 the Food and Drug Administration launched an investigation into direct-to-consumer genetic information providers.[1] This formal examination followed on the heels of discomfort from the scientific community and the public about exaggerated marketing claims and improper dissemination of information by these genetic testing companies. The investigation was further motivated by the findings of the United States Government Accountability Office (GAO). The GAO recently conducted an informal, undercover operation in which they examined the genetic product offerings of four companies.[2] The results of the investigation showed the following failings of direct-to-consumer genetic testing:

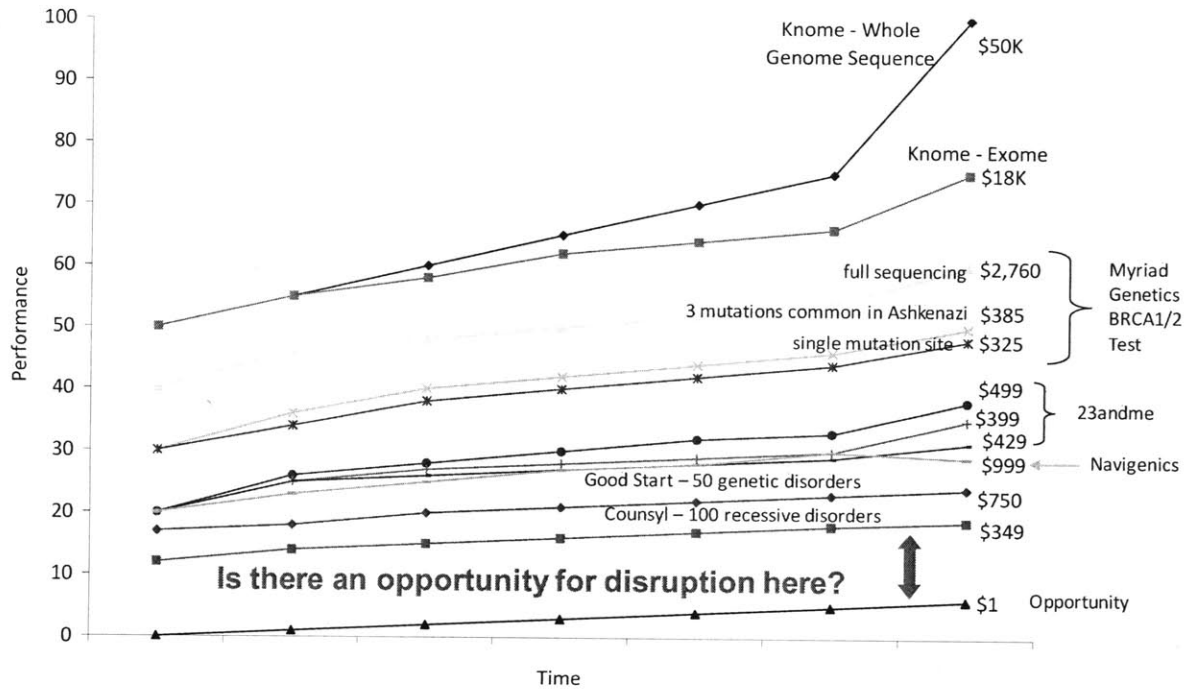
- **Consistency and standardization:** DNA samples from the same individual sent to different companies will yield different results. One individual could be given completely contradictory disease risk profiles by multiple vendors.[3]
- **Credibility, an incomplete understanding of the etiology of disease and an appreciation of test limitations:** Disease risk assessments can vary greatly from the individual's actual condition. The genetic test could state a very low probability of developing a disease which the customer already has.[4]
- **Limited understanding of diverse ethnicities:** the companies do not clarify and highlight the fact that they cannot provide a complete picture of the markers which influence conditions in less well-studied ethnic groups, such as those from Africa or Asia.[5]
- **Discrepancy between expert advice promised and delivered to customers:** Many of the companies failed to provide the expert counseling the customer was expecting.[6]
- **Wildly inaccurate marketing claims:** Some companies actually claimed to be able to make personalized supplements able to cure diseases. Two companies claimed to be able to foretell a proficiency in certain sports for children based on DNA analysis.[7]

These missteps have complicated the opportunity for successful deployment of the latest scientific research. Since the scientific community reached a critical mass of genomes decoded, researchers have been moving at a breakneck speed to make meaningful associations between genotype and phenotype. As soon as statistically significant associations can be made between particular genomic variations and disease states, we can begin to understand the trajectory of sickness. This understanding will be critical to cures, on-going patient care, therapy and prevention.

However, we are at the inception of this very nascent field—genetics. We are still working through the ways to collect, analyze, relate and act on the plethora of data provided by our DNA. Many companies such as 23andme, Navigenics, deCODE, Knome, Counsyl and others have tried to find a business model that empowers consumers to own and access the information in their DNA. As Figure 1 below shows, they have different price points for varying levels of information. Some companies provide information about ancestry alone as a recreational way to use your genetic make-up. Companies such as Knome are trying to carve out a niche as the ultimate service provider with a whole genome sequence, an updated understanding of that genome based on the latest research and high touch counseling. Companies such as Myriad Genetics have become associated with a very utilitarian niche of BRCA1/2 testing. Others still,

such as Counsyl and Good Start, are beginning to explore the carrier testing space with an eye towards prevention of fatal diseases in newborns. It is important to note that (see Figure 1) even the most affordable test is well over $100. The value proposition of a health care test which gives non-actionable or difficult to interpret information is further deteriorated by a costly price tag not covered by insurance.

Figure 1: Genetic Tests and Price Points Currently Offered



Please Note: the x-axis of performace is a subjective assignment of value by the author as to the quantity and quality of the information

The level of activity in this space is a good indicator of the excitement and hopes we all hold for the eventual utility of genetics. Unfortunately, the hopes have not been actualized yet for business ventures. After a cash burn of $676 million, one of the industry's brightest stars, deCODE, declared bankruptcy in 2009.[8] 23andme, which was founded in 2006 with the backing of Kleiner Perkins and Google, only has 35,000 customers to date.[9] Andrew Pollack of the New York Times reports that at least 25% of those 35,000 customers got the service for free or for $25.[10] Pollack goes on to point out that the direct competitors of 23andme, Navigenics and DeCode, can boast even fewer customers.[11] Another player, Pathway Genomics, geared up to provide an over-the-counter genetic kit at CVS / Walgreens, but had to halt its plans after public concern.[12] The lack of adoption is forcing other players to edit their original business model. Navigenics is now marketing to physicians rather than directly to consumers.[13]

Questions about price, utility, value and regulatory uncertainty are all serious challenges. These setbacks are hurdles for current ventures and will continue to be so for future endeavors. Further failures in this space will diminish the public's trust in companies which provide genetic insight and hinder the integration of genetics into our health care paradigm. It is imperative that we find a useful and successful model for utilizing genetic information to make better decisions.

I postulate that a successful model is really dependent on identifying the "right" consumer who would see value in paying for a genetic test out-of-pocket. The objective of this thesis, then, is to try and identify the characteristics of such a consumer. This broad query encompasses context, country, disease and target population. Fundamentally, this thesis has been designed to first investigate the elements which would make an opportunity for genetic testing attractive. Based on the background research conducted, I arrive at a hypothesis as to the characteristics of the exact target consumer who is likely to purchase, use and *value* a genetic test. Then, the hypothesis is tested by conducting a worldwide survey to gauge the attitudes and perspectives of different populations towards genetic testing. Finally, the results are analyzed to arrive at a more accurate picture of the target consumer and target disease for a successful deployment of direct-to-consumer genetics.

BACKGROUND

The "right" consumer is a product of her nationality, socio-economic status, genetic make-up and culture. From primary research in India, I found the middle to upper middle class individual in India to be an ideal candidate for genetic testing. Below, I lay out the foundation for the aspects of Indian life, culture and genetics which make people of that ethno-cultural group more amenable to genetic diagnostics. These factors also form the basis of my hypothesis.

Clear Points of Actionable Intervention

In the past few years, many summaries and assessments of genetic companies have pointed out a fundamental flaw in the value proposition of a genetic product offering: a lack of "actionable" information.[14] Finding out a percent predisposition towards a disease affected by multiple variables is minimally helpful. Often, guidance based on this information is limited to maintaining a healthy diet and regular exercise. Such generic advice reduces the value of genetic insight to the average consumer.

Companies are beginning to accept and respond to this consumer demand. First, companies such as Pathway Genomics, 23andme and Navigenics have begun to offer pharmacogenomic information to help customers understand how they will metabolize a drug based on their genetic make-up.[15] This service has patent utility and can help patients manage medical dosing and subsequent side effects. It is also an indication that the maturing industry is beginning to understand the need for product utility.

In genetics, utility is a subtle combination of ***relevant information*** provided at the ***right time*** which can ***prevent or guide*** good decision making. Pharmacogenomic insight offers guidance to both doctors and patients on how to prescribe and manage medication. This can have a significant impact on therapy recommended and final prognosis. By incorporating pharmacogenomic data into their service offerings, players in this space are adapting to a new understanding of what their customers want.

Another phenomenon which points to a deeper understanding of the importance of utility in this space is the rise of companies targeting fertility clinics. Companies such as Counsyl and Good Start offer prospective parents an opportunity to find out their carrier status for autosomal recessive diseases prior to pregnancy. Two carriers for recessive disorders can then make a more informed decision about how to proceed in family planning. Armed with carrier status information, parents can decide whether testing a fetus for a fatal genetic disorder is necessary or whether they would like to pursue in-vitro fertilization options which allow for pre-implantation diagnosis of the embryo.

This second phenomenon has a basis and model for success in other genetic organizations. Most prominently, Dor Yeshorim is a genetic screening organization which offers its services to the Jewish community.[16] It screens children of the Jewish faith for carrier status of recessive disorders. It then holds that information until such time as these individuals begin dating or considering marriage options. At that point, two prospective candidates can contact the organization to determine whether they are "compatible" or "incompatible." Incompatibility is a reflection of two carriers of the same disease. This service has been especially helpful in identifying carriers of Tay-Sachs disease and reducing the number of births affected by this condition.

Dor Yeshorim

By deconstructing the factors which lead Dor Yeshorim to be an effective model for genetic testing, we can derive basic principles for other successful implementations. These first principles can then be used to identify further opportunities / settings for the integration of genetic testing into the health care landscape. Dor Yeshorim serves a small, in-marrying community which originated from Eastern Europe: the Ashkenazi Jewish population. The Ashkenazi population is thought to have experienced the "founder effect" whereby a few mutations which occur in the "founder" of a community are then propagated through future generations.[17] The frequency of the mutation is exacerbated by the tradition and tendency for members to marry within the community.[18] This desire to marry others within a closely-knit community increases the likelihood of encountering others with the same mutation, having children with the disease or having children who are carriers for the mutation. Figure 2 below shows the high carrier frequencies for common genetic diseases in the Ashkenazi population. Another interesting characteristic of mutations which are a result of a founder effect is that a small number of mutations will account for most variants in the community and will result in good detection rates.[19]

Figure 2: Carrier Frequency of Common Diseases in the Ashkenazi Population

Disease	Carrier frequency in the Ashkenazi Jewish population	Carrier detection rate in the Ashkenazi Jewish population
Tay Sachs	1 / 30	94% or 98%
Canavan	1 / 40	98%
Niemann-Pick (Type A)	1 / 90	95%
Cystic Fibrosis	1 / 26 -29	97%
Gaucher (Type I)	1 / 15	95%
Fanconi Anemia (Group C)	1 / 89	99%
Bloom Syndrome	1 / 100	97%

Source: New York Methodist Hospital Website

Dor Yeshorim has been most effectively used by the orthodox Jewish community which still practices arranged marriages. Shidduch is the Jewish matchmaking system in which individuals are introduced for the purposes of marriage.[20] A specific website dedicated to shidduch encourages members to get tested for genetic conditions that may "put a shidduch at risk."[21] The orthodox Jewish community also stresses the importance of reproduction.[22] In addition, abortion is not viewed favorably by the Judaic moral code.[23] The simultaneous importance of procreation and disapproval of abortion make early intervention and prevention very attractive to this community.

Finally, a keen awareness of the stigma associated with genetic conditions has influenced the design of the Dor Yeshorim model. Individuals are tested at an early age (anywhere from middle school to high school) and are not immediately informed of their carrier status. Instead, they are given a de-identified PIN number which they can submit along with a prospective partner's when considering a marriage. This allows the community to begin to conceptualize "compatibility" or "incompatibility" as an idea

associated with a couple instead of an individual.[24] No individual's genetic make-up is "good" or "bad". Only certain unions are deemed "compatible" or "incompatible". This tactical move helps frame the idea of genetic testing in a way to remove individual stigma. In addition, individuals are tested for a panel of diseases. Therefore, a verdict of "incompatible" cannot be associated with a particular disease unless the consumers specifically seek such information. This also helps de-stigmatize genetic testing.

In summary, the elements of Dor Yeshorim which facilitate the integration of genetic testing in a community are as follows:

- Endogamous communities
- Arranged marriage practices
- Founder effect
- Autosomal recessive condition
- Inferior treatment / no cure for disease conditions
- Importance of procreation as a social and religious duty
- Fundamental belief against early termination of pregnancy
- Mitigation of stigma by testing for multiple diseases but delivering only a generic response
- Associating genetic testing as an assessment of a couple, not an individual

Applying the framework in an Indian context

Based on the aforementioned conditions of successful adoption, I examined the Indian culture as an appropriate framework for genetic testing. The Indian community resembles the Ashkenazi Jewish community in many of its cultural norms and marriage customs.

Arranged Marriage

The country study of India in the US Library of Congress notes that, "In India there is no greater event in a family than a wedding, dramatically evoking every possible social obligation, kinship bond, traditional value, impassioned sentiment, and economic resources. In the arranging and conducting of weddings, the complex permutations of Indian social systems best display themselves."[25] The report goes on to clarify how marriage is the result of efforts taken on by many people and is the most important responsibility of parents. Marriage is an important tool in establishing alliances, redistributing wealth and building social networks.[26] Not only do parents see it as their responsibility to arrange the marriages of their children, but children themselves see it as a parent's responsibility.

These sentiments have not changed due to the modernization and Westernization India is seeing as a natural consequence of globalization. In fact, modern conveniences such as the internet are enabling parents to continue the tradition of arranging marriages across greater distances and with more options. Wedding portals which aggregate suitable candidates across India and the Diaspora are gaining in popularity. One of the most popular marriage websites, Bharatmatrimony.com, already has between 12 to 15 members worldwide. The overall market is estimated to be more than 25 million members strong. The demand for such services is so keen that these on-line companies have successfully launched brick

and mortar store fronts as an extension of their presence. Below (Figure 3) summary statistics of the rank in website traffic and average time spent on the most popular wedding portals reaffirm the desires of the middle and upper middle class to continue the tradition of arranged marriage.

Figure 3: Statistics for Popular Wedding Portals in India

Website Statistics	Global Rank of website traffic	Rank in India	Avg time on site (in past 3 months)	Sites linking in	Members	Other metrics	demographics	Brick & Mortar centers	Cost to sign up
Overall market					over 25 MM	$63 MM revenue			
shaadi.com	946	70	6.5 - 9.5 min	1231	11 MM	6000 new profiles created / day, 200 MM page views / month	mostly middle class, ~70% from india	250 (in 87 cities)	free to $189
jeevansathi.com	2436	159	7.3 - 8.0 min	532	2.5 MM			14	$15 - $100
bharatmatrimony.com	3051	229	2.1 - 2.6 min	446	12 MM				$79 - $258
simplymarry.com	10544	723	3.7 - 4.1 min	146					
matrimonialsindia.com	100250	8791	8.8 - 9.5 min	188					

Source: Alexa and company websites

Furthermore, a survey conducted by BharatMatrimony.com which reached 1,058 women in tier I and tier II cities found that 49% of the responders declared a preference for an arranged marriage. These were women between the ages of 20 and 30—a prime marriage age in India. More importantly 59% of these women stated that parental decision was the most important factor in the marriage process.[27]

I conclude that arranged marriage practices are still a vibrant norm in India and hypothesize that they can provide an interesting point of intervention for fatal genetic disorders. Part of Dor Yeshorim's success can be attributed to its ability to inform prospective couples of carrier status prior to marriage. At that stage, a prospective couple has multiple options. They can choose to not pursue a relationship, proceed with the marriage but be vigilant in the use of genetic testing on a fetus, choose to adopt a child or take no action. Whichever route the couple selects, they are at least informed and aware.

Endogamous Practices

Marrying within specific ethnic or social groups has long been a custom in Indian culture. In India the practice has been codified in an intricate social structure—the caste system. The caste system consists of four varnas or large super-groupings which are affiliated with occupation. The varnas are Brahmin (priests), Kshatriya (nobility), Vaishya (merchants) and Shudra (workers).[28] Within varnas are more specific castes referred to as jati. Within a jati, an individual may then belong to an even more narrow sub-caste.[29] It is this narrow sub-caste level that defines the limits of one's marriage options and forms a part of an individual's identity in India.[30]

The rules that govern in-marrying within a sub-caste are enforced by family, society and the panchayat—a caste council.[31] Punishments for breaking a caste rule can vary from payments to being kicked out of the caste for grave violations. One such extreme infraction is marrying someone from a

lower caste.[32] Public displays of violence and retribution often follow such flagrant flouting of traditional norms.

In May 2009, economists at MIT examined the importance and relevance of caste in arranged marriage decisions in India. The economists noted that caste is such a common framework; matrimonial ads were organized under caste headings to facilitate specific searches.[33] The study followed the ad placements, preferences and eventual selection of 783 random individuals in Bengal.[34] This random sample consisted mostly of upper-middle class, educated constituents with a reputation for being freethinking.[35] The economists highlighted this fact to assert that the attitudes and preferences of this cohort would probably form the lower bound of caste preference. The study found that even amongst this liberal group, marrying within caste was of high import. In fact, people preferred to marry within their caste even over "marrying up."[36] The study also found that people were willing to give up more on attributes such as beauty, education and skin color to marry within their caste. Finally, the economists determined that there was a balance in the number of adequate options for individuals within caste groups to form an "equilibrium". This suggested that the caste system would remain in place and a critical framework as India faced further economic growth and progress.

Furthermore, other, more easily tracked popular trends point to resilience in caste preferences in modern India. A study by researchers for Urban Knowledge, Action and Research found a substantial increase in caste-based communities on Orkut (the number one social networking site in India) over a short period of time. A closer analysis of these caste based communities showed that most members were highly educated (with graduate degrees) and lived in urban metropolises.[37] This fact contradicts the theory that caste affiliation is fading in India and if it exists as a relevant factor, it only exists in rural areas amongst under-educated individuals. A quick internet search will find many sub-caste specific on-line matrimonial sites that cater to very specific niches. These on-line caste groups utilize facebook, blogs and twitter accounts in order to aggregate and affiliate.

In conclusion, endogamous customs in India are significant and resilient over time. It is possible that the access and anonymity of the internet even allows for further communal cohesion. Caste is a taboo topic to address in public in India today. Therefore, it is not often discussed openly. This phenomenon could cause a lay observer to underestimate its consequence in Indian society. We will assume from this data that modern India does in fact still have a cultural context which promotes arranged marriages within small, endogamous groups. Indians who follows these traditions, then, might be preferentially inclined to find value in genetic testing which allows them to continue to follow traditional norms of marrying within small, endogamous groups while managing the concomitant risk of disease.

Founder Effect & the Consequences of Endogamy

In September 2009, a publication by David Reich examined genetic variation in the Indian population.[38] The study analyzed 132 Indians from 25 groups. The results of the study were consistent with a hypothesis that suggests a population of discrete groups founded by a few people followed by endogamy limiting gene flow.[39] Founder events ranged from 30 generations ago to 100 generations ago. The paper asserts that for genetic signatures of founders to still be evident, average gene flow had

to be very limited.[40] Notably, the paper states that these founder events predict an increased rate of recessive disorders.[41] These diseases should be possible to identify, screen and serve as a basis for genetic diagnosis. Thus the Indian population meets another criterion for serving as a good target for genetic testing.

Importance of Marriage and Procreation as a Social and Religious Obligation

Hinduism is the religion with the largest following in India with over 800 million members, 80.5% of the population.[42] For a Hindu, every stage of life is marked by rites of passage called samskaras. These are defined by custom and commemorate critical life events.[43] There are sixteen generally accepted samskaras, and eight are regularly performed in India.[44] These rites are organized around the four most important events in a Hindu's life: Jatakarma (Birth), Upanayana (Initiation), Vivaha (Marriage) and Antyeshti (Death).[45]

Specifically, two samskaras highlight the importance of marriage and child bearing in Hindu culture. The first sacrament of Garbhadhana is the rite of conception and ensures a healthy baby. The twelfth sacrament of Vivaha is the rite of marriage and consumes a great proportion of a family's budget. These formal, religious observances of marriage and birth emphasize the pivotal role an adequate marriage and healthy children play in Indian life. They compare closely with the importance of marriage and children in the orthodox Judaic tradition which forms a part of Dor Yeshorim's success.

I hypothesize that cultures which place a great deal of value in a successful marriage and healthy children will see greater value in using genetic testing as a tool to prevent disease. In India, as explained above, elaborate religious ceremonies anchor marriage and child-birth as pivotal life events in an individual's life. To augment the effect, social customs underscore the significance of the events. Funding a daughter's marriage often drives a family into debt with interest rates of over 200%.[46] Dowries and wedding celebrations are more than six times a family's annual income on average. [47] Wedding expenses alone, which are shadowed by the much larger dowry costs, average over Rs 5,000—one third of an average family's income. I posit that a genetic test which can ensure the "success" of a marriage, as defined by healthy progeny, will be viewed favorably in the context of the large investment parents make into unions.

Familiarity with Genetics

In addition to rules of endogamy which limit the genetic diversity of its sub-caste groups, the Hindu culture also has rules of exogamy which prohibit the in-marrying of descendents of the same line. The concept of *gotra* refers to patrilineal lineage in which two individuals share a common ancestor.[48] Culturally and from a religious perspective, two partners from the same gotra cannot marry each other.[49] These rules display a basic understanding of genetic concepts and at least provide a framework for the Indian mindset to understand the utility of genetic testing.

It is interesting and important to note that some groups within India (particularly in South India) still encourage marriage between uncles and nieces as well as cross cousins. Some estimates put the number of uncle-niece marriages in Bangalore and Mysore to be as high as 21% of the Hindu unions.[50]

However, scientific studies are beginning to document and reveal the significantly increased odds of disorders that result from these consanguineous unions.[51] Furthermore, the traditional idea of not marrying someone within your own gotra is getting more recent press and national attention in India. Politicians are using it as an issue to organize around and engage public sentiment. It is being discussed in terms of continuity with long-held traditions, as well as in more scientific terms of promoting genetic diversity by eschewing inbreeding.[52]

Finally, as a case study, I examined the use of genetic services already employed in India by the lay public. A close analysis of the Indo-Aryan ethnic Jat group shows a growing comfort with DNA analysis in the Southeast Asian sub-continent. The Jat community has created a wiki page which serves as a resource for people who share this common heritage to maintain ties to the community and learn about their specific culture.[53] The wiki references genetic tools people of Jat descent can use validate that someone with the same surname is actually related to them or to maintain family history records. Even more progressive are the directions which encourage DNA testing in order to comply with tribal laws of not marrying a relative less than four generations removed. [54]

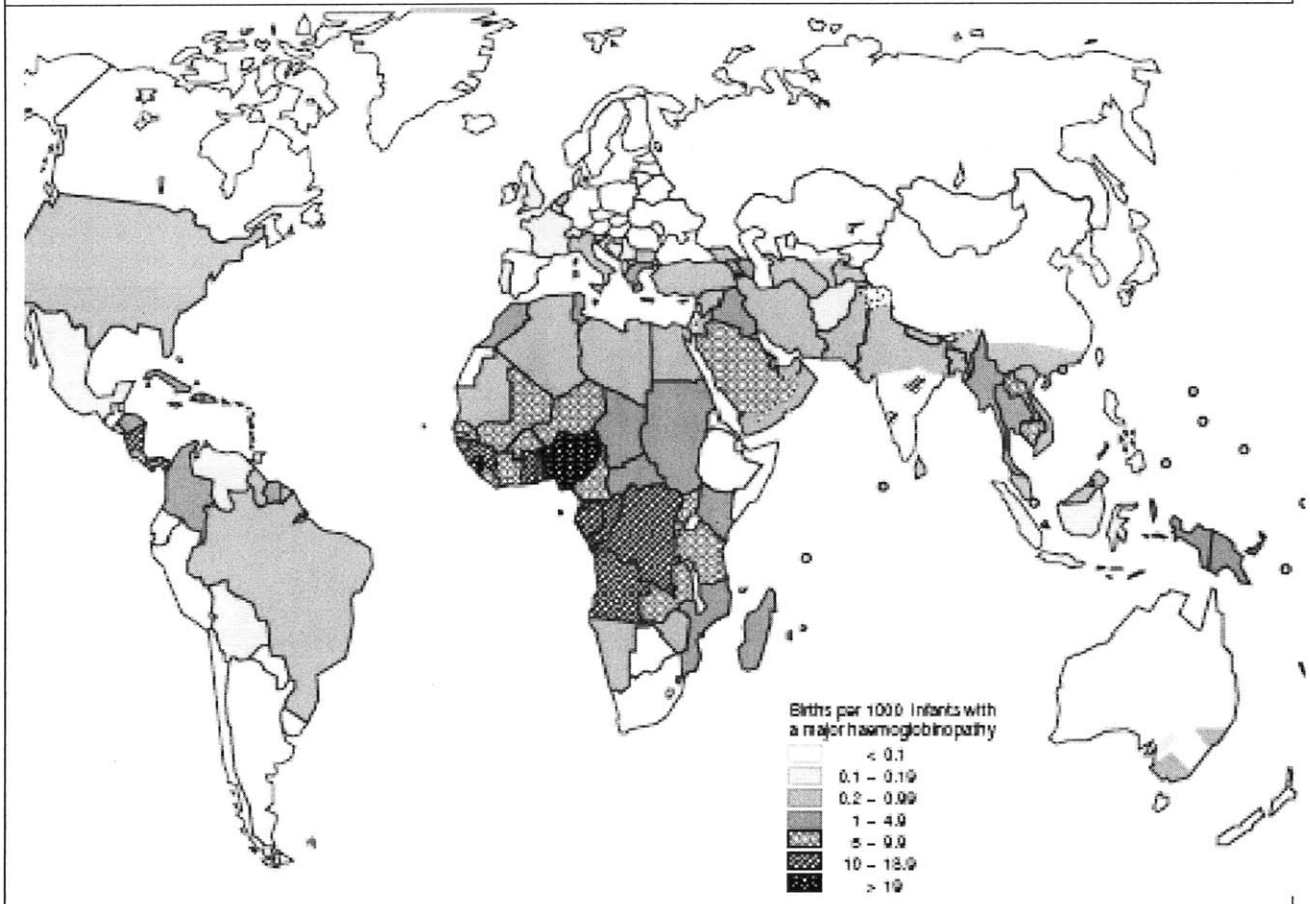
The trends of 1) a growing awareness of the scientific impetus for traditional norms such as rules of exogamy; 2) national media attention for the conversation about gotra; and 3) a familiarity with the tools of genetics to sustain ancient customs instead of abolish them are significant. The culmination of these trends will prepare the public for further genetic utility and perhaps make Indians a more amenable consumer group for more sophisticated genetic testing.

Autosomal Recessive Condition

The next objective is to identify a recessive disorder which is prevalent in the Indian subcontinent that could benefit from preventative action. The natural initial targets that I consider are the hemoglobinopathies.

Hemoglobin disorders are the most common monogenic diseases in humans[55]. The incidence of these diseases, 400,000 births annually with serious hemoglobinopathies, is a growing burden in the world[56]. Unfortunately, that burden is disproportionately felt in the developing world (see Figure 4).

Figure 4: Global distribution of hemoglobin disorders, in terms of births of affected infants per 1000 births



Source: World Health Organization

Many areas of the developing world fall into the malaria belt— which ranges from the Southern Mediterranean to sub-Saharan Africa, the Middle East, India, Southeast and Island Southeast Asia, and Northern Australia. The selective pressure placed on mankind by malaria allowed the survival of carriers of certain hemoglobin mutations to have an advantage over others. Heterozygotes for Hemoglobin S, Hemoglobin C, Hemoglobin E and B thalassemia mutations are thought to have some resistance to severe and fatal malaria infections[57]. Consequently, developing world countries see higher carrier frequencies for these hemoglobin mutations. Figure 5 below shows carrier frequencies for common hemoglobin disorders by regions as designated by the World Health Organization.

Figure 5: Carrier Frequencies for Hemoglobin Disorders (2001)

Region	Hb S	Hb C	Hb E	β thalassemia	α^0 thalassemia	α^+ thalassemia
Americas	1-20%	0-10%	0-20%	0-3%	0-5%	0-40%

Eastern Mediterranean	0-60%	0-3%	0-2%	2-18%	2-18%	1-60%
Europe	0-30%	0-5%	0-20%	0-19%	0-19%	0-12%
Southeast Asia	0-40%	0	0-70%	0-11%	0-11%	3-40%
Sub-Saharan Africa	1-38%	0-21%	0	0-12%	0-12%	10-50%
Western Pacific	0	0	0	0-13%	0-13%	2-60%
Source: *Disease Control Priorities in Developing Countries*, Weatherall et al[58]						

This thesis examines the possibility of disease prevention in India with the aid of thoughtful genetic testing. Since hemoglobinopathies are the most prevalent monogenic diseases in the world, blood disorders make a perfect test case for the hypothesis. The thalassemias in particular provide an ideal opportunity for prevention through early screening. The thalassemias (α and β are the most common) are a family of diseases characterized by a reduction in hemoglobin production. Numerous permutations of possible mutations or deletions lead to diseases of varying severity. In the most extreme case, the genetic make-up of a fetus is incompatible with life and the baby is usually lost in utero. On the other end of the spectrum, some defects are so subtle that they can only be detected by PCR. To add to the complexity, two heterozygotes who present only with mild anemia can have a child with severe disease. This disconnect between genotype and phenotypic expression is a serious concern for societies which lack sophisticated diagnostics.

Epidemiological studies estimate over 15 million people worldwide to have clinical manifestations of thalassemia.[59] Estimates also put β thalassemia carrier numbers alone at 240 million worldwide and 30 million in India.[60] Approximately 200 variations of the β globin gene which cause β thalassemia have been discovered.[61] The combination of disease severity, cumbersome treatment and location of incidence (most severe β thalassemia cases are in low and middle income countries) result in high death rates in children.[62] Globally, estimates suggest that β thalassemia is responsible for 50,000 to 100,000 deaths per year. This translates to almost 1% of all deaths of children under 5 in these lower income countries.[63]

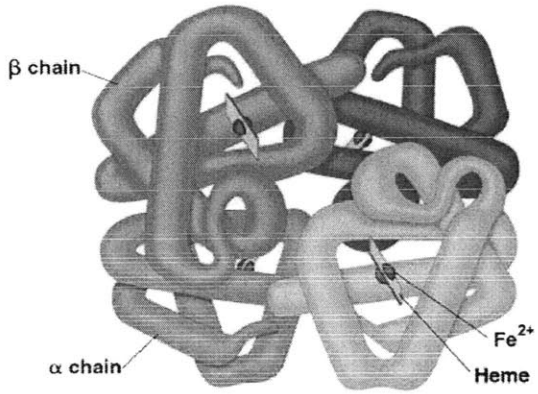
Molecular Manifestation of the Genetic Mutation

Thalassemia is, in its essence, a disease of reduced hemoglobin production. Hemoglobin is the protein within red blood cells which carries oxygen from the lungs and delivers it to the tissues in the body. Hemoglobin is composed of four subunits—two α globin chains and two non-α globin chains. As Figure 6 shows, in adults a majority of the hemoglobin is composed of two α globin chains, and specifically, two β globin chains. In normal circumstances, the ratio of α-globin chains to β-globin chains is 1 to 1. A

defect in the production of either α or β globin chains causes a critical chain imbalance. In β thalassemia, for example, reduced synthesis of β globin chains will result in excess α globin chains in red blood cells. The excess α chains will clump together, form α chain precipitates in erythroid precursors and initiate accelerated apoptosis in these red blood cells.[64]

The body responds to the accelerated apoptosis by trying to increase red blood cell production—the number of red blood cell precursors in the bone marrow of thalassemia patients is 5 to 6 times that of healthy controls.[65] This leads to skeletal changes such as bone expansion and thinning of bones. The high rate of hemolysis also causes the spleen to become hyperactive and enlarge.

Figure 6: Hemoglobin Structure



Source: The Medical Biochemistry Page, http://themedicalbiochemistrypage.org/hemoglobin-myoglobin.html

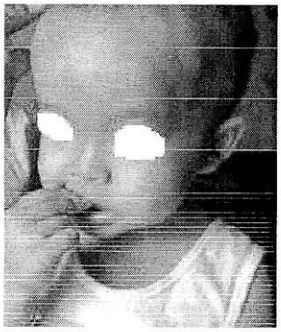
Clinical Manifestations of the Genetic Mutation

For the purposes of a test case, I focus on β thalassemia as a reference point for a prospective genetic test in the Indian market. The clinical manifestations for β thalassemia vary depending on the severity of the condition. A carrier of the trait (a single β globin gene mutation) can present with mild to no anemia at all.[66] A patient with Thalassemia Intermedia (two β globin gene mutations, at least one of which is mild) will present with mild to moderate anemia.[67] The level of transfusion required will vary with the severity of the anemia. These patients can also present with enlarged spleen and other bone deformities depending on the effectiveness of treatment. Patients with Thalassemia Major (two β globin gene mutations, both of which are severe) will present with severe anemia. They require frequent blood transfusion and subsequently have to be managed for iron overload. Iron deposits in the liver, heart and pancreas can be fatal.[68] These patients display growth retardation, delayed development, have leg ulcers and are prone to infections.[69]

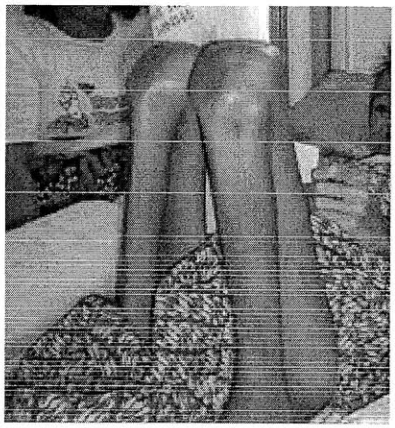
The only cure for hemoglobin disorders, currently, is a successful bone marrow transplant.[70] The affordability, accessibility and lack of adequate HLA matches keep this option out of the reach of most patients in India. The standard of care treatment involves monthly blood transfusions with companion iron chelation therapy. Compliance with current chelating therapies is a significant issue. Children with major to intermediate forms of thalassemia also often require a splenectomy.[71]

In summary, thalassemia is a grave disease with onerous symptoms and complications. It has no easy cure and the gold standard of therapy is cumbersome (frequent, lifelong) and expensive. The disease is also monogenic and genetically well characterized. The disease has a large impact on the quality of life of both children and parents. The lack of great treatment options and well-understood genetic etiology make this disease an ideal target for genetic testing for preventative purposes.

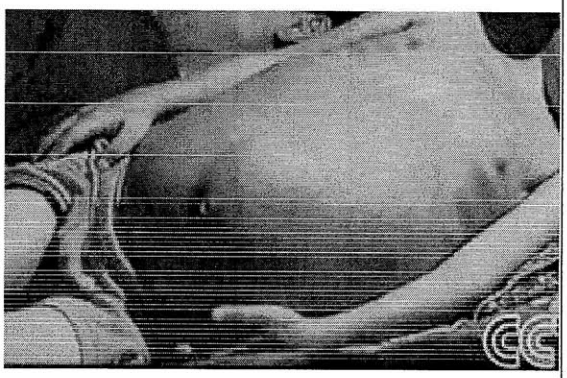
Figure 7: Clinical Manifestations of Thalassemia



Bone deformities



Abnormal bone expansion



Splenomegaly

The Thalassemia Problem in an Indian Context

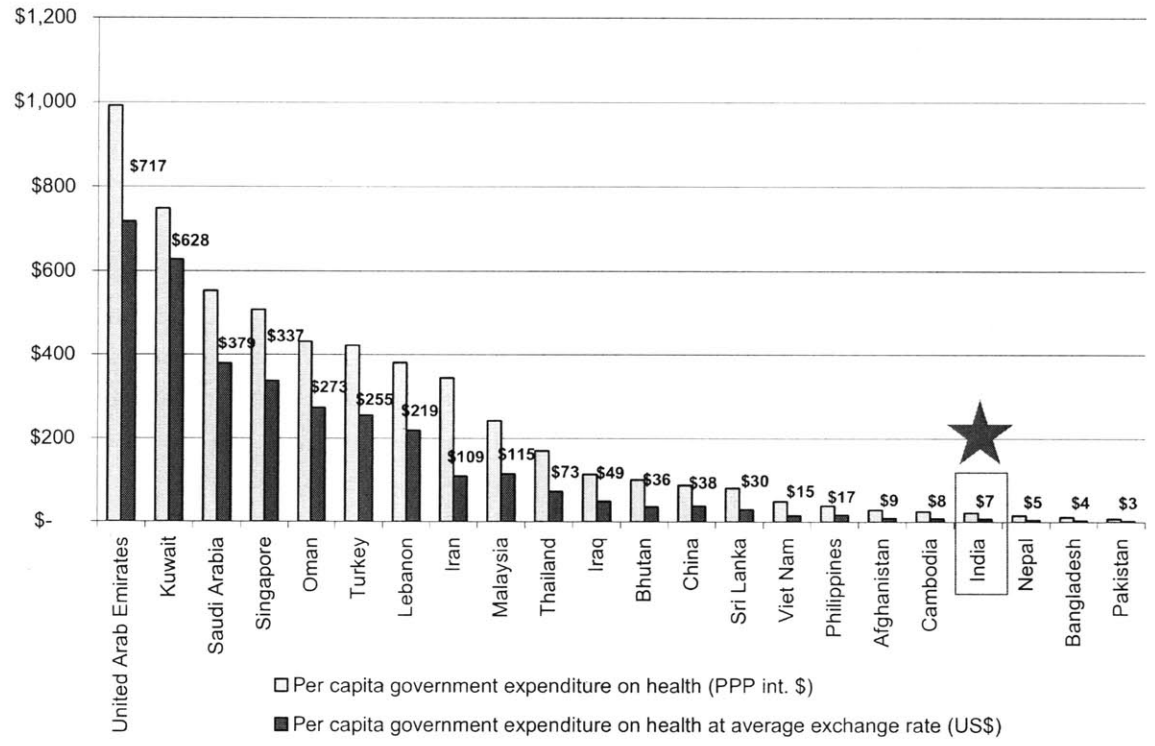
A report by the president of the Indian Academy of Pediatrics in 2007 highlighted the fact that of the 100,000 children born annually with a severe form of thalassemia, 10,000 are accounted for by India alone.[72] Estimates of prevalence in India for β thalassemia are between 65,000 and 67,000.[73] The report also emphasizes that the while the mean prevalence of carriers for β thalassemia across India is around 3.3%, it can be as high as 15% in certain communities in India.[74] The report explicitly calls out the higher carrier rates for "Sindhis and Punjabis from Northern India, Bhanushali's, Kutchis, Lohana's from Gujarat, Mahar's, Neobuddhist's, Koli's and Agri's from Maharashtra, & Gowda's and Lingayat's from Karnataka."[75]

The higher carrier rate in these communities accounts for higher levels of disease incidence and prevalence as well. As an example, Gujarat alone (a single state in Western India) accounts for 10% of

the annual thalassemia births in the country.[76] The problem is so grave in one of the insular, in-marrying communities, the Kutch Bhanushalis, that community leaders mandate a carrier test be taken by both prospective partners before a marriage is allowed to proceed.[77] The leaders do not have the legal power to enforce such mandates but resolutions generally carry the same weight as formal laws within the community.[78] The biggest obstacle to acceptance of this rule is driven by the fear of stigma associated with females who are labeled as carriers.[79] Still, the high rate of incidence of the disease combined with the exorbitant cost of treatment for the disease has provoked action and has motivated very long-term preventative care.

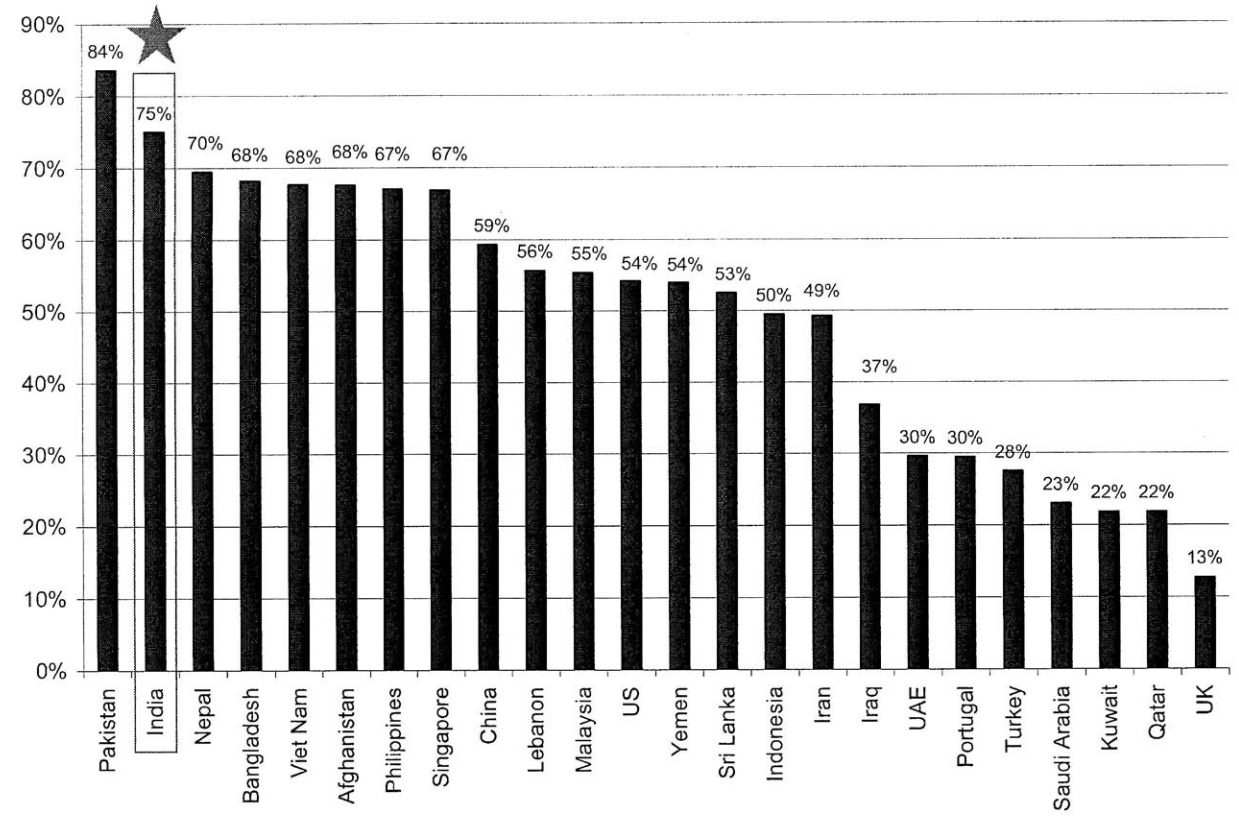
It is important and relative to mention cost in this setting. The cost of a bone marrow transplant can range from Rs 600,000 to Rs 1,000,000.[80] Even if a few are able to afford this cure, currently no bone marrow bank or registry exists in the country. This makes finding an exact HLA match difficult. The other alternative of monthly transfusions cost can be as much as Rs 600 to Rs 2000 per treatment. Iron chelation therapy is an additional Rs 500 to Rs 2000 on top of the monthly transfusion amount. Estimates put all-in costs for optimal care at Rs 100,000 / year per child.[81] Based on those estimates, thalassemia could add up to Rs 1 billion annually to India's burden of health care. Unfortunately, the government does not provide the financial support necessary to manage on-going care for thalassemia patients. In fact, as Figure 8 shows, India spends only $7 / year / capita on health care. The next chart in Figure 9 shows that 75% of the cost of healthcare is funded by private individuals.

Figure 8: Per Capita Government Expenditure on Health – minimal government support



Source: World Health Organization

Figure 9: Private Expenditure on Health as a Percentage of Total Expenditure on Health: Brunt of Cost is Carried by the Consumer



Source: World Health Organization

The overwhelming cost of care for chronic conditions in India is paid for out of pocket and carried by private families. This healthcare paradigm naturally forces many people to abandon optimal therapeutic regimens in favor of traditional (less expensive) ayurvedic medicines or no treatment at all. A study by Bernadette Modell and Matthew Darlison tracked the practice of optimal care in different regions around the world and confirmed a glaring gap between affected patients and use of transfusions in Asia.[82] As Figure 10 below shows, the number of transfusion-dependent babies born every year in Asia who actually receive transfusions is small. Furthermore, the number of patients who receive adequate iron chelation is also minimal. By any definition of the phrase, the majority of individuals born with thalassemia in Southeast Asia do not receive "optimal care".

Figure 10: Access to Treatment for β-Thalassemia

WHO region	Estimated annual births β thalassaemias		Transfusion			No. of known patients	Adequate iron chelation		Inadequate or no iron chelation	
	Total	Transfusion-dependent	Annual no. starting transfusion	% of transfusion-dependent patients transfused	Annual deaths because not transfused		% with chelation	No. with chelation	No. of patients	Annual deaths due to iron overload
African	1 386	1 278	35	2.7	1 243	–	–	–	–	–
American	341	255	134	52.4	121	2 750	58	1 604	1 146	57
Eastern Mediter-ranean	9 914	9 053	1 610	17.8	7 443	39 700	27	10 818	28 882	1 444
European	1 019	920	140	15.5	780	16 230	91	14 754	1 476	74
South-east Asian	20 420	9 983	962	9.6	9 021	35 500	19	6 621	28 879	1 444
Western Pacific	7 538	4 022	108	2.7	3 914	3 450	44	1 504	1 946	97
World	**40 618**	**25 511**	**2 989**	**11.7**	**22 522**	**97 630**	**39**	**37 866**	**59 764**	**2 988**

* All figures are minimum estimates.

Source: Bernadette Modell & Matthew Darlison, "Global epidemiology of haemoglobin disorders and derived service indicators", Bulletin of the World Health Organization, June 2008.

Even more specifically, the president of the Indian Academy of Pediatrics points out that no more than 5% to 10% of children born with thalassemia in India receive optimal treatment.[83] Therefore, we can confirm that the specific circumstance of thalassemia in India meets another criterion for an attractive context for genetic testing. Interestingly, since the government does not directly bear the cost of care for these thalassemic patients, the government is also not necessarily the most favorable target for financing a carrier test. Parents who feel the social pressures of arranging a "successful" marriage and have allocated a large budget to ensure a successful wedding may be more appropriate targets. I postulate that these social dynamics will make India a more appropriate environment for direct-to-consumer genetic tests.

Stigma

Another reason why the government is not an ideal candidate for administering genetic screening is because of the sensitive nature of genetic information. All carriers, but perhaps especially women in India, may unduly bear the consequences of being identified as a "carrier of a mutation". It would take a sophisticated understanding of genetics to appreciate the protective nature of being a carrier of a hemoglobin mutation. In a lay environment with a superficial understanding of genetics, carrier status could bring negative connotations the individual would have to manage. In close-knit communities,

where marriages are arranged based on a set of independent factors, an ill-understood designation of "carrier" might be detrimental to an individual's chances of marriage. These conditions make the value proposition of a direct-to-consumer genetic test even more relevant in India. A health imperative exists for Indians to find out if they are carriers for thalassemia, but it must be done with the utmost privacy and discretion. This information ideally would be provided to the individuals being tested alone and they would then be empowered to use it at the most appropriate decision point in their estimation.

Luckily, attitudes towards disease and carrier status are progressing. In a study done in 1990, researchers examined attitudes towards screening for thalassemia specifically amongst 200 families in India.[84] These were families of index cases, so an increased probability of being a carrier existed amongst their relatives. The parents of the index cases expressed a fear of social alienation and kept the affected condition of their children a secret.[85] In a follow-up study in 1997, researchers found that out of 70 carriers identified in a high-risk community screening, only 46% of the carriers had their siblings tested. 42% had not even told their siblings that they were carriers.[86] In contrast, a study published in 2002 showed that 96% of the parents of 100 index cases were willing to share the diagnosis with their relatives. [87] The chronological progression of attitudes is encouraging and may imply an evolution towards testing.

The government is also pushing the public towards a more open-minded understanding of genetic diseases through educational programs. The president of the India Academy of Pediatrics wrote a memo in 2007 encouraging inter-governmental cooperation in order to form a National Thalassemia Prevention Program.[88] The advocacy and education efforts of such a program would substantially improve the awareness of the public and leave them better prepared to use the services of a genetic test.

A Limited Set of Mutations

Finally, even though hundreds of mutations have been discovered and reported for β thalassemia, for any one region only a few are relevant.[89] For Indians, five common mutations and twelve rare ones have been documented. These mutations are more or less prevalent depending on the region of India an individual is born. In 1997, a study examined and categorized the mutations of over 1,000 β - thalassemia major patients. It then organized individuals based on their region of origination and not where they currently lived. Using this methodology, they found very coherent patterns of mutations according to region. 91.8% of the successfully characterized carriers had one of the five most common mutations.[90] The most prevalent mutation was IVS-I-5 (G→C). This single mutation accounted for 85% of the carriers from South India, 76% of the carriers from Bengal and 47.6% of the carriers from Punjab.[91]

The narrow range of mutations relevant in any region makes it possible to imagine an affordable and accessible diagnostic could be developed for this market. Genetic tests for critical, inherited diseases in a developing world context will be adopted much more quickly if they are priced within the means of a middle class consumer. This middle class consumer will have the education to understand the application of such a test as well as the resources to purchase it. Currently, companies are beginning to

examine technology which would allow the confirmation of a limited number of mutations in a point-of-care platform without the burden of intensive, upfront capital expenditure.

Other Models

Other communities around the world have experimented with various genetic testing models. These endeavors merit a brief analysis to understand how they may have succeeded or failed.

Sardinia – population screening model

One of the most relevant and famous attempts to use genetic screening to bring down the incidence of disease was for thalassemia in the Mediterranean. In the early 1970s, Sardinia realized that it faced an oncoming crisis in healthcare. Estimates indicated that if Sardinia continued on its existing trajectory, in 40 years, it would require 78,000 units of blood annually to meet the transfusion demands of severely affected thalassemic children.[92] The burden of care of for such a widespread, taxing disease would have bankrupted the island.

At the time, 13% of the island's 1.4 million inhabitants were β -thalassemia carriers. 1 out of 60 couples were at risk and the incidence of thalassemia in newborns was 1 out of 238.[93] In addition, life expectancy for a homozygous individual, with the best of treatments, was 20 years.[94]

Therefore, Sardinia launched a genetic screening program that consisted of education and screening. The initiative involved community outreach: meeting with community leaders, educating the populace about the disease, and leading discussion groups for 3 months. It also utilized television advertising, news print and educational talks at high schools and large offices to prepare the people. Then blood sampling commenced at local places and hospitals at convenient times. The results were relayed back to individuals in private interviews after the blood sample had been analyzed. Carriers were given information on prenatal diagnosis and educational materials regarding implications of carrier status.[95]

Of the individuals who voluntarily came in to be tested through the outreach community program, 68.9% were female. 65.3% of the tested individuals in the secondary hospital program were also female.[96] A high representation of females requesting testing probably reflects their greater involvement in family planning matters.[97] In total, 2,664 β thalassemia carriers were identified out of 16,584 tested individuals. Most of the couples that were found to be "at risk" (85%) requested prenatal testing. Of the 42 homozygous β thalassemia fetuses identified by prenatal diagnosis, 39 were terminated.[98]

This study was conducted over a 3 year period. During that time, incidence of thalassemia n the target counties where the study was conducted went down from 1 out of 213 births in 1976 to 1 out of 290 births in 1978.[99] With continued vigilance and over time, the incidence has declined further. Today, according to World Health Organization statistics, thalassemia major is present in 1 out of 4000 births in Sardinia.

In this instance, government sponsored education, vigilant screening and prenatal diagnosis were able to impact the course of the epidemic. It is important to note that Sardinia is a small island community of

1.4 million people. It is possible, and indeed was successful, for a federal authority to manage such an initiative. This model may have less relevance in a country as large and complicated as India.

Dor Yeshorim – the anonymous model

Dor Yeshorim is such a critical prototype for this thesis that it warrants a deeper dive. The organization was designed in the 1980s by an Orthodox rabbi, Joseph Ekstein, to fit within the religious and cultural context of Orthodox Judaism. The literal translation of the organization's name is "generation of the righteous." Rabbi Joseph Ekstein lost four children to Tay-Sachs prior to the founding of Dor Yeshorim.[100]

The impetus for the organization—the incurable condition Tay Sachs disease—was highly prevalent in the Ashkenazi community (1 out of 3000 births).[101] Tay-Sachs disease results in deterioration of mental and physical abilities in babies and usually ends in death by age 4. It is a single gene autosomal recessive disorder with no treatment options. Dor Yeshorim decided to take on this disease from a prophylactic perspective.

The Dor Yeshorim model takes advantage of the Jewish custom of Shidduch. It is a matchmaking system which introduces single Jewish individuals to each other for the purpose of marriage. It can be launched by recommendations from family members and friends or, more formally, through a professional matchmaker (shadchan). Families make inquiries about prospective candidates, allow a variable time for acquaintance and move relatively quickly towards marriage.

Dor Yeshorim inserts itself into this matchmaking process by getting involved in testing very early. In the Dor Yeshorim model, representatives from the organization take blood samples from high school students (at Orthodox schools) and give each student a random identification number. The samples are screened and the results stored. When these same students reach a marriageable age and begin to participate in the custom of Shidduch, Dor Yeshorim reappears into the process. Prospective candidates (or their parents) call Dor Yeshorim. The organization administrators then cross reference the two ID numbers and only provide the family with an assessment of whether the marriage is advisable. No information about carrier status for any particular disease is provided. Therefore, the information is "anonymous."

The timing of this phone call varies. Some families check the "compatibility" prior to the first date. Others wait to determine whether an actual basis for a union exists before making the call. The final decision about moving forward is left to the families. Given the Orthodox community's aversion to abortion, a preventative measure is even more relevant when it comes to genetic disorders.

This system of identification numbers, no revelation of carrier status and an undifferentiated response for compatibility (no clarity on which of the 10 tested diseases is the obstacle) does not completely avoid stigma. Both the candidates and the families know that a recommendation against marriage means both partners are carriers for some disease. The community also perceives a potential union which disintegrates after the Dor Yeshorim check as a bad signal.

The ten diseases tested for are: Tay-Sachs disease, cystic fibrosis, Canavan disease, familial dysautonomia, Fanconi anemia type C, Bloom's syndrome, Gaucher disease type I, mucolipidosis type IV, glycogen storage disorder type I, and Niemann-Pick disease. The participation cost of the program is $200.[102]

This model, though not ideal, resonates the most closely with the Indian social and religious structure. It is worth mentioning that it has been very successful in reducing the incidence of Tay-Sachs in the community.

Israel – voluntary population screening at an earlier time point

In 2008, Israel started providing free population screening to its citizens for cystic fibrosis.[103] This program was specifically designed so that couples would have alternatives to natural pregnancy and early termination based on a negative prenatal diagnosis. The couples could now consider options such as separation, adoption, or pre-implantation diagnosis with an earlier diagnosis.

In total, most couples who partake of carrier screening programs (for Tay-Sachs and other diseases) usually come in for examination once they are already pregnant.[104] This leads to detection at a later point in time and a much higher risk of a problematic abortion. Some have postulated that the less than ideal timing of carrier screening is due to the lack of awareness in the lay population about genetic testing. The Israeli Ministry of Health has sought to tackle this problem through introductory genetic lectures in high school augmented with refresher meetings in the army and university settings.

Up to 2008, the Ministry of Health provided free testing for Tay Sachs in regional clinics once a week. In the last ten years, 25,000 to 27,000 tests were performed on an annual basis. As a result, very few children are born with Tay Sachs today in Israel.[105]

This model highlights the importance of early awareness. Many parents in India also find out about their carrier status only after they have already had one child with thalassemia. It is critical to intervene prior to the first pregnancy in order to make the largest impact in a family and bring down the incidence of disease.

Saudi Arabia – mandatory population screening

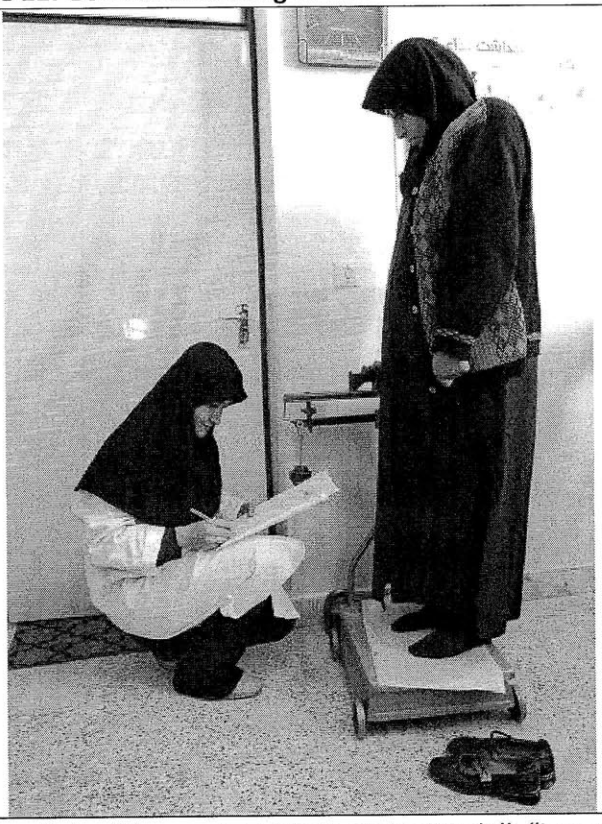
In 2002, a royal decree in Saudi Arabia underscored the importance of premarital screening for genetic disorders. In 2004, a second royal decree made it mandatory for couples planning to marry to get a premarital test—specifically for sickle cell anemia and thalassemia. 207,333 couples were screened in the first 2 years of the program. In a survey of half of the couples found to be "at risk" (2.1% of those screened), 90.8% in the first year married anyway. However, in the second year, that number dropped to 88.4%. One of the reasons proposed for the large percentage of high risk couples who decided to proceed with the marriage is, again, timing. Many couples took the premarital test as a final required step to marriage. The information made less of an impact on couples who had already decided to marry and had a formal engagement. As a result, earlier screening is now being implemented.

Similar mandatory programs exist in other Islamic countries (UAE, Bahrain, Qatar). These premarital tests are especially important because these very countries prohibit abortions due to religious and social reasons.[106]

Once again, a key lesson from the Saudi model is the importance of timing in a genetic intervention.

Iran / Tunisia – mandatory premarital screening, an interesting progression

Figure 11: Genetic Screening in Iran



Source: Ashraf Samavat and Bernadette Modell, "Iranan national thalassemia screening programme," British Medical Journal

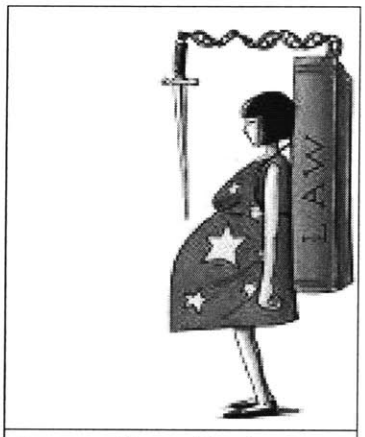
Iran and Tunisia have also launched dedicated premarital screening programs. Premarital consultations are, in fact, mandatory.[107] When Iran first launched this program, abortion after prenatal diagnosis was not allowed in the country.[108] In the first five years of the program, almost 3 million couples were tested. 3.9% of them were determined to be at risk. In 1997, the first year of the program, 45% of these couples decided to separate instead of proceed with marriage.[109] The options for a couple "at risk" were very limited in 1997. This led to an intense national debate about allowing early abortion for an affected fetus. In 1998, the government responded by permitting termination of a pregnancy within 16 weeks of the last menstrual cycle after a negative prenatal diagnosis. Interestingly, the percent of at risk couples choosing to separate declined in lock-step with this loosening of the law. In 2001, only 24% (versus 45% at the inception of the program) at risk couples chose to separate after premarital testing.

Since the establishment of the program, the number of new patients registered at treatment centers has declined and in 2002, was at 7% of the expected number without the program.[110]

The Iran experiment also speaks to the success of genetic testing at the pivotal occasion of marriage.

China – eugenics or yousheng?

The Chinese concept of "Yousheng" (which means "healthy birth") has driven public policy in the past in China.[111] In 1995, China passed the Maternal and Infant Healthcare Law which also required mandatory premarital screening, like Iran. However, it went a step further and required that at risk couples commit to sterilization or long term contraception if they chose to get married.[112] This caused an outcry in the West and was perceived as a violation of human rights.



Source: Herve Pinel

In 2003, the compulsory component of the law was removed. The premarital exam in China is now voluntary. However, it is interesting to note the results of a survey conducted in 2001 in China. The survey found that while 61% of the respondents believed that the Chinese government should provide for the care of handicaps, 78% said they would not consider bearing a child with even a 5% probability of being handicapped. 83% confirmed that they would terminate the pregnancy with a 5% risk of having a handicapped child.[113] The study only had 28 participants, but this was attributed to the fact that people are reticent to offer their opinions due to fear of persecution. The survey responders were thus culled from personal acquaintances who would have less reason to fear a revelation of their identity. If the data can be believed from such a small sample size, it would indicate a great market demand for a premarital or prenatal diagnostic to identify carrier status and / or disease status in China.

It would also be insightful to understand the Indian attitude and perspective on perceived handicaps. This goal was outside of the purview of this thesis, but informal interviews with citizens in India could provide a more refined understanding of their approach to "defects."

HYPOTHESIS

Based on the research documented above, I wanted to explore three main hypotheses.

Specific Major Hypotheses to Explore

1. People who claimed to be ethnically Indian (born in India or part of the Diaspora) would be more inclined to utilize genetic testing than a control group such as Caucasians.
2. People who had considered an arranged marriage (regardless of ethnic background) would be more acclimated to making life partner choices on a complex array of factors and therefore more comfortable using genetics as a criteria for exclusion.
3. People who identified as Mormon, Catholic or Christian might have a bias against early termination of a pregnancy for religious reasons, and so, would be preferentially interested in a pre-marital genetic test for deleterious mutations.

Minor Hypothesis to Explore

1. Females with a greater role in childcare in many societies may be more concerned about the health of a child and be more inclined to pursue genetic tests as a means of ensuring a healthy infant.

Open-ended Questions

1. What other characteristics were indicative of a preference for genetic testing?

METHODOLOGY

In order to answer the questions posed by the hypothesis, an on-line survey was created to query the attitudes and habits of varying individuals. The survey was organized into four meta –sections: demographics, long term planning & health habits, marriage attitudes and attitude towards utilizing genetic knowledge. The questions and objectives of each section will be described in detail below.

The link for the survey was emailed out to friends, acquaintances and friends of friends. The method of dissemination limited the survey responders to those with internet access. The survey was only offered in English and used some scientific terminology. Therefore, the responders needed a strong grasp of English. This may have exposed the results of the survey to some selection bias. However, the selection bias is limited to a narrow sampling of socio-economic status. For the purposes of this analysis, the diverse and random selection of people who responded allows a robust assessment of attitudes *within a specific socio-economic* stratum: the middle and upper middle class.

218 individuals responded to the survey. The initial set of questions posed tried to characterize the population according to typical demographic categories. The questions were as follows:

Demographics:

Figure 12: Survey Questions about Demographics

#	Question	Type of Response	Objective	Quick Look at Responses
1	Age	Open	Stratify data by age groups	Mean= 32.8, Median= 29
2	Gender	Male / Female	Stratify data by gender	Female= 125, Male= 93
3	Ethnicity	Open, for classification purposes, self-reported ethnicity was reorganized into super groupings (e.g. "Chinese" was included under "Asian")	Stratify data by ethnicity	Caucasian= 101, Indian= 66, Asian= 20, African / African American= 12, Latin= 9, Middle Eastern= 6, Mixed= 4
4	Region of world you were born (city, state, country)	Open	Stratify data by area of origin	US= 129, India= 42, EU= 14, Asia= 13, Africa= 7, All Others= 13
5	Region of world your parents were born (city, state, country)	Open	Gain an understanding of immigration status	US=86, India= 64, Asia= 19, Africa= 11, All others= 38
6	Region of world your grandparents were born (city, state, country)	Open	Gain an understanding of immigration status	India= 65, US= 63, EU= 22, Asia= 18, Africa= 11, Italy=10, All Others= 29

7	Religious background of family you were born into	Open	Stratify data by religion	Hindu= 60, Christian= 57, Catholic= 44, Jewish= 24, Mormon= 12, All Others= 21
8	Where applicable, please identify caste/ sub-caste / tribe / religious subgroup (please be as specific as possible, e.g. Ashkenazi, Marwari, Parsi)	Open	Stratify data by specific caste group	97 No Responses, Other responses very diverse, no statistically significant number
9	Where do you currently live? (city, state, country)	Open	Stratify data by current location	US= 177, India= 19, All Other= 22
10	Do you live in an extended family? (e.g. with grandparents or aunts and uncles, etc.)	Yes / No	Gain understanding of level of maintenance of traditional norms	No= 201, Yes= 14, No Response= 3
11	Are you or have you ever been married?	Yes / No	Stratify data by marriage status	No= 119, Yes= 99
12	How many children do you have?	Open	Stratify data by parent vs non-parent	No Response= 147, 1 or More= 63, None= 8
13	College Name and Location	Open	Stratify data by level of education	Yes= 210, No= 8
14	Graduate school name and location	Open	Stratify data by level of education	Yes= 150, No= 68
15	Do you have any prior training or knowledge of genetics or medicine?	Range: 1=none, 5 = doctor	Gain understanding of prior genetics knowledge	1= 122, 2= 43, 3=26, 4= 17, 5=8, No response= 2
16	Do you own your house?	Yes / No	Gain understanding of socio-economic status	No= 137, Yes=79, No response= 2
17	Do you own a car?	Yes / No	Gain understanding of socio-economic status	Yes= 149, No= 67, No response= 2
18	Do you own a washing machine?	Yes / No	Gain understanding of socio-economic status	Yes= 120, No= 95, No response= 3
19	How often do you travel outside of the country of your primary residence (annually)?	Range: 1=not at all, 4= >4 times / year	Gain understanding of socio-economic status	1= 40, 2= 119, 3= 31, 4=24, No response= 4

20	How often do you travel within the country of your primary residence (to different regions) annually?	Range: 1=not at all, 4= >4 times / year	Gain understanding of socio-economic status	1= 4, 2=41, 3= 76, 4= 94

The second section asks questions which try to determine an individual's position on long term planning and healthcare.

Long term planning & health habits

Figure 13: Survey Questions about Long Term Planning & Health Habits

#	Question	Type of Response	Objective	Quick Look at Responses
21	Did you / do you plan to save for your child's high school education?	Range: 1=no, 3=to the extent I can, 5=top priority	Gain understanding of long term planning habits	1= 46, 2= 12, 3= 54, 4= 34, 5= 65, No response= 7
22	Did you / do you plan to save for your child's college education?	Range: 1=no, 3=to the extent I can, 5=top priority	Gain understanding of long term planning habits	1= 11, 2= 3, 3= 35, 4= 56, 5= 104, No response= 9
23	Did you / do you plan to save for your child's graduate school education?	Range: 1=no, 3=to the extent I can, 5=top priority	Gain understanding of long term planning habits	1= 44, 2= 30, 3= 74, 4= 26, 5= 36, No response= 8
24	How often do you see a doctor?	Range: 1=more than 2x a year, 2=once a year, 3=once every 2 years, 4=once every 5 years	Gain understanding of comfort using the healthcare system	1= 107, 2= 79, 3= 20, 4= 9, No response= 3
25	Have you or will you have your children vaccinated?	Yes / No	Gain understanding of long term thinking concerning health of children	Yes= 200, No= 10, No response= 8
26	Have you or has anyone in your family been tested (pap smear) for the HPV virus (a major risk factor for cervical cancer)?	Yes / No / Don't Know	Gain understanding of individual's familiarity with prevention	Yes= 121, No= 37, Don't know= 56, No response= 4
27	Have you or has anyone you know in your family been vaccinated for HPV (with a vaccine such as	Yes / No / Don't Know	Gain understanding of individual's familiarity with prevention	No= 91, Don't know= 78, Yes= 46, No response= 3

	Gardasil)?			
28	Have you ever heard of the blood disorder thalassemia / cooley's anemia?	Yes / No	Stratify data on knowledge of this particular disease	No= 131, Yes= 83, No response= 4
29	Do you know any child who has thalassemia / cooley's anemia?	Yes / No	Stratify data on intimate knowledge of this disease	No= 196, Yes= 19, No response= 3
30	Do you know of any children with health conditions which handicap them or prevent them from attending school?	Yes / No	Stratify data on knowledge of any debilitating handicap	No= 145, Yes= 68, No response= 5

The third section is comprised of questions regarding an individual's attitude towards marriage.

Marriage Attitudes

Figure 14: Survey Questions about Marriage Attitudes

#	Question	Type of Response	Objective	Quick Look at Responses
31	Did you or would you consider an arranged marriage?	Yes / No	Stratify data on attitude towards arranged marriage	No= 184, Yes= 26, No response= 8
32	Have you ever used or would you consider using the services of a matchmaker, yenta or dating website (match, eharmony, shaadi, etc.)?	Yes / No	Stratify data on attitude towards matchmaking	No= 121, Yes= 89, No response= 8
33	Will you or have you compared religious horoscopes (Hindu) with a prospective candidate?	Yes / No	Stratify data on acceptance of other traditional cultural norms	No= 182, Yes= 28, No response= 8
34	Marriage to someone of the same ethnic and cultural background	Range: 1=least importance, 5=high importance	Gain understanding of importance of ethnic similarity in partner choice	1= 58, 2= 46, 3= 52, 4= 38, 5= 15, No response= 9
35	Marriage to someone of	Range: 1=least	Gain understanding of	1= 54, 2= 37, 3= 43, 4= 42,

	the same faith / religion?	importance, 5=high importance	importance of religion in partner choice	5= 33, No response= 9
36	Marriage to someone within your caste / sub-caste / tribe / religious sub-group?	Range: 1=least importance, 5=high importance	Gain understanding of importance of caste in partner choice	1= 128, 2= 33, 3= 26, 4= 6, 5= 6, No response= 19
37	Marriage to someone from the same geographic area in country of origin (e.g. from state of Punjab in India if you were born in Punjab or your parents or grandparents were born in Punjab but have since moved)?	Range: 1=least importance, 5=high importance	Gain understanding of importance of region in partner choice	1= 140, 2= 34, 3= 18, 4= 7, 5= 3, No response= 16
38	Marriage to someone with the same education level	Range: 1=least importance, 5=high importance	Gain understanding of importance of equivalent education in partner choice	1= 15, 2= 23, 3= 56, 4= 73, 5= 39, No response= 12
39	Marriage to someone from the same socio-economic status	Range: 1=least importance, 5=high importance	Gain understanding of importance of equivalent socio-economic status in partner choice	1= 34, 2= 43, 3= 70, 4= 52, 5= 9, No response= 10
40	Consulting a doctor prior to marriage to check partner's health	Range: 1=least importance, 5=high importance	Gain understanding of attitude towards early health screens prior to partner choice	1= 58, 2= 51, 3= 46, 4= 33, 5= 20, No response= 10
41	Consulting a priest / pundit / rabbi about a prospective match	Range: 1=least importance, 5=high importance	Gain understanding of importance of religious figure in partner choice	1= 148, 2= 28, 3= 16, 4= 8, 5= 5, No response= 13
42	If the government sponsored an overall physical exam prior to marriage, would you participate?	Yes / No	Gain understanding of attitude towards government intervention	Yes= 143, No= 65, No response= 10
43	If the government sponsored a test for infectious diseases such as syphilis or hepatitis C prior to marriage, would you participate?	Yes / No	Gain understanding of attitude towards government intervention	Yes= 162, No= 47, No response= 9

The final section asks the individual's response to early genetic screening.

Attitude towards genetic screening

Figure 15: Survey Questions about Attitudes Towards Genetic Screening				
#	Question	Type of Response	Objective	Quick Look at Responses
	The following questions followed a brief intro to thalassemia: Thalassemia is an inherited blood disorder which can range in severity from mild forms in which children are anemic to severe forms in which children have slowed growth, jaundice, bone problems and need monthly blood transfusions. Current therapies for this condition are limited to blood transfusions and bone marrow transplants for severe cases. Being a carrier (having 1 gene from 1 parent) for this condition can be protective against malaria. Having both genes for this condition (1 from each parent) leads to the more severe manifestations of the blood disorder. There is a high rate of carriers in populations in the "malaria belt" (India, Thailand, China, Mediterranean, etc.) With this knowledge, please answer the following questions.			
44	If you (or your wife) were pregnant, would you want to know if your child had the possibility of being born with thalassemia?	Yes / No	Stratify data based on attitude towards prenatal testing	Yes= 186, No= 19, No response= 13
45	If you confirmed through a pre-natal test that the unborn fetus did have the disease, would you consider an abortion?	Yes / No	Stratify data based on early termination of pregnancy	Yes= 102, No= 96, No response= 20
46	If you were about to get married, would you want to get genetically tested as a couple to determine whether you were a carrier for the disease (and thus able to pass the gene to your children?)	Yes / No	Stratify data on attitude towards pre-marriage testing	Yes= 153, No= 49, No response= 16
47	If you were ready to be	Yes / No	Stratify data on attitude	No= 140, Yes= 61, No

	married and looking for a prospective partner, would you want to only be introduced to candidates with whom you had an almost 0% likelihood of having a child with this disease?		towards candidate screening	response= 17
48	If you found out that both partners in a prospective arrangement (yourself and the other candidate) were carriers for thalassemia and had a 25% chance of having a child with a severe form of this disease, would this change your decision to get married to each other?	Yes / No	Stratify data on attitude towards partner selection based on genetics	No= 162, Yes= 37, No response= 19
49	If you decided to marry anyway, would you want a pre-natal test to determine the disease status of an unborn child?	Yes / No	Gain understanding of potential intervention points	Yes= 179, No= 21, No response= 18
50	If you decided not to move forward with the marriage because of this knowledge of carrier status, would you then narrow your search to other non-carriers?	Yes / No	Gain understanding of potential intervention points	Yes= 102, No= 86, No response= 30
51	If you decided not to move forward, would you be concerned about who knew this information?	Yes / No	Gain understanding of attitude towards stigma	Yes= 109, No= 81, No response= 28
52	Having your parents tested, therefore, allows you to be assured that you are not a carrier (if neither of your parents is a carrier) OR make the decision to find out your	Range: 1=yes, 2=no, 3=maybe, need more info	Gain understanding of attitude towards 2-tier testing	No= 83, Yes= 58, Need more info= 57, No response= 20

	own carrier status if at least 1 of them is a carrier. Would this option be more attractive to you?			
53	How much would you be willing to pay ($USD) for a test which identified whether you were a carrier for this disease? (Please note, that genetic testing can range from $300 to upwards of $50,000 for an entire genome reading.)	Open	Gain understanding of value of test to individual	Average= $1,034 Median= $300 158 individuals responded
54	How much do you expect to pay or did pay for your wedding (including festivities, dowry, etc.)?	Open	Gain understanding of relative importance of genetic test to individual	Average= $29,745 Median= $15,000 158 individuals responded

RESULTS & ANALYSIS

A Coherent Picture of Who Responded:

The target population for a pre-marital or pre-natal genetic exam would be a marriage-age, educated cohort still within potential child-bearing years. I make the assumption that the responses of such a cohort, loosely defined as aged 18 to 35, would be most attractive as a target for prophylactic genetic screening. As Figure 16 shows below, most of the survey responders were under 35, and thus, met the criteria of interest.

Figure 16: Age Range of Survey Responders versus Median Age in Benchmark Nations

	Median Age[1]				Age Brackets in Survey[2]			
	US	China	Ghana	India	<=25	26 - 35	36 - 45	>45
male	35.5	34.5	20.8	25.4	13	64	8	8
female	38.1	35.8	21.3	26.6	28	63	15	19

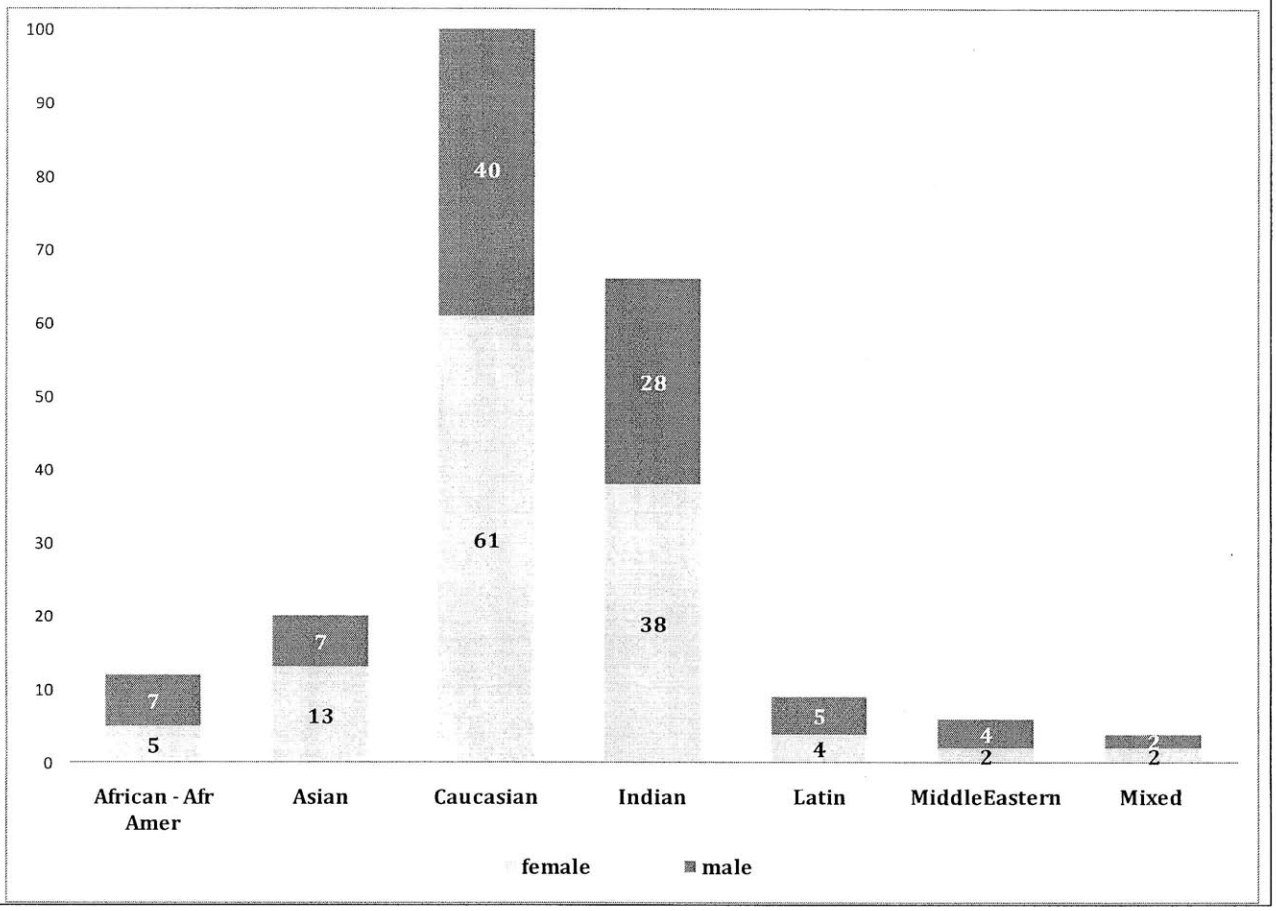
[1] Relative comparison of median age across various countries.

[2] Number of individuals in each age bracket who responded to the survey questions.

The hypothesis centers on a statistically significant difference between Indians versus non-Indian participants in response to pre-marital and pre-natal testing. In order to adequately test this hypothesis, the survey had to include over 30 responses from individuals who claimed Indian heritage and at least 30 responses from those that did not. As Figure 17 shows, I collected 66 responses from people who identified as of Indian descent as well as 101 responses from people who identified as of Caucasian descent.

Figure 16 also reveals that both males and females had substantial representation in the Indian and Caucasian ethnic categories. It is interesting to note that; overall, females were more likely to fill out the survey than men. The survey was not sent out to a disproportionate number of female versus male connections, which might have accounted for a more heavy female representation in responses.

Figure 17: Distribution of Males and Females by Ethnicity



Out of the 66 people who claimed Indian ethnicity, 43 currently live in the United States, 17 live in India and 6 live in various other countries. 96% of the Caucasians who filled out the survey live in the United States. (See Figure 18).

Figure 18: Current Location of Participants of Diverse Ethnicity

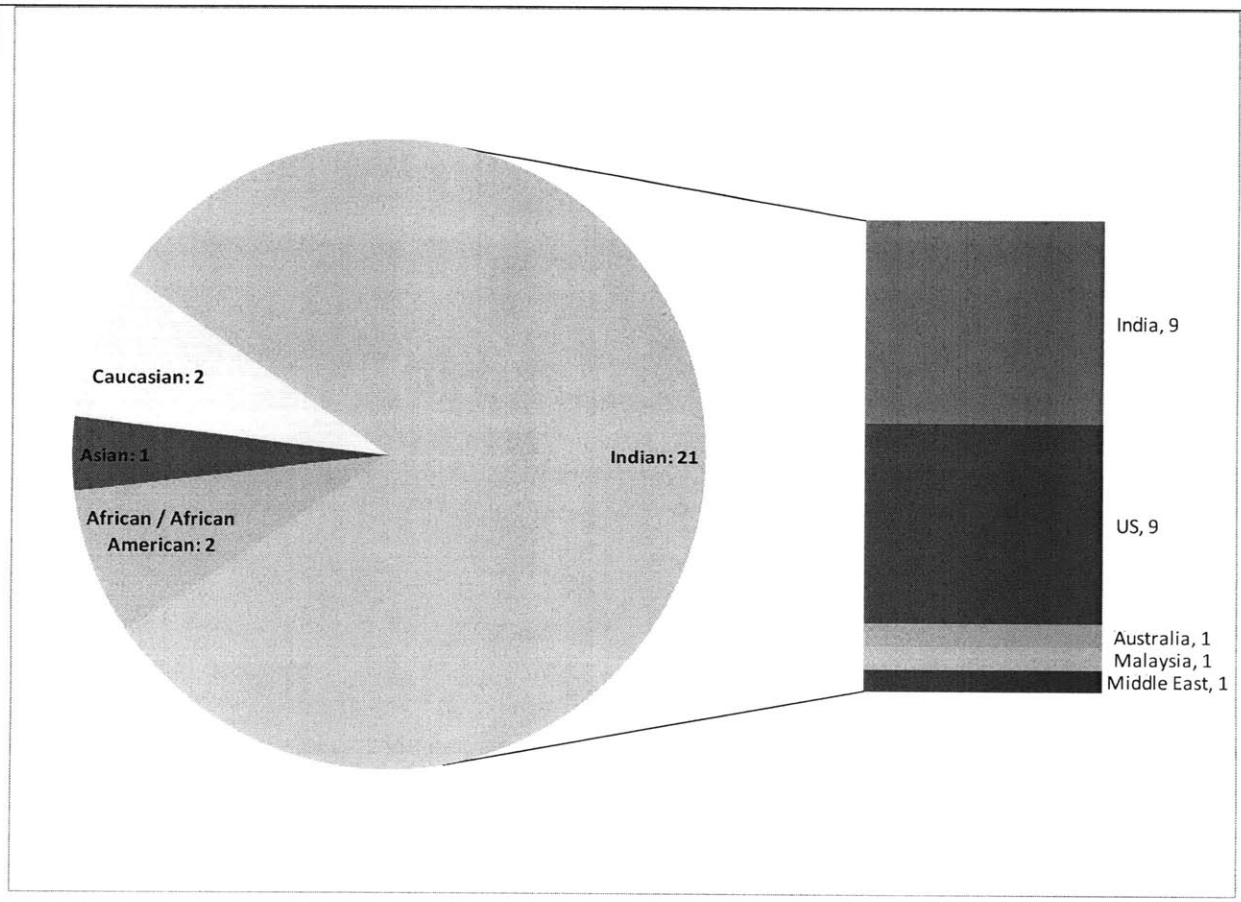
Current Location	Ethnicity						
	African or African American	Asian	Caucasian	Indian	Latin	Middle Eastern	Mixed
US	10	12	97	43	9	4	4
India		2		17			
Asia		5	1	1			
Middle East				3		1	
EU			2			1	
Australia		1		2			
Africa	2		1				

One of the hypotheses posits that an acceptance of arranged marriage practices might also indicate an acceptance of pre-marital genetic screening. The survey found 25 out of the 218 responders open to considering an arranged marriage. 84% of these individuals who would consider the practice self-identified as of Indian descent. Interestingly, almost half of the 21 Indians currently reside in the US while the other half still resides in India (see Figure 19 for a breakdown of where all 21 affirmative Indian responders currently reside).

This fact hints at the strength of traditional norms outside of national boundaries amongst the Diaspora. It also suggests continuity of arranged marriages in India even as the country faces modernization and Westernization.

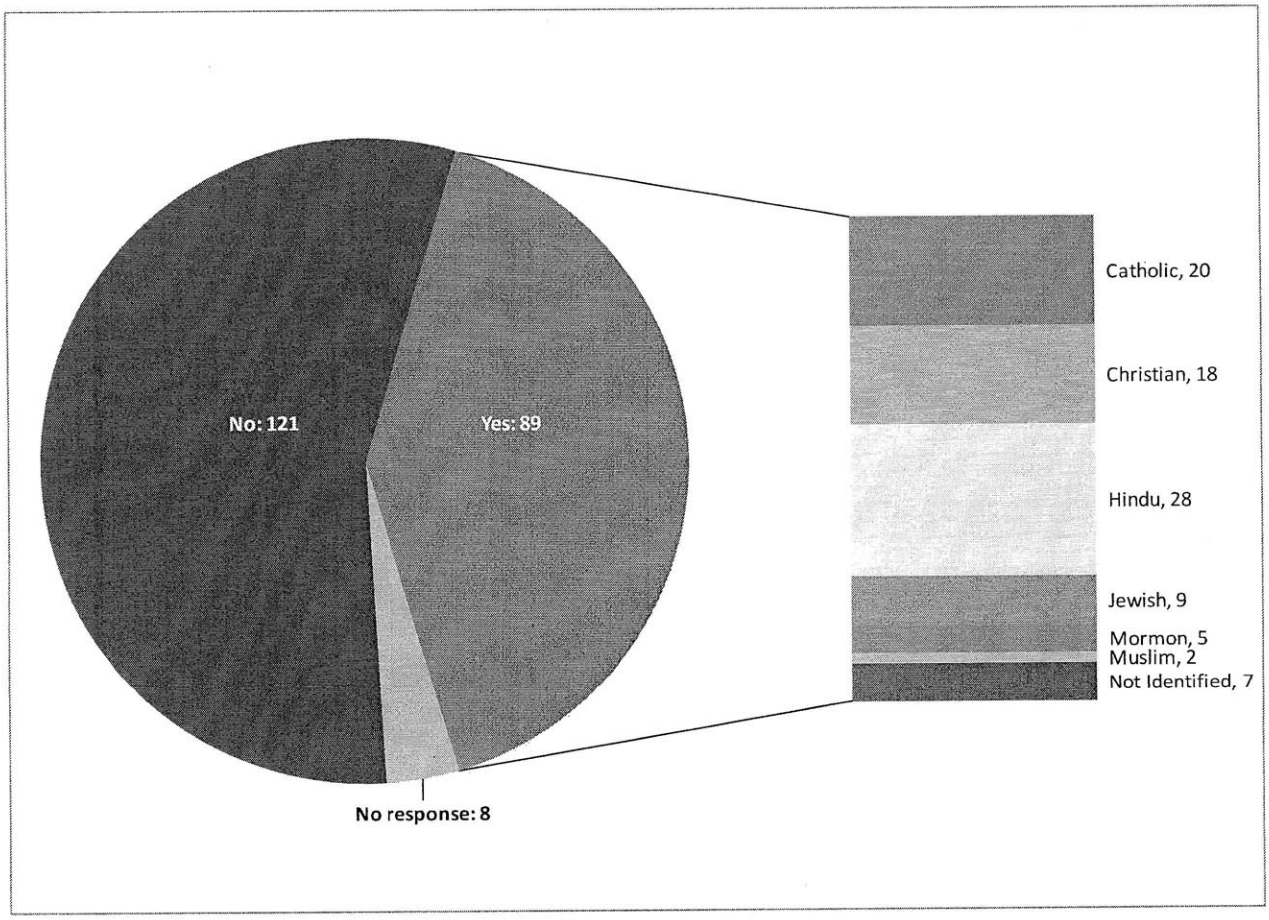
If this is the case, a pre-marital or pre-natal genetic test may find easier adoption in Indian communities all over the world or other ethnic groups which practice arranged marriage customs. However, the diversity of the dataset does not allow us to examine whether the latter point is true. Proving the correlation between the practice of arranged marriages in ethnicities outside of Indian and the acceptance of pre-marital genetic testing would be an interesting topic for further exploration.

Figure 19: 25 Participants Declared They Had Considered an Arranged Marriage and their Current Location



Arranged marriage is a custom more popular in the South East Asian subcontinent. The survey responders were also asked about their openness to matchmaking. This statistic was of interest because matchmaking may be considered a soft proxy to arranged marriage in Western cultures. Out of the 218 responders, 89 said they would consider matchmaking. Individuals who would consider a matchmaker might be preferentially inclined to know the carrier status of prospective partners for grave or fatal diseases. The breakout of these 89 individuals by religion is shown in Figure 20 below.

Figure 20: 89 Participants Who Declared They Have or Would Use a Matchmaker



As Figure 21 shows below, the number of married versus unmarried participants was fairly evenly distributed amongst the ethnic group. The two ethnic groups of interest, Indian and Caucasian, were nearly evenly split with regards to matrimonial status.

Figure 21 Distribution of Participants by Marital Status and Ethnicity

Married	African / African American	Asian	Caucasian	Indian	Latin	Middle Eastern	Mixed
no	7	12	52	35	8	2	3
yes	5	8	49	31	1	4	1

As mentioned earlier, due to the form, content and method of distribution, the survey reached a group of highly educated individuals. As Figure 22 below reveals, 96% of the participants graduated from college. Furthermore, 68% of the participants actually pursued graduate studies as well.

Figure 22: Distribution of Participants by Education and Ethnicity

College	Graduate School	African - African American	Asian	Caucasian	Indian	Latin	Middle Eastern	Mixed
No	No	2		5	1			
Yes	No	2	9	32	17	1		
Yes	Yes	8	11	64	48	8	6	4

The survey asked participants to indicate their knowledge of genetics on a scale of 1 to 5. A score of 1 indicated "no knowledge of genetics" while a score of 5 indicated a "physician status knowledge of genetics." As Figure 23 shows, most responders had a minimal knowledge of genetics. This may make responses more applicable to the population at large.

Figure 23: Knowledge of Genetics

	no response	1	2	3	4	5
African / African American	2	6	1	2	1	
Asian		10	5	2	2	1
Caucasian		48	26	17	8	2
Indian		47	7	5	5	2
Latin		8				1
MiddleEastern		2	2			2
Mixed		1	2		1	

The next two charts in Figures 24 and 25 show the participant's position on saving for a child's education. Figure 24 reveals that most responders thought saving for college education was very important—as indicated by the high scores of 4 and 5. However, there is a more normal (bell curve) distribution of responses to the importance of saving for a child's graduate school education. Overall, the data indicates that long term planning and saving for education is a top priority for this entire cohort.

Figure 24: Relative Importance of Saving for a Child's College Education

	no response	1	2	3	4	5
African / African American	2				2	8
Asian	1			1	6	12
Caucasian	4	4	2	16	26	49
Indian	1	3	1	14	17	30
Latin		1		4	1	3
MiddleEastern	1	3			2	
Mixed					2	2

Figure 25: Relative Importance of Saving for a Child's Graduate School Education

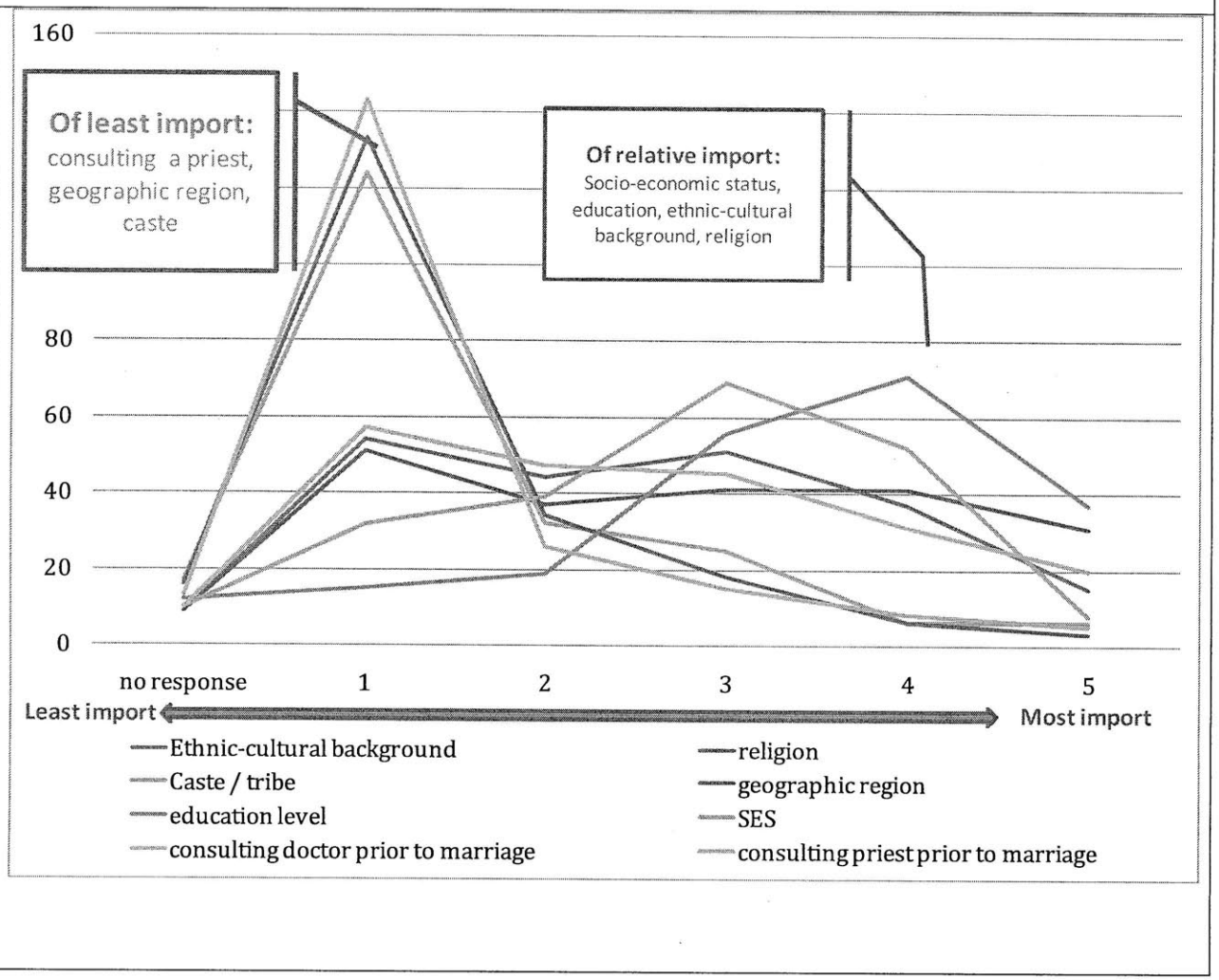
	no response	1	2	3	4	5
African / African American	2		3	5	1	1
Asian	1	1	3	9	4	2
Caucasian	5	27	16	32	10	11
Indian		7	6	25	8	20
Latin		6	1	1		1
MiddleEastern		3		1	2	
Mixed			1	1	1	1

Figure 26 shows how all 218 participants ranked 8 selected qualities and practices. Please note each responder ranked each criteria on a scale of 1 to 5. A score of 1 indicated of "little import", while a score of 5 indicated of "great import." The questions were posed to determine how important it was to find a partner as closely matching in characteristics to you. For example, the participant was asked, "Please rank the following: Marriage to someone of the same ethnic and cultural background: 1 = least importance, 5 = high importance." This question was then posed for marriage to someone of the same religion, education level, socio-economic background, geographic region and caste.

The data show that consulting a priest, finding a partner from the same geographic region and of the same caste is of "least import" to the participants. I postulate that part of the reason that caste ranks as of little import is due to the stigma associated with making decisions based on caste. As discussed in the background section, recent on-line trends indicate a desire for Indians to continue to affiliate and marry according to traditional caste divisions. It is important to recognize the pivotal part that caste plays in marriage decisions in India. Caste and sub-caste groups are narrow communities which have been practicing endogamous marriage customs for centuries. Therefore, these groups are especially vulnerable to the expression and propagation of deleterious mutations. A formal recognition of the desire to continue to marry within specific caste groups will allow the more effective targeting, delivery and utilization of genetic screening to prevent fatal diseases.

Perhaps of equal interest is the fact that socio-economic status, education, religion and cultural background rank as "of great import" to many of the participants in the survey. The importance of such criteria has a narrowing effect on the pool of candidates available for marriage. I would pose the question whether these criteria allow for diversity or do they necessarily lead to a narrow pool of endogamous options? This is especially relevant in countries such as India. If the importance of such criteria does necessarily lead to more endogamous marriages, then genetic screening is still relevant in these communities even if they have indicated that caste is of little import.

Figure 26: Ranking of Criteria Used in Making Partner Selection for Marriage



The next few Figures (27, 28, 29, 30 and 31) show a breakout of these rankings by ethnic group. This will allow us to understand whether any one criterion is more important to any one ethnic group. Specific nuances may be lost in the blended data as presented above in Figure 26.

Each graph also calls out the ethnicities which overwhelmingly (over 50% response of 3 or higher) indicated a criterion as important.

Figure 27 shows that people who identified as Indian, Latin or Asian declared marrying someone from the same ethnic background as an important criterion for them.

Figure 27: Importance of Marrying an Individual of the Same Cultural Background by Ethnicity

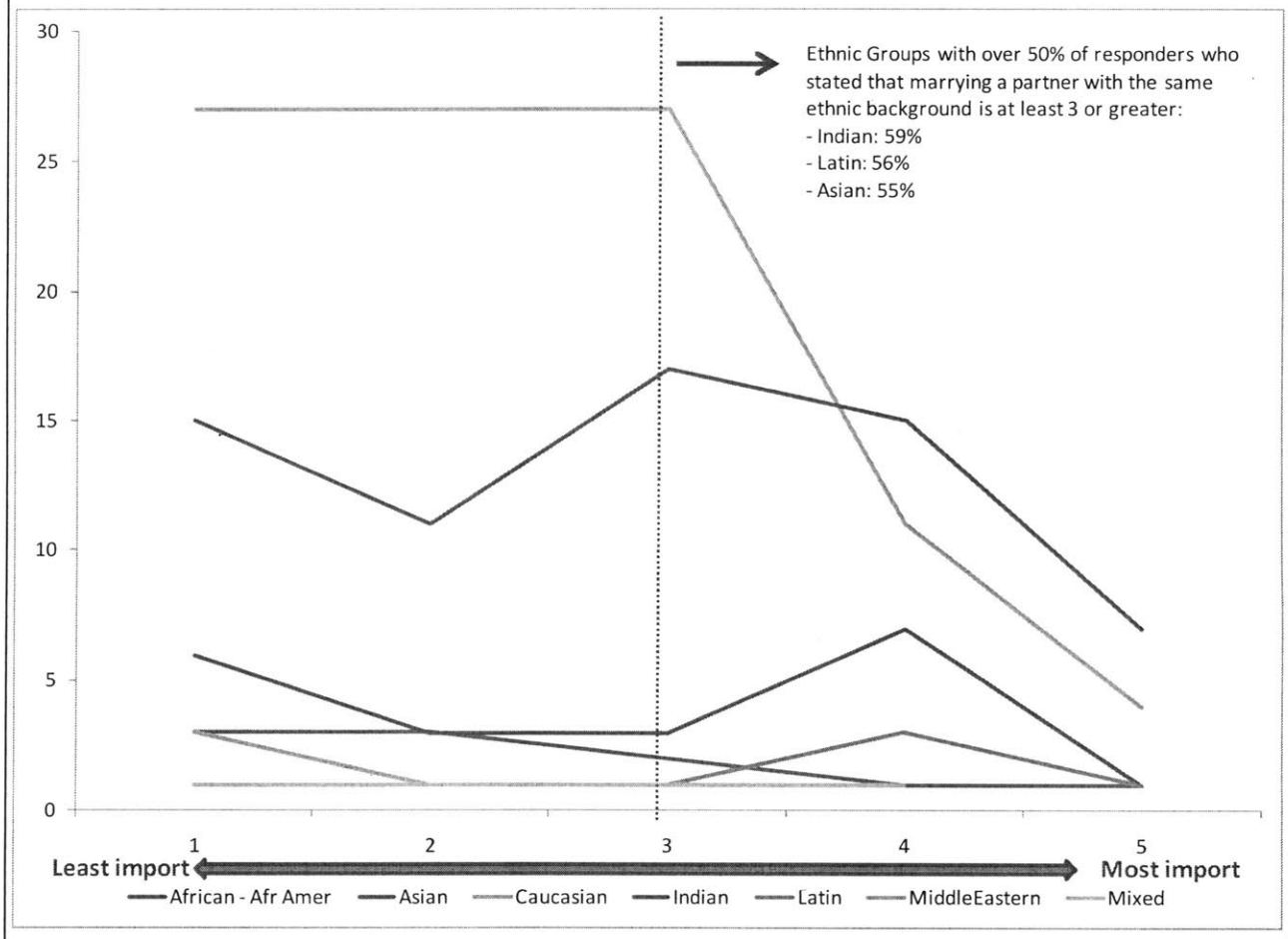


Figure 28 shows that people who identified as African / African American, Latin, Asian or of Mixed ancestry declared marrying someone with the same religious beliefs as an important criterion for them.

Figure 28: Importance of Marrying an Individual of the Same Religion by Ethnicity

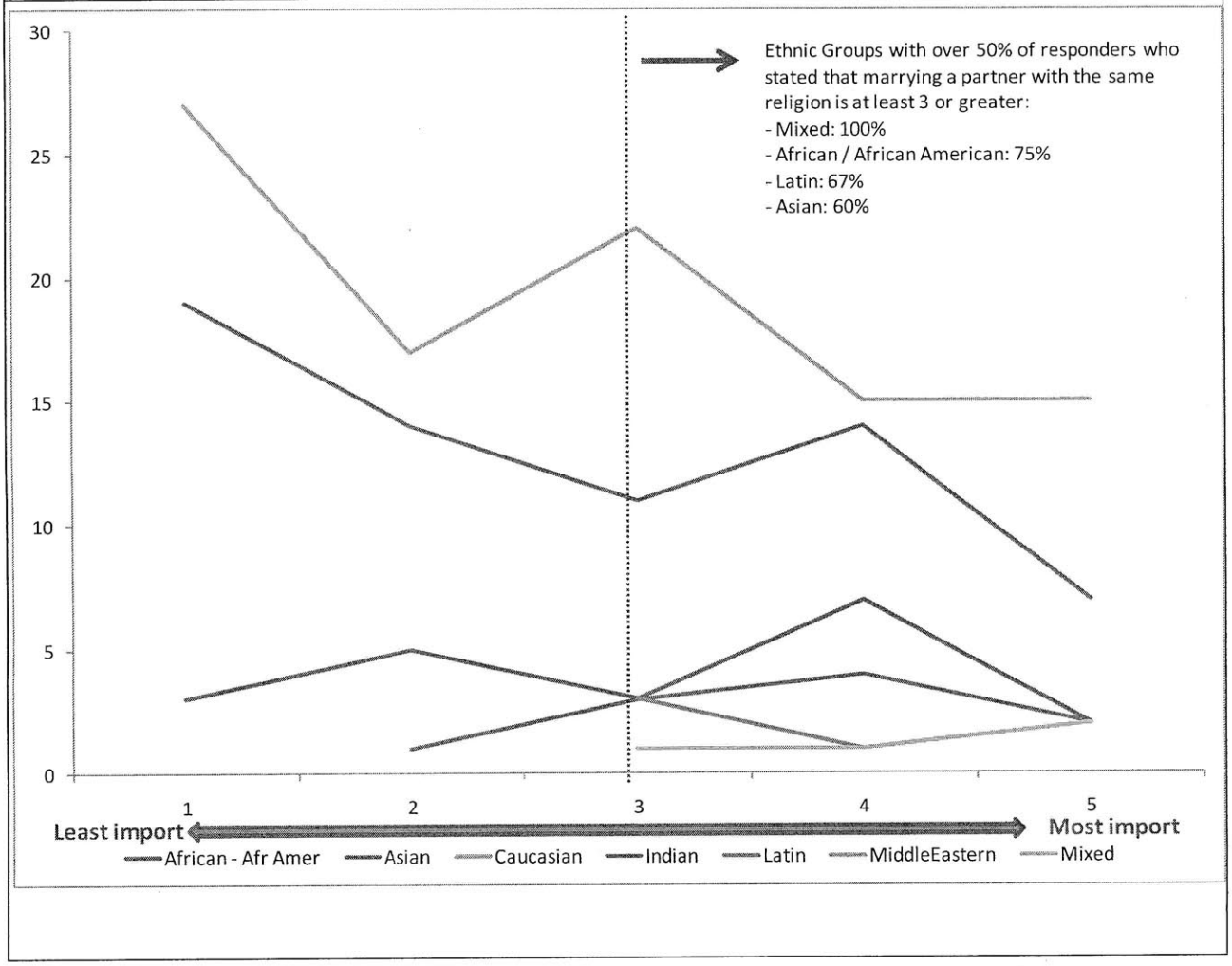


Figure 29 shows that no overwhelming majority indicated that marrying someone from the same geographic region as an important criterion for marriage.

Figure 29: Importance of Marrying an Individual from the Same Region by Ethnicity

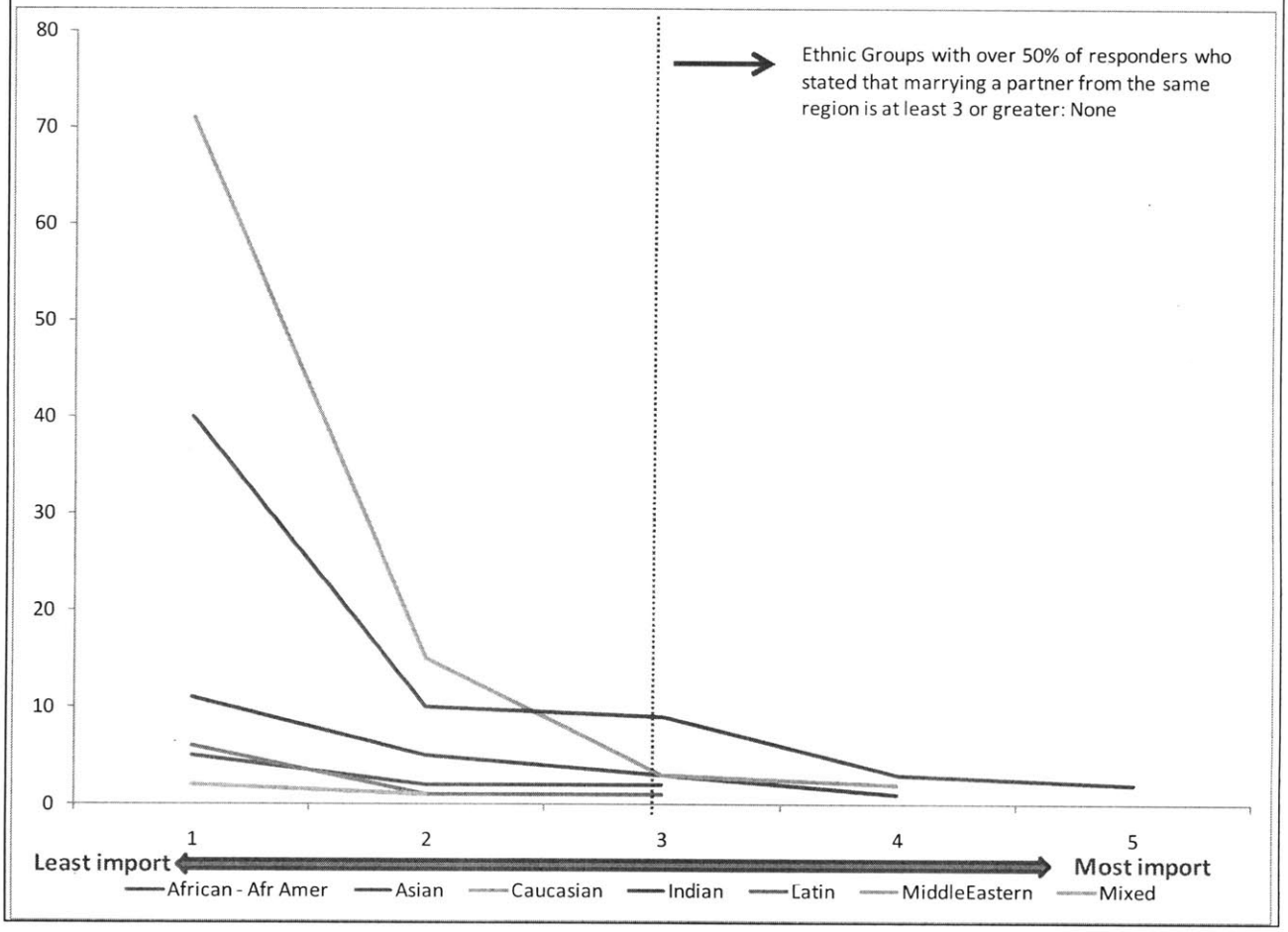


Figure30 shows that people from all ethnic groups overwhelmingly indicate that marrying someone with the same educational pedigree was as an important criterion for marriage.

Figure 30: Importance of Marrying an Individual with the Same Education Level by Ethnicity

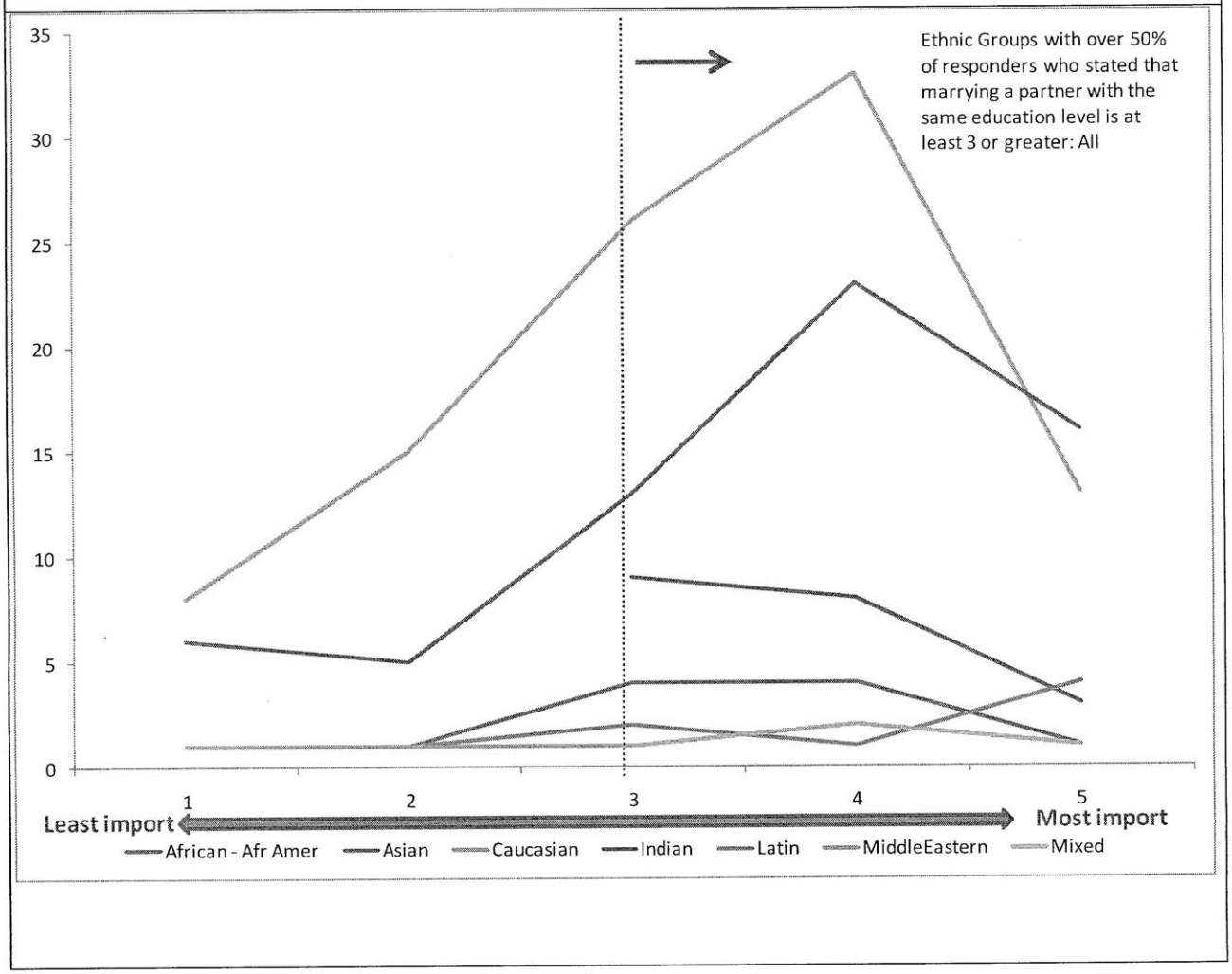
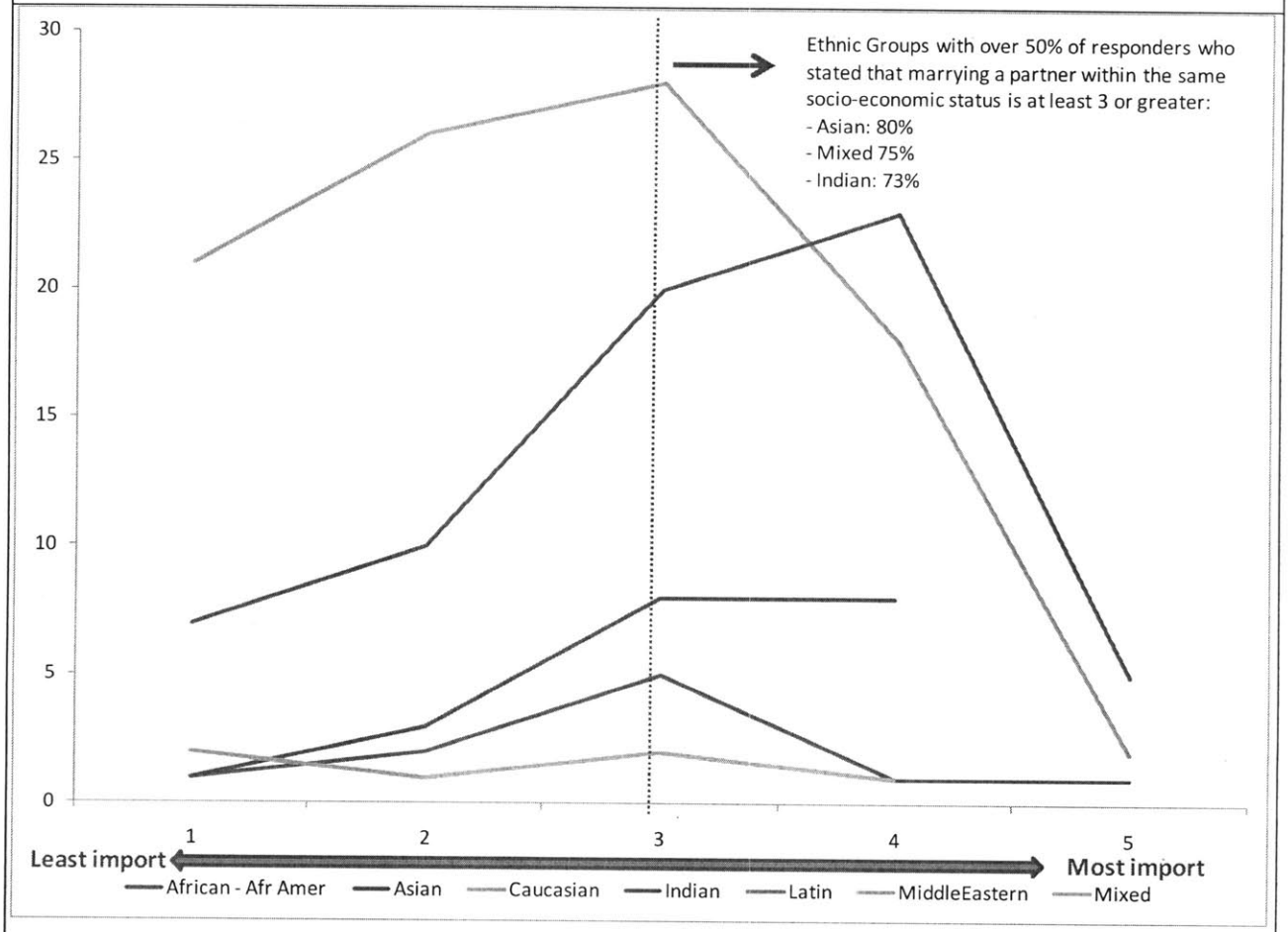


Figure 31 shows that people who identified as Asian, Indian or of Mixed descent indicated marrying someone from the same socio-economic status as an important criterion for marriage.

Figure 31: Importance of Marrying an Individual within the Same Socio-Economic Status by Ethnicity



Another objective of the thesis was to determine the most appropriate time point for intervention. As Figure 32 lays out, there are 3 critical moments in the timeline from candidate selection to childbirth during which an individual could use genetic testing to assist in decision making.

1) First, two individuals who are considering marriage could have their carrier status determined prior to the nuptials. This information could be used later when the couple begins to consider family planning.
2) Second, a husband and wife couple could have their carrier status determined after marriage but prior to child bearing.
3) Third, a pregnant couple could have their carrier status determined to decide whether it is necessary to explore chorionic villi sampling or amniocentesis.

Below, the diagram in Figure 32 explicitly clarifies these options. A series of questions posed to survey participants tried to establish each responder's likelihood of wanting a pre-marital genetic test, a prenatal genetic test and a responder's attitude towards early termination of pregnancy based on a genetic test.

Figure 32: Trying to Determine Participant Preference When it Comes to Timing of Intervention

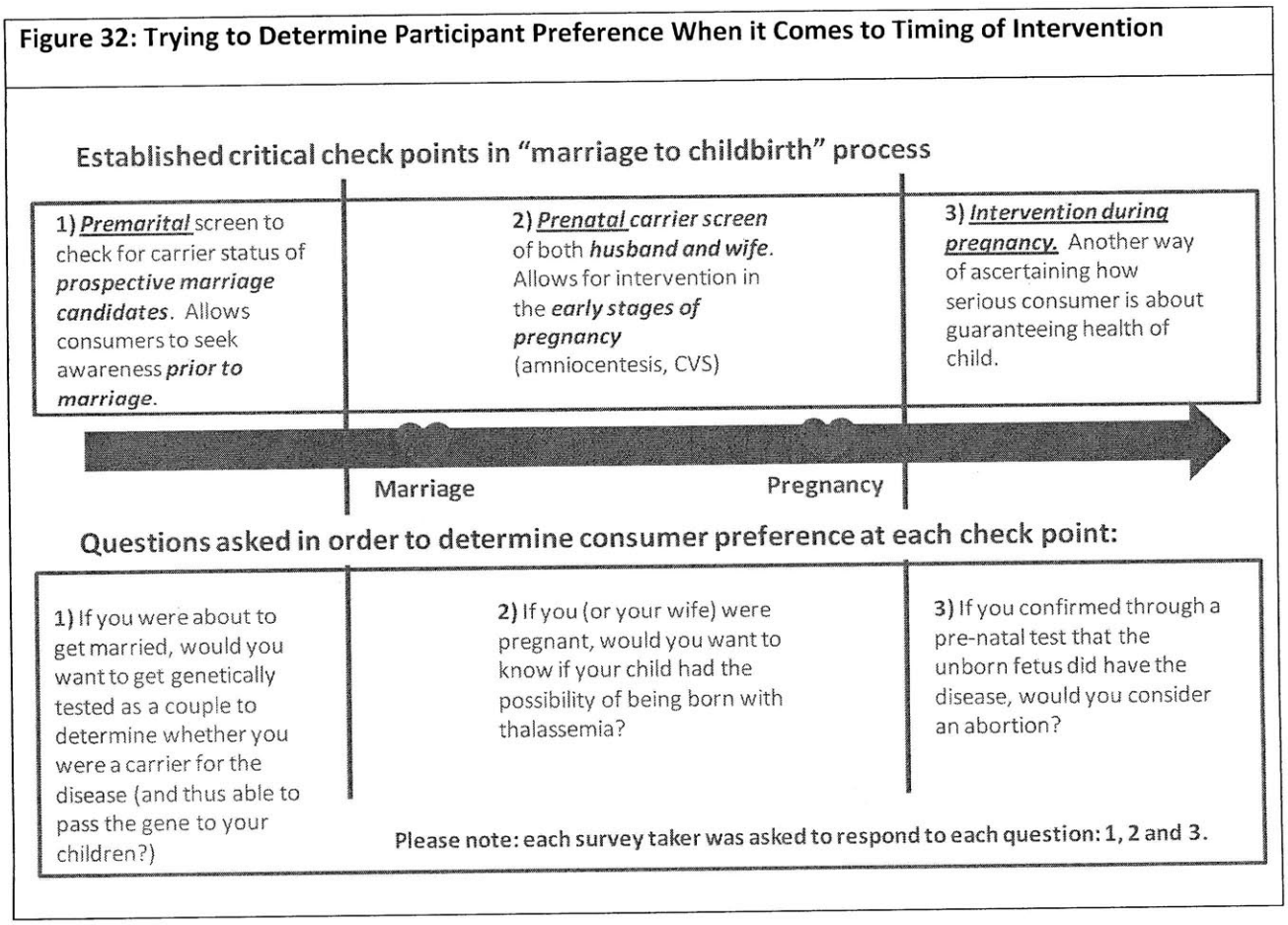


Figure 33 below shows the output from querying the survey responders about whether they would be interested in a pre-marital test, a pre-natal test and whether they would consider an abortion based on a negative test outcome. The data has been parsed by religion. Individuals who self-identified as "Catholic", "Christian", or "Mormon" overwhelmingly responded against early termination of pregnancy based on genetic test results. From the data, one could speculate that this group would be a target for early (pre-pregnancy) identification of carrier status. A couple with a cultural or religious bias against abortion may be preferentially interested in in-vitro fertilization in conjunction with pre-implantation diagnosis.

Figure 33: Preference for Intervention at Various Data Points by Religion

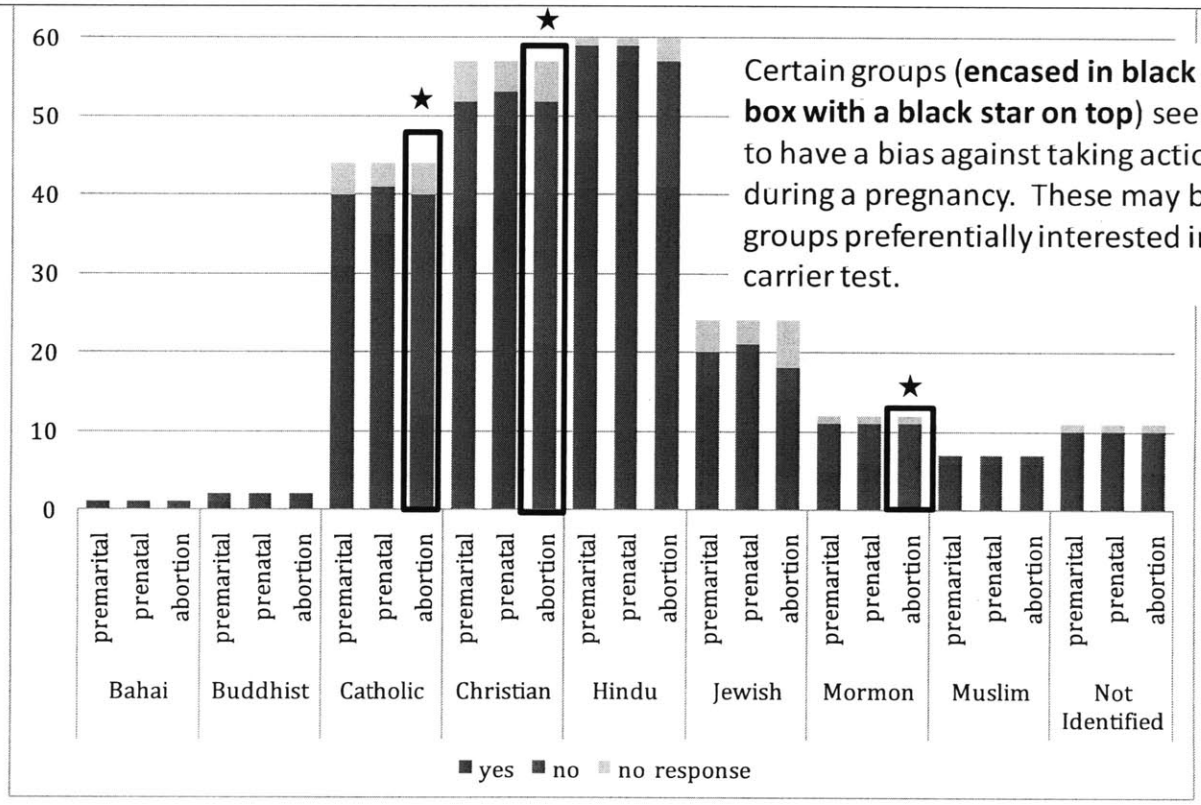
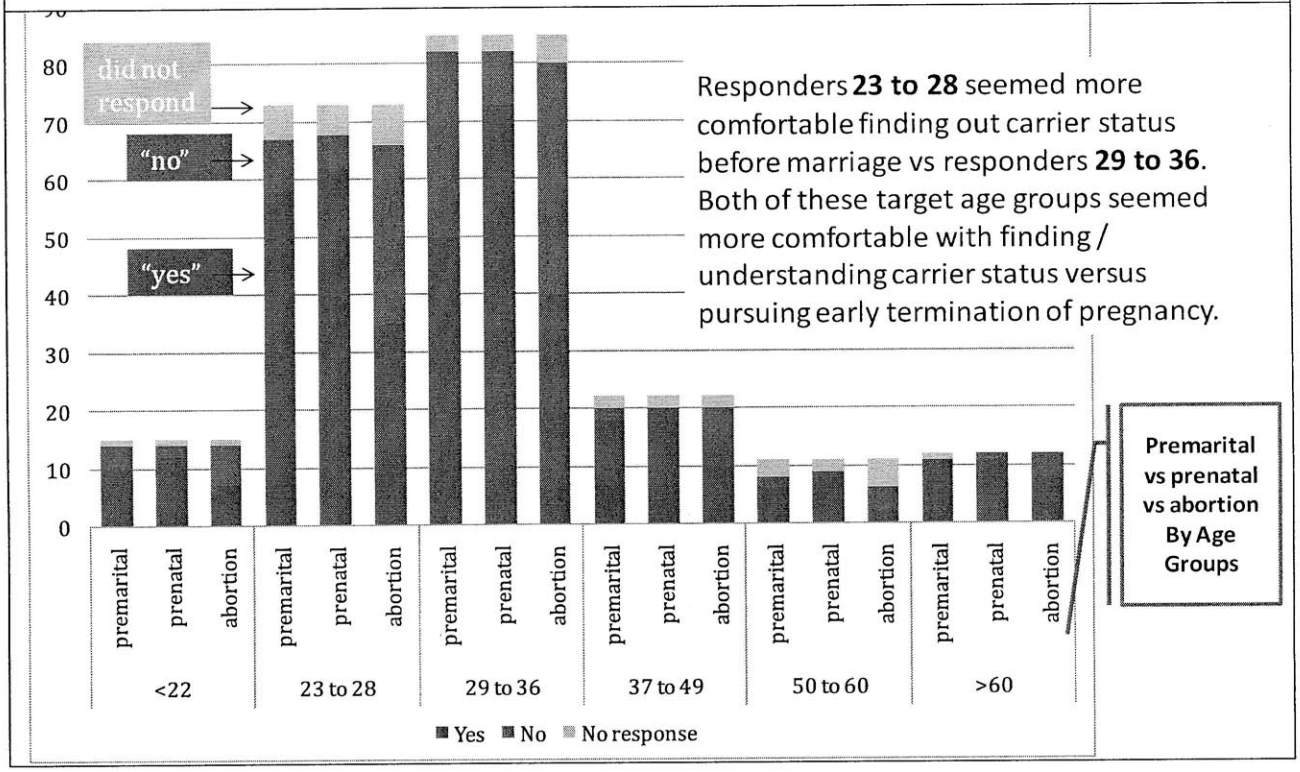


Figure 34 shows the same data parsed by age group brackets. As a group, responders 23 to 28 indicated a keener interest to find out their carrier status than responders aged 29 to 36.

Figure 34: Preference for Intervention at Various Data Points by Age Bracket



In order to address the questions posed by the hypothesis directly, I calculated odds ratios to estimate the relationship between key characteristics and 4 questions with binary outcomes: "yes" or "no". The next four figures, Figures 35, 36, 37 and 38 examine the effect of multiple variables on these four "yes / no" questions. The figures display odds ratios for each predictor value—the relative amount by which the odds of the outcome increase with an increase in the value of the predictor variable. The questions are as follows:

1) Would you want to know the carrier status of a prospective partner ***prior to marriage***?

2) Would you want to know the carrier status of a spouse ***after marriage but before the birth of a child (pre-natal stage)***?

3) Would you consider ***early termination of a pregnancy*** based on the outcome of a genetic test?

4) Would you ***reconsider partner choice*** based on the outcome of a genetic test?

The purpose of calculating these odds ratios is to measure the effect size of each predictor value. Please note that the results are not statistically significant if the confidence interval includes the value of "1". However, if the p-value was small enough but larger than 0.05, I included it in the charts. I hope that these estimates can provide directional guidance on which predictor values are likely to affect the outcome value.

The first figure, Figure 35, shows the effect of predictor values on whether an individual is likely to find out the carrier status at the pre-marital stage. With every year increase in age, the individual is 1.05 more likely to find out carrier status pre-martially. The model indicates that a female is 1.44 times more likely to want a carrier test pre-martially but the increase is not statistically significant at the 5% level. The most startling indicator for a pre-marital genetic test is whether an individual had considered an arranged marriage. People who had considered an arranged marriage were 6.5 times more likely to have a carrier screen prior to marriage.

Figure 35: Which Groups are More or Less Likely to Find Out Carrier Status at the Pre-marital Stage?

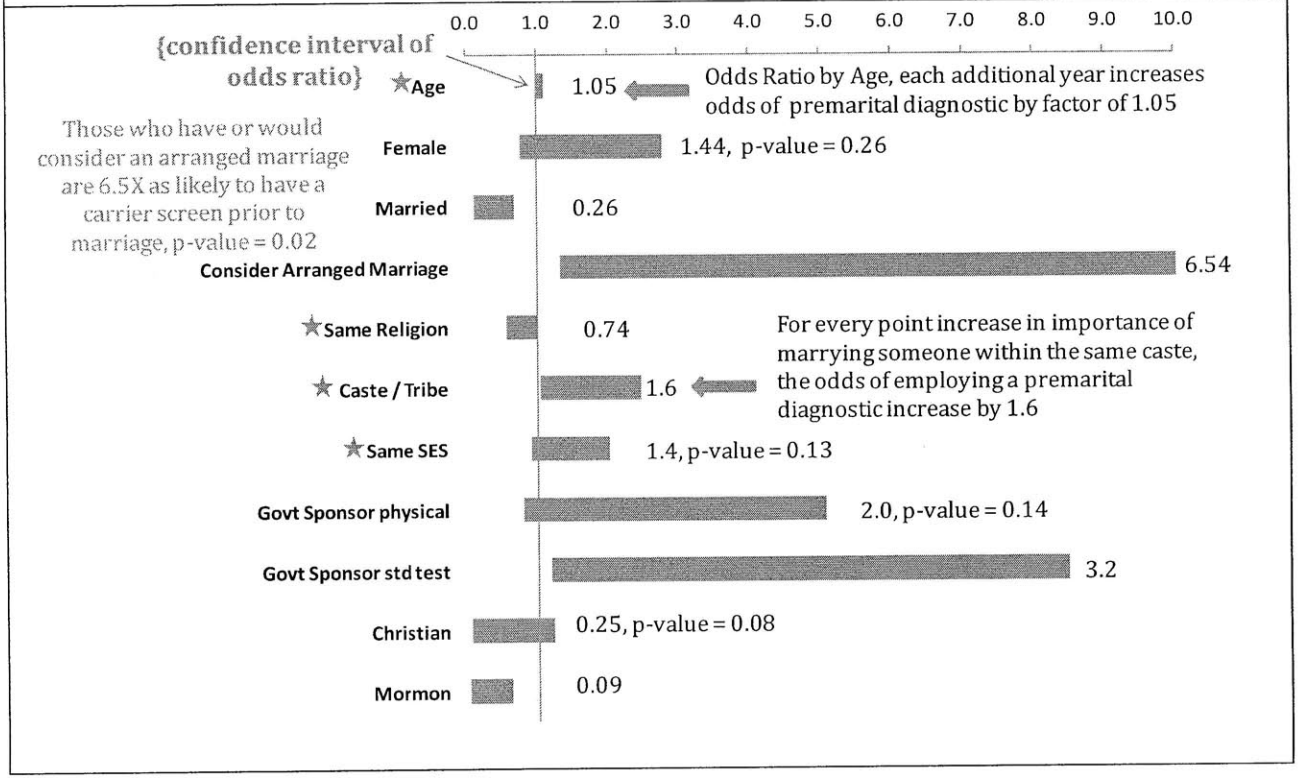


Figure 36 below shows the effect of predictor values on whether an individual is likely to find out the carrier status at the pre-natal stage. The data reveals that having considered an arranged marriage is still a strong indicator of taking a carrier test at the pre-natal stage. The other statistic of note derived from this particular question is that individuals who already have children were less likely to want a pre-natal carrier test (p-vale of 0.09).

Figure 36: Which Groups are More or Less Likely to Find out Carrier Status at the Prenatal Stage?

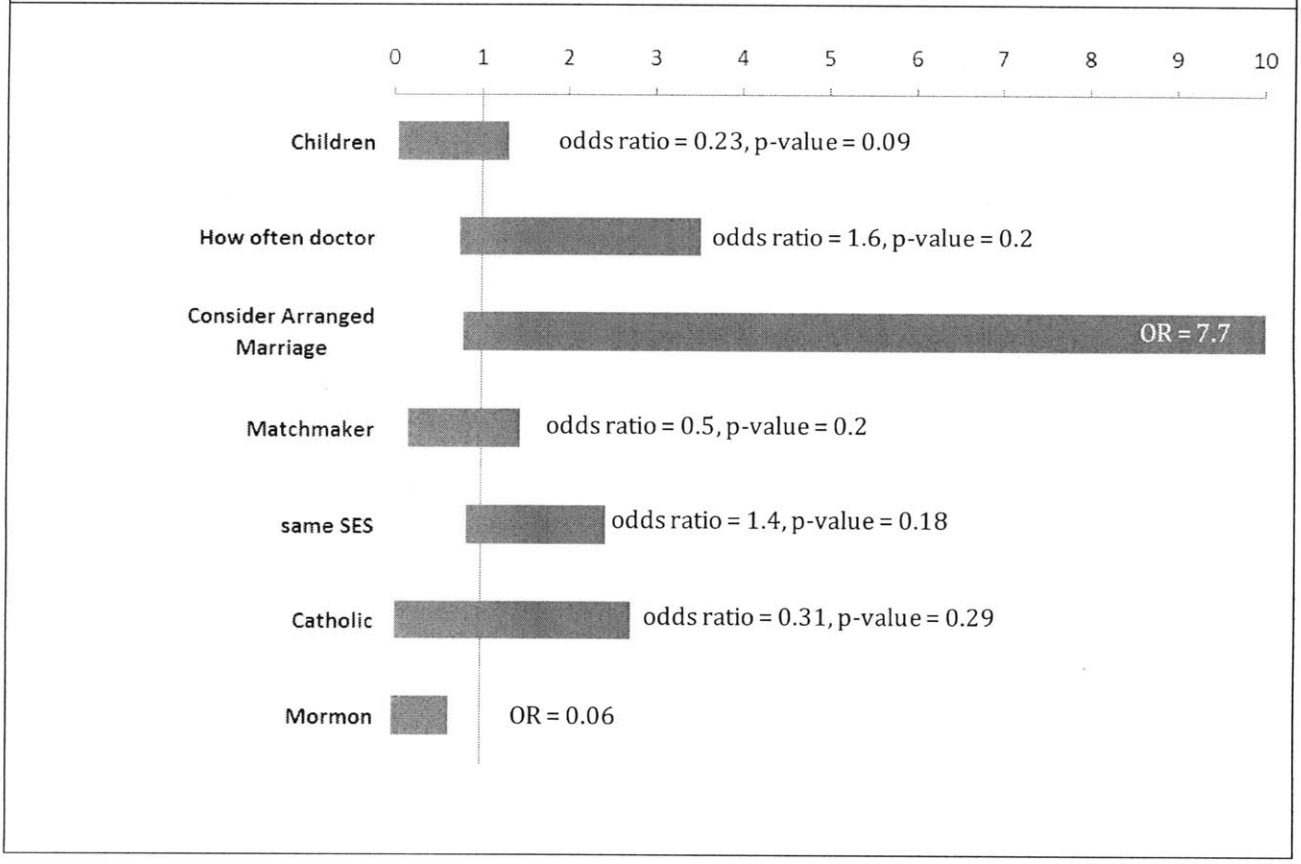
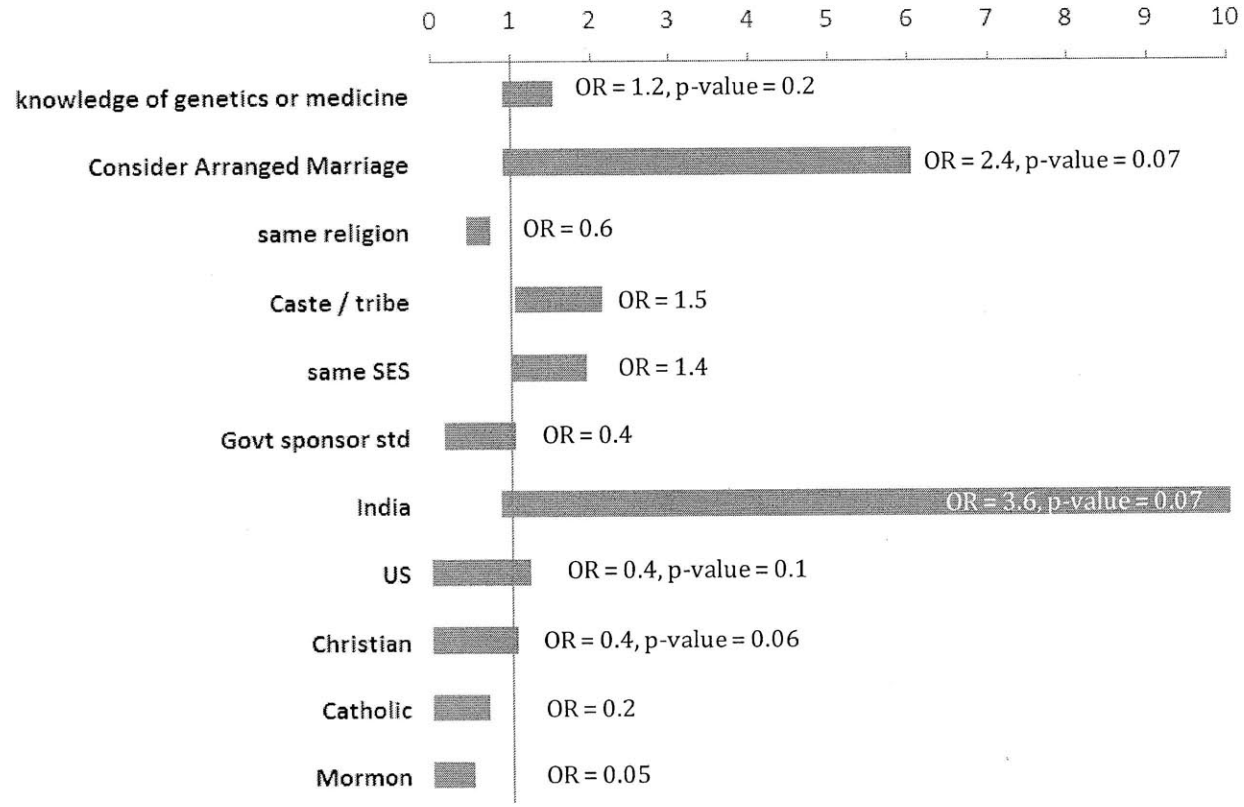


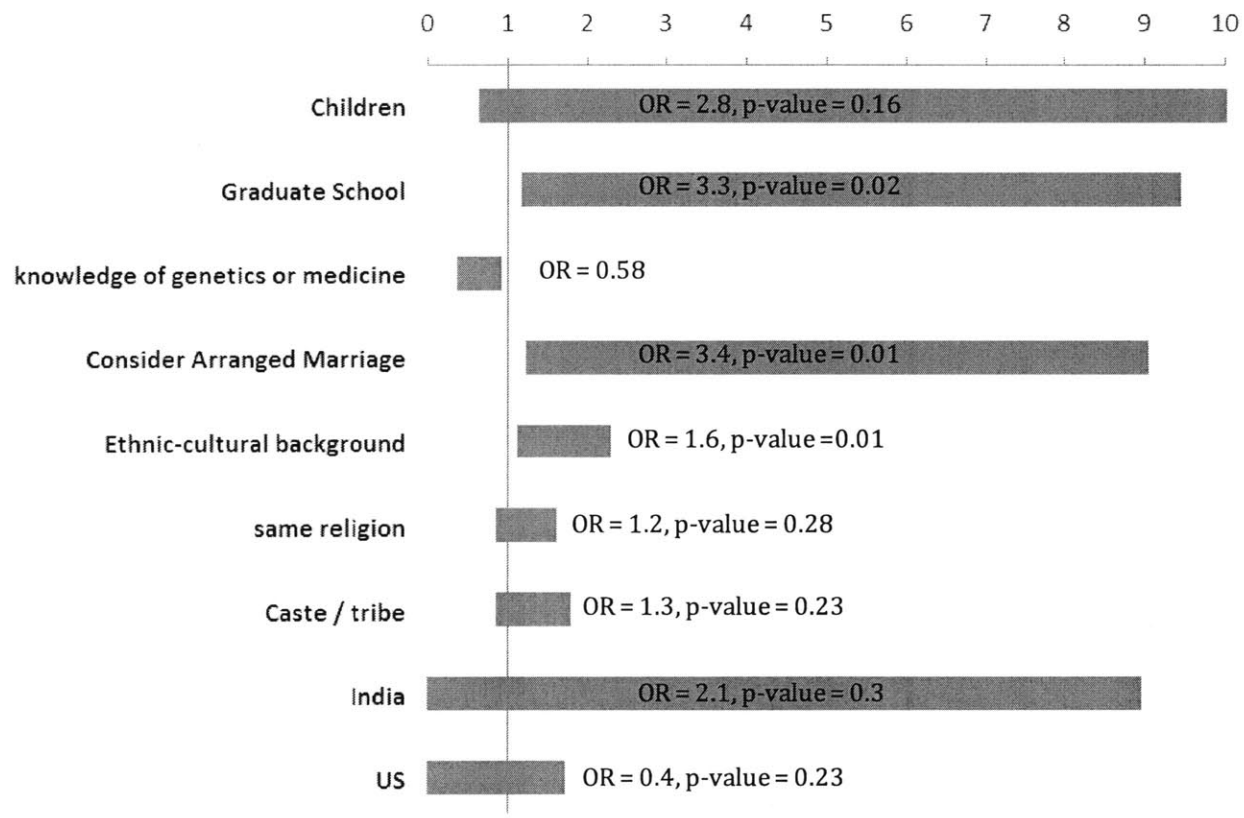
Figure 37 summarizes the results for individuals who would consider early termination of a pregnancy based on the results of a genetic test. As expected, having considered arranged marriage once again makes one more likely to consider abortion based on the outcome of a genetic test. Knowledge of genetics or medicine was also a predictor, but not statistically significant at a 5% level. If you were born in India, you were 3.6 times more likely to consider early termination of a pregnancy. This is in direct contrast to being born in the US, which the survey data showed to be an indicator that an individual would be less likely to consider early termination based on a genetic test.

Figure 37: Which Groups are More or Less Likely to Consider Early Termination of Pregnancy?



Finally, the four most predictive variables for actually reconsidering partner choice based on a genetic test were: 1) if you had children already; 2) if you went to graduate school; 3) if you had considered an arranged marriage; and 4) if you were born in India. (See Figure 38).

Figure 38: Which Groups are More or Less Likely to Reconsider Partner Choice Based on Carrier Status?



Discussion & Conclusion

In the final analysis, I was able to address and answer the three main hypotheses with a fair degree of confidence. The data reveal that people born in India were not more or less likely to declare a desire to use a genetic test at the pre-marital or pre-natal stage. However, they were more likely to consider early termination of a pregnancy (OR = 3.6, p = 0.07) and they were more likely to reconsider partner choice based on the outcome of a genetic test (OR = 2.1, p = 0.3). For both of these intervention points, people who were born in the US were less likely to consider an abortion (OR = 0.4, p = 0.1) and less likely to reconsider partner choice based on a genetics screen (OR = 0.4, p = 0.23).

The data show that having considered an arranged marriage is the strongest predictor for use of genetic testing at every intervention point. People who had considered an arranged marriage were more likely to use a genetic test at the pre-marital stage (OR =6.54, p =0.02) and the pre-natal stage (OR =7.7, p = 0.07). These individuals were also more likely to consider early termination of a pregnancy based on the outcome of the test (OR = 2.4, p =0.07) and reconsider partner choice (OR =3.4, p = 0.01).

Finally, the data actually show that people of religious backgrounds traditionally against abortion are still not more likely to pursue early genetic screening for carrier status. I hypothesized that this group would preferentially seek carrier status information at the pre-marital and pre-natal stage in order to pursue other options (adoption or in-vitro fertilization with pre-implantation diagnosis). However, both Christians (OR = 0.25) and Mormons (OR = 0.09) were less likely to seek genetic testing at the pre-marital stage.

For the minor hypothesis, the data show that females are slightly more likely (OR = 1.44, p = 0.26) to pursue genetic testing at the pre-marital stage. This statistic was not significant at the 5% level. I believe the reason for this is because in higher socio-economic circles women share the responsibility for childcare more evenly with men. A future hypothesis to explore would include a lower socio-economic demographic to tease out whether there is a difference between women's attitudes based on this characteristic alone.

One final observation worth noting is the effect that "knowledge of genetics" had on the question "would you reconsider partner choice based on a genetic test." My own reservations in conducting this thesis centered on the sensitive topic of using genomic data to make life choices, not about health, but about marriage. The two can be and are intertwined when it comes to small, endogamous communities. In the case of thalassemia and in the case of a developing world / Indian context, the use of genetic testing to make arranged marriage choices is easier to grapple with and grasp. Thalassemia is a grave disease with no cure and little access to optimal treatment in an environment like India's. Furthermore, post-marriage interventions such as in-vitro fertilization are out of reach for most people living in India. Still, the question remains: how will this translate into other mutations, other countries and other cultures. Will this trend lead people to start making marriage decision based on other genetic data? The survey data indicates that as knowledge of genetic increases, the likelihood of individuals reconsidering partner choice based on genetic insight actually decreases (OR = 0.58). I interpret this to mean that as people become more knowledgeable about the concepts behind genetics, they are less

likely to stigmatize individuals with mutations and more likely to make marriage decisions outside of genetic variables.

As we continue down this path of genetic discovery, we, as a society, will have to manage how we utilize this powerful information. With thoughtful application, genetic tools can dramatically reduce the incidence of fatal disease. I hope this thesis has shed some light on a niche where genetic diagnostics can be used with care and great utility.

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