A characterization of the coevolutionary shift model of treatable hereditary illness based on cystic fibrosis

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ABSTRACT

The purpose of this paper is to create and define a model for the effects of treatable, hereditary illnesses on human culture and biology based on the trends displayed by Cystic Fibrosis. This disease has passed through different stages during human history that can be characterized by a given status of the gene frequency and an associated attitude towards fertility held by families and individuals affected by the disease. With each stage there are characteristic attitudes resulting from different factors and these attitudes in turn lead to changes in gene frequencies. It is beyond the scope of this paper to quantify the movement of gene frequencies characterized by the Coevolutionary Shift Model. It is sufficient at this point to characterize these movements by intuitive, theoretical background and to correlate these movements with well-documented support for the corresponding attitudes towards fertility. Sickie Cell Anemia, Phenylketonuria, and Tay Sachs are also fitted to this model to determine if it applies widely to other diseases. Although they are not described to the extent that Cystic Fibrosis is, they help to further define and modify the model.

Keywords: Cystic fibrosis, gene frequency, gene therapy, sickle cell anemia, Tay-Sachs.


Cystic Fibrosis (CF) is the most prevalent hereditary illness in Caucasian populations, affecting 1 in 2500 live births. One in 25 Caucasians are carriers for one of over 200 defects on the CF gene located on the long arm of chromosome 7. Cystic fibrosis is a defect in the regulation of ion transport in secretory epithelia, and researchers are just beginning to elucidate the specific biochemical mechanisms involved in CF. It was first named because of the cysts and fibroses that form in the pancreas, but CF is a complex multisystem illness that has many manifestations that inevitably lead to a fatal outcome. The disease causes sterility in men and it affects exocrine function in the pancreas, liver, skin, and gastrointestinal tract, but ultimately, the final cause of death is usually from respiratory infections.

Since CF was first accurately described in 1938, our knowledge of the disease has led to an increase in average life expectancy. The median survival age for a child born in 1960 was less than 5 years, whereas for an individual born in 1990, this age has risen dramatically to 40 years. These gains have not come about from a cure for CF, but rather from improvements in treating its manifestations. In the past 40 years, medical care has yielded encouraging prognosis for this illness. Our culture-given ability to combat illness has affected the frequency of this gene. Furthermore, the frequency may covary with attitudes towards fertility created by CF. The general aim of this paper is to explore and characterize this relationship between our genome and our culture.

In 1989, researchers identified the CF gene and this development has made prenatal diagnosis possible by directly identifying specific mutations on the gene. Before such techniques were available,

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clinical diagnosis of CF relied solely on identifying its phenotypic effects, clinically through several tests. Parents without prior history of illness have no reason to seek prenatal diagnosis. Given this, and the somewhat ambiguous nature of clinical diagnoses, it is no surprise that only 70% of CF patients are diagnosed within the first year of life. Naturally, the earlier CF is diagnosed, the earlier treatment can begin.

According to Peter Goodfellow, there are 3 primary reasons why the prognosis for CF patients has improved in the past 50 years: the advent of antibiotics, improvement in other methods of treatment, and the identification of milder cases of the disease and their inclusion in reported figures for CF. Today, specific centers are available for CF patients and their families that specialize in providing support, education, and treatment. Treatment of CF focuses on alleviating the severe damage to each affected organ system. Physicians and researchers are most commonly associated with the effectiveness of the treatments for any disease. However, there are many social and economic factors that can contribute to the success of any medical treatment. Three factors specifically affect treatment for CF: the knowledge patients and families have about CF and treatment, the level of income of a family, and the support a CF family receives from their extended family and community. Cystic fibrosis families and patients are required to participate in a great extent with treatment. Compliance with treatment is dependent on a family’s understanding and knowledge of CF. Cystic fibrosis families have a better understanding of the disease than healthy families, in fact CF families and patients feel that they need more information from physicians and researchers. Families with high levels of education and social class are more knowledgeable about the disease, and presumably they comply better with treatment protocols.

A study in Norway found that over 21% of a family’s income is portioned off towards health care of an affected child, compared to only 7% for families with healthy children. Compound this with the fact that one parent must stay home to care for a sick child. Furthermore, repeated hospitalization imposes a burden on the ability of CF adults to seek employment. In the United States, treatment is just as financially burdensome to a family. At one clinic, 10 of 12 children and 13 of 15 adults needed disability assistance from the government. The majority of these same CF adults had negative feelings about needing this support, citing feelings of worthlessness and failure. Cystic fibrosis families also require support from each other. The stress and daily demands of treating a chronic, fatal illness such as CF can be overwhelming. In a cross-cultural study between families with varying kinship support networks, it was found that families who had help from extended family and friends experienced less stress related to CF. Medical care for CF requires many resources from the CF patient and his or her family. This places a great demand on the finances, time, and energy of everyone involved with the illness. The ability of a family to utilize these resources will affect the success of any treatment as well as any attitudes towards treatment that may affect future decisions.

The coevolutionary shift model of treatable hereditary illness. Cystic fibrosis was first accurately described in 1938, but this hereditary disease has been part of human’s genetic heritage for far longer. Given the frequency of CF among Northern European populations, there is a strong indication that it conferred an advantage for heterozygote carriers. One theory of what this advantage may entail was put forward by Richard Meindl. He hypothesizes that it aids with resistance to Pulmonary Tuberculosis (TB). Given the extent to which TB afflicted Northern European populations in the 17th and 18th Centuries, there would have been substantial selective pressure favoring any advantage over TB. At this time, it is unclear whether this hypothesis is correct but it is certainly one of the more compelling theories for heterozygote advantage with CF.

In the past, certain CF studies focused on its “eugenic effects” or the decrease in the frequency for a specific allele of a gene. While this paper discusses the movement of genes in a population, “eugenic” is merely a descriptive term, and does not entail any judgment on policy or morality in family planning decisions. John Hartung and Peter Ellison highlight 2 concepts in their discussion on eugenics; Parental Investment (PI) and Reproductive Compensation (RC). Parental Investment is a means to characterize the cost of having children for parents in terms of their ability to have other children. There are “costs” to having children that can include any number of biological, economic, or psychological factors and parents may have a limit to the resources required for bearing and raising children. Reproductive Compensation refers to the ability of parents to reproduce towards their theoretical capacity despite bearing nonreproductive offspring, given that they do not consume much PI. This concept applies in circumstances where the child dies at an early age and does not consume too much PI so that the parents are still able to meet their reproductive potential. However, if the child has a high PI, then this adversely affects the RC - there is an inverse relationship between PI and RC.

It is easy to imagine a situation in which medical care is available for a particular patient, but he or she requires so much PI that the parents are not able to reproduce to their potential. In 1974, this was certainly the case with CF as studies clearly illustrate...
this point. In a comparison between 2 communities, one in which children received adequate health care and one where they did not, there was a marked difference in homozygous survivorship. The relevant point from this study is that average family size was significantly smaller in the group with increased survivorship, presumably because these children demanded a greater PI. In communities and populations where health care is adequate and available, there are fewer heterozygote carriers because homozygotes effectively cause parents to have fewer children. Hartung and Ellison illustrate this point simply with: Medical Care increase, Homozygote Longevity increase, Homozygote PI increase, Heterozygote RC decrease, Heterozygote Selective Disadvantage increase, Gene Frequency decrease. These concepts are tempting to base models of this illness on because of their quantifiable nature. But, there are important factors involved in the coevolution of CF that require our attention as well, specifically attitudes towards fertility. These attitudes represent a family’s values, ideals, and religious beliefs. In other words, these feelings could come to signify how parents view themselves, their children, and future progeny. In a broader sense, they represent social mores and norms as well. Attitudes towards fertility manifest themselves in the decisions families make regarding birth control and abortion among others. The attitudes created by CF and the attitudes towards CF represent another facet of this robust concept.

Many researchers and theorists have focused their attention on the effect that genes have on behavior. The idea that genetics and culture interact at some level also implies that behavior may, in turn, influence human biology. For any relationship between these 2, it would be too simple to assume that one exclusively alters the other. The relationship is usually more complex, with genes and culture both affecting each other, continually, in what is commonly referred to as “coevolution.” The Mendelian and Darwinian principles by which CF operates is very well understood. However, human behavior and the attitudes behind it remain the focus of much debate and discussion. At different points in human history, the frequency of CF among populations has been increasing, decreasing, or has maintained an equilibrium frequency. Cystic fibrosis can be characterized by different stages based on this movement of gene frequencies. Likewise, each of these stages can be characterized by a prevailing attitude towards fertility by CF families. The Coevolutionary Shift Model of Treatable Hereditary Illness characterizes how gene frequencies for an illness and fertility attitudes of families afflicted by this illness may exhibit covarying shifts over time through successive stages (Table 1). Note that this model is based on the stages that CF has passed through and that not all illnesses will pass through every stage outlined below. The key aspect of the model is the nature in which gene frequencies and attitudes towards fertility are dependent on each other.

The first, and earliest stage of CF to be described by this model is the Heterozygote Advantage Stage. As discussed above, when an allele for a gene provides an advantage for heterozygotes over both homozygous states, then there is said to be a heterozygote advantage at work. In this stage, there is an equilibrium frequency for the gene in a population and the frequency does not increase or decrease. Correspondingly, heterozygotes and wild-type homozygotes do not exhibit any particular condition that would set them apart from the rest of the population. This stage of the disease took place before CF was identified, and at that point, CF was fatal very early on in life. In accordance with Hartung and Ellison’s model, there would be little PI for such a child and a high RC. At a time when infant mortality was relatively high to begin with, parents of a child who died of CF would not substantially differ from any other parent who lost a child. Presumably therefore, CF would have no effect on the attitudes towards fertility in a given

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<td>Comparable life history</td>
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* The movement of gene frequency of cystic fibrosis in this stage is dependent on the model of the cure necessary for this stage to occur: gene frequencies will decline with gene therapy and will equilibrate with advance treatments.
population during the Heterozygote Advantage Stage. This is followed by the Heterozygote Carrier Stage in which it is no longer advantageous to be a carrier for the allele. Assuming CF did provide an advantage against TB, this stage began when TB had a less dramatic effect on European populations. During this stage, CF gene frequencies would decline because there would be no advantage to being a carrier, and the homozygous condition was still fatal at a very young age. There would be a change in gene frequency but the attitudes towards fertility would remain unchanged. Cystic fibrosis was still unidentified at this point, and PI and RC remained low and high respectively. Although there is no data from this period to support these conclusions, it is almost intuitive to assume that heterozygote parents held attitudes towards family planning that were consistent with those of the population at the time. Hartung and Ellison were writing during the High Parental Investment Stage, where it was possible to treat the disease but at a great cost to the patient and family. As mentioned above, this would inevitably lead to a decrease in the frequency of the gene based on the fact that the heterozygote parents were not having as many children. In contrast to the 2 earlier stages, PI would be high and RC would be low. In other words, homozygote children were preventing heterozygote children from being born. Although declining gene frequencies also marked the previous stage, the High Parental Investment Stage is characterized by an acceleration in this decrease. The other important consequence of this stage is the change in the attitudes towards fertility held by CF families. These attitudes are a subject of deeper inquiry later, but suffice it to say that CF families hold dramatically different views on fertility than the general population in this stage.

We currently find ourselves entering the Heterozygote Carrier Stage. Today, CF children are becoming CF adults as a result of many factors and these individuals are having children of their own. Unlike heterozygote parents who have a 25% chance of bearing a child without the CF gene, homozygote parents will pass on the CF gene to all of their children and this will presumably result in an increase in gene frequency. In every previous stage, the agents of reproduction formed their attitudes on fertility based on the effects of CF children on the family. However, in this stage, the agent of reproduction and the CF patient are the same individual and this leads to a markedly different perspective from which fertility attitudes are formed. We also propose a stage in the future called the Comparable Life History Stage where CF homozygotes would lead lives comparable to individuals affected by nearsightedness or lactose malabsorption for example. Once again, we will deal with both of these stages later.

**Attitudes created by cystic fibrosis towards cystic fibrosis.** The attitudes of the High Parental Investment and Heterozygote Carrier stages have been extensively studied by researchers and accordingly we will explore these stages in depth at this point to illustrate the shift in attitudes that accompany the movement of gene frequencies in our model. The attitudes of CF families towards Prenatal Diagnosis (PD) represent the attitudes during the High Parental Investment Stage and the attitudes of parents with CF will serve to characterize the attitudes of the Heterozygote Carrier Stage.

**Prenatal diagnosis.** When a couple marries, they have certain general expectations towards having kids and of the kids themselves. Most parents have an ideal family size in mind, and all parents hope for, if not expect their children to be healthy. As much as parents think they understand what they want from a family, most CF parents have little indication that they are carriers for CF and the birth of a CF child is usually a shocking occurrence. The stress and burden of raising a CF child affects family-planning decisions dramatically. A survey among 50 mothers found that 20% of them would rather commit suicide than have another child with CF. These are strong feelings indeed and they are representative of the high burden that parents are placed under when raising a CF child. A study conducted in the United States found that among families where one partner had been sterilized, a CF diagnosis had affected the decision to be sterilized in 62% of the respondents. In another study of CF families attending a CF clinic in Belgium, parents were more likely to be sterilized and at an earlier age than the general population. In this same study, researchers found that the most important factor influencing the parents' pregnancy planning was the risk of having another affected child. Since identifying the gene for CF, the possibility of knowing whether a child is affected or not has been realized through PD. However, this availability has raised some very complex issues within CF families. Prenatal diagnosis does not imply abortion at an emotional level despite its logical cognitive implications. Among families at CF clinics in Verona, Italy, 80% of the families studied felt that PD was an important option to have, yet only 32% believed they might actually take advantage of it. Knowing that a child will have CF puts parents in a position where they must decide between 2 undesirable outcomes, each of which has dramatic emotional implications: declining to use PD is a way parents avoid this decision, or what psychologists call an 'avoidance-avoidance' conflict. Most parents do not want to have another child with CF, nor do they want to face the tacit implications of a positive PD result.

One investigation confirmed these results when it was found that there was a strong correlation between willingness to use PD and three factors, one of which was a willingness to opt for abortion of a
CF fetus. The other 2 factors reveal deeper motivations behind parents' decisions concerning PD and abortion. The second factor is the perception of whether or not their siblings would approve of aborting a CF fetus. Presumably, this is a reflection of the values a family may have and how difficult it would be to act in opposition of them. We may find it convenient to include religious beliefs with family values. In a cross-cultural study that included groups of differing religious backgrounds, it is little surprise that the more religious groups were far less likely to opt for abortion in CF cases than other groups. The third factor linked to willingness to abort is perhaps the most compelling. Parents were asked to list accomplishments for their CF children and it was found that parents are more likely to choose to interrupt a pregnancy if they were unable to list any accomplishments. This goes beyond the perceived burden of raising a CF child or of one's beliefs and values. The decision to abort clearly reflects on the way parents view existing CF children and when parents can list accomplishments they may be effectively describing the value of their child's life. Quality-of-life is certainly a strong factor in making decisions about having children. One survey showed that 100% of respondents said they would abort if the child had severe mental retardation and would die within the first 5 years. Another sample of CF parents were asked about their attitudes towards this subject, and PD alone would represent a "disdain and disrespect" for the CF child for 33% of them. Prenatal diagnosis has created a dilemma for CF parents, and the rationale behind the decision-making opportunities created by PD offer a unique insight into the attitudes CF parents have towards fertility. Parents have views on abortion irrespective of their children's illness based on religious and family ideals and these attitudes affect whether parents will utilize PD. But, existing CF children also play a major role in this decision as well. These children provide expectations for future progeny and accordingly the perceived quality of the lives they might lead. More importantly in the minds of parents, the decisions to use PD or opt for abortion reflects directly on the value they place on the life of their CF child.

**Homzygote parents.** Steady improvements in treatment over the past 50 years has allowed children with CF to reach adulthood; the figures for life expectancy discussed earlier reflect this trend. With increasing age comes the choices and life-decisions of adulthood and CF adults must face these with the reality of their own mortality. To say that CF individuals are homogeneously comparable to their healthy counterparts is incorrect. Some researchers suggest there may be CF-specific mental and social disorders among many individuals. However, others contend that CF has no associated psychopathologies. Despite the disagreement on this issue, there are differences between CF adults and their healthy peers, and specifically in the attitudes that motivate their decisions towards marriage and having children. In the High Parental Investment Stage, reproductive behavior of parents was influenced by their view of existing CF children and presumably parents with CF in the Homzygote Carrier Stage make decisions based on their view of themselves.

In a study performed with CF adults, researchers found that sexually active women were less likely to use contraception than the general population. In fact, menarchal delay may be the only significant difference in sexual activity between women with CF and other young women. Recall that CF men are sterile, yet in another study a significant number of men either adopted children or utilized artificial insemination to have a child. All of this information seems to indicate individuals with CF want to have children. Recall that parents of CF children were more likely to be sterilized or use reliable forms of contraception. With CF adults, this trend is reversed and this is a strong indication that individuals with CF have different attitudes towards fertility than their healthy counterparts. The simple desire to become a parent may outweigh any negative feelings towards having a child with CF. A group of CF adults were asked a series of questions concerning their general opinions on PD and abortion. They overwhelmingly support PD for parents who may be suspected carriers or may already have had a child with CF. Based on these results and interviews with patients and physicians, they felt other children or parents should not have to experience what they endured with CF. Further, when asked if they would abort a CF fetus, 35% did not know, 42% said that they would not, and 23% would abort. Researchers contrast these figures with another survey that asked CF adults whether it was acceptable for others to choose abortion of an affected fetus and 68% of the respondents found it acceptable, a number significantly greater than the 23% who would choose abortion for themselves. Now, we must reconcile the following facts: CF adults would not wish a CF child on another family and they would understand if they chose selective abortion but they are unlikely to choose abortion themselves. In order to understand how CF adults form their views on PD and abortion, it is important to consider how their own experiences with CF play a role. For an individual to live to an age where they have the option of having children is truly a triumph of medicine, but medical advances alone cannot account for these gains. As discussed earlier, these patients must have had more than financial resources, they must have had tremendous support from family, friends, and physicians. Living with a chronic, fatal illness also requires effective coping strategies.
noted previously, most individuals with CF are well educated about the disease and they understand that there is varying severity among its manifestations. Almost all are aware of their own impending mortality and many have had a sibling die from CF. Taken together, these points all seem to indicate that CF adults who wouldn't accept selective abortion can empathize with other CF individuals who might choose abortion for themselves. These patients have a self-esteem that may stem from their own achievements and how their families, friends, and health care professionals place value on their lives. This feeling of self-worth does not allow CF adults to feel stigmatized by the use of selective abortion of fetuses with CF. Parents of CF children may be hesitant to utilize PD and abortion because it might devalue the lives of existing children, but CF adults contrast this situation. They may not think that these choices reflect on them personally, so it is easier for them to condone them for others even if they don't accept them as an option for themselves. Some researchers have raised the concern that many CF women are not aware of all of the potential dangers of having children. If this is truly the case, one may ask whether these women would change their views on childbearing if they were better informed. However, one can argue that their attitudes towards fertility affect the manner in which they interpret information about CF, and that knowledge deficits are not a result of patients unwilling to learn more. A study conducted among CF teens may support this thought - it found that 35% actually did have specific concerns dealing with fertility issues. Certainly, further research is needed to clarify this issue. However, CF adults clearly have markedly differing attitudes towards fertility than their parents.

The shift. The fundamental cause of these changes in the frequency of the CF gene and attitudes towards fertility is the improvement in medical treatment over time. We have used the feelings of homozygote adults to reflect the attitudes of the Homozygote Carrier Stage, but they represent just part of a larger trend brought on by this treatment. Heterozygote parents still comprise the majority of adults having children, but their attitudes are changing as well. Perhaps the treatment-induced shift between the stages of our model is best illustrated by addressing the attitudes of these parents. Researchers assume that parents are more likely to find with improved medical care that their children are not noticeably different from other healthy children and when this is coupled with high expectations for future therapies, it may explain the lower than intended use of PD. This also brings up a point pertaining to the optimism parents have concerning future advances in treatment. Another study found that a majority of CF parents were optimistic that their child would live past 40 years of age. Indeed, future treatment does bring hope to many individuals affected by CF, but we should not disregard how far treatment has come to this point. Three hundred and eighty five adults were informed about CF and the present state of treatment protocols, and 95% indicated that given this information, they felt that they would be able to care for an affected child. Although attitudes of parents generally coincide with the attitudes attributed to the High Parental Investment Stage, there are indications of a change, at least among some parents. As treatments and prognosis for CF continue to improve, the use of selective abortion and the feelings behind it may change further. Taken together, these changing attitudes among CF parents and the emerging attitudes of CF adults, there is a strong indication that a shift in attitudes towards fertility is taking place. As more families choose to carry CF fetuses to term, and more CF adults choose to have kids of their own, the frequency for the CF gene will increase. With continued improvements in treatment, these trends will grow stronger as more parents come to accept their child and more CF children live to childbearing age. As the Homozygote Carrier Stage begins, many parents still reflect attitudes of the High Parental Investment Stage. This brings up another characteristic of the Coevolutionary Shift Model: stages overlap as shifts between them take place over a period of time.

A potential model for other treatable hereditary illnesses. The true test for our model comes when we attempt to characterize other hereditary illness with it. In the following section, we will briefly discuss 3 diseases and whether they support our model. A thorough background of each of these diseases and their treatments is beyond the scope of this paper, but sufficient information will be provided to fit them to our model. Recall that CF was the basis for the sequence of stages described and that other diseases may not pass through all of the stages. However, the strength of The Coevolutionary Shift Model comes in characterizing the shift in the attitudes towards fertility that may accompany changes in the gene frequency.

Sickle cell anemia. Sickle Cell Anemia (SCA) is a disease most commonly associated with populations of African descent with an incidence of 1 in 250 births among black populations in the United States. However, this disease is not limited to Africa-populations in the Mediterranean, Arabian Peninsula, and the Indian Subcontinent there are also relatively high percentages of affected individuals. In contrast to our knowledge of the origins of the CF gene, SCA does provide a heterozygote advantage against malaria. Sickle cell anemia is a disease that compromises the ability of hemoglobin to bind oxygen in the blood. The hemoglobin of an afflicted individual will polymerize and cause red blood cells to 'sickle'. This sickling of red blood cells causes them to become trapped in small blood vessels and
this leads to damage of many different organ systems. Individuals with SCA do not usually live past the age of 40 with the cause of death attributed to infections, cardiac failure, renal failure, and thrombosis. Because SCA manifests itself in so many ways, there is a very intensive treatment regimen SCA families must follow. Like CF, there is considerable variability in the severity of symptoms attributed to SCA because of the complex interactions of the multitude of mutations. Given all the similarities SCA and CF have, it is pleasing to note that many aspects of SCA can be explained by the Coevolutionary Shift Model. The Heterozygote Advantage Stage of SCA still applies to many of the world’s populations because malaria is still prevalent and treatments for it are unavailable. Because of this phenomenon, SCA does not proceed along the same course of stages as CF. Instead, there can be shifts directly to the other stages from the Heterozygote Advantage Stage depending on the contributing cause. In the past, before treatments for SCA were available, individuals would enter the Heterozygote Carrier Stage when they moved from an area where malaria was prevalent to one where it was not. Sadly, we are reminded of the era of slave trading and the massive movements of Africans around the world. This appalling practice provides an example of a cultural cause for a shift between stages. As time passed and treatments for SCA became available, these and other populations shifted into the High Parental Investment Stage. Since the first advances in treatment areas with a high frequency of SCA, families have moved directly to the High Parental Investment Stage from the Heterozygote Advantage Stage. Just as in the case of CF, these treatments exact a toll on a family’s resources and they affect attitudes towards fertility as well. In a study conducted among Cuban women who were expecting or planning a child, 46 of 52 of them had chosen PD. This statistic is certainly consistent with the views of CF women in this stage. As treatment continues to improve and more SCA individuals reach adulthood, a greater shift into the Heterozygote Carrier Stage and away from the High Parental Stage can be expected.

With CF, there was a progression of stages through time, but with SCA on the other hand, populations are not limited to this variable, shifts can occur with a movement through space as well. Furthermore, the history of SCA has demonstrated that it is possible to skip stages characteristic of the course of CF. Finally, SCA may be the exception to shifts resulting from medical care improvements. No matter what the cause of the shift may be however, it may be characterized by a change in attitudes and gene frequencies.

Phenylketonuria. Now we shall consider a disease that is considerably different than CF to test our model. Phenylketonuria (PKU) is the most common biochemical cause of mental retardation. There is an incidence of 1 in 10,000 live births for PKU. Researchers believe that PKU exists in the human genome because it reduces the chances for spontaneous miscarriage. Thus, women are more likely to bear children regardless of whether it is a heterozygote or an afflicted homozygote. Phenylketonuria is caused by a family of mutations in the gene that specifies for an enzyme that converts phenylalanine into tyrosine. When phenylalanine builds up in the body, it leads to severe mental retardation of a developing fetus or newborn. To date, treatment for PKU has been highly successful. Of course, once a child has suffered brain damage there is little medical science can do, but if a diagnosis for PKU is made early then restricting phenylalanine in the diet can prevent damage. This type of intervention requires strict compliance on the part of parents until the patient has finished childhood. The advantage conferred by PKU cannot be described as a heterozygote advantage because it does not improve the survival of the carrier. The burdens of raising a PKU child must have always been great and this leads us to believe that the High Parental Investment Stage was the first stage in the course of this disease. Just as in CF, parents in this stage may have held negative views towards fertility. Since initiatives to identify carriers and treat their offspring were initiated in the 1960’s, the burden on parents has changed from raising a severely handicapped child to complying with treatment regimens. Given what we have learned so far, these changes amount to a shift into the Heterozygote Carrier Stage.

Tay-Sachs. Finally, we consider a disease with a less promising prognosis: Tay-Sachs (TS). Tay-Sachs is an illness that results from one of several specific genetic mutations for the genes responsible for the activity of an enzyme necessary for the breakdown of GM2 ganglioside. People with Tay-Sachs accumulate this sphingolipid in various tissues, particularly the brain. The result is a degeneration of the nervous system that results in severe mental retardation and by 4 years of age proves to be fatal. Tay-Sachs (TS) is a recessive disorder associated with the Ashkenazi Jewish populations. It is thought that TS confers an advantage for heterozygotes against TB. However, some researchers believe that the high RC among the Ashkenazi Jews is partly responsible for the equilibrium gene frequency for TS found today. Under this hypothesis, a family will make sure that a healthy sibling “replaces” an affected child. So, despite the treatability of TB, the gene frequency would remain steady. Starting in the early 1970’s, screening programs were set up to identify carriers for TS. It is thought that the success of these efforts is responsible for the decreased incidence of TS among Ashkenazi Jews since 1970.
from 1969 to 1992, 469 fetal diagnoses were identified for TS and parents opted for abortion in 451 of these cases. Clearly, despite the high RC among Ashkenazi Jews, there is a strong desire to avoid having children with TS.

With CF, identification of the gene followed improvements for medical treatment so the High Parental Investment Stage was actually defined by high PI. However, with TS, the identification of the gene has preceded any future treatments, so the attitudes today do reflect the High Parental Investment Stage without high PI. It is very probable that illnesses in the future will follow the same trend as TS as far as the sequence of developments and this may require a change in the title of this stage. However, the basic attitudes, their causes, and their effects characterized by this stage remain unchanged. TS has highlighted a vital part of the Coevolutionary Shift Model: medical care does not change gene frequencies directly, rather it does so by changing attitudes towards reproduction. If treatments improve the life span of TS individuals in the future, it would be interesting to note what effects this will have on the attitudes of individuals associated with the illness.

None of these diseases provides a perfect match for the trends for CF in the Coevolutionary Shift Model, however, they do add further meaning to it. The danger of creating a model based on a single disease is that it may not apply to other illnesses. Each of these diseases has forced our model to become more general so that characteristics of each of them can fit any expected trends. For example, not every stage described by CF will apply to other diseases, nor will the mode of the shift between them. Finally, shifts can occur between stages within subpopulations. However, the basic principle remains the same: for any shift between stages for any group of people afflicted by a treatable hereditary disease, it is possible to identify a change in the attitudes towards fertility in this group.

In conclusion, we mentioned the Comparable Life History Stage earlier in the paper and now it may be appropriate to explain its significance. At some point in the future, it is plausible to say that there will be a cure for each of the diseases discussed. Gene therapy offers the most promising avenue towards this end,35 but treatment may possibly become so effective that it could virtually be considered a cure. The attitudes for this final stage would resemble those of unafflicted individuals and families. The movement of the gene frequency is dependent on the mode of this cure. Gene therapy would slowly remove mutations from the population whereas treatment would presumably lead to an equilibrium frequency in the population. This part of the Coevolutionary Shift Model remains to be tested. Any discussion of the attitudes towards fertility must address the issues of selective abortion and prenatal diagnosis. It is not our aim to advocate any course of action for any type of individual mentioned in this paper. On the contrary, we believe that any policy on these subjects would be dangerous, and that decisions concerning such matters should be left in the hands of the individuals themselves. This paper has created a model for heritable disease based on the history of CF and has supplemented it based on the characteristics of several other diseases. We recognize that this model must face the scrutiny of further illnesses and that it may need to be altered accordingly. A further caveat to consider is that the populations studied are not homogenous and that attitudes and decisions vary on an individual basis. It may be necessary therefore to use the Coevolutionary Shift Model among smaller subgroups, rather than global populations. Despite these possible misgivings, we are confident that this model has great potential utility in describing the relationship between cultural changes and changes in the human genome. The fitness of an individual is not only determined by his or her genes, but also by the cultural interpretation of the genes themselves. With few exceptions, Medicine serves as the link between our genes and our culture. By altering the manner in which an illness affects individuals and families, Medicine is changing the way humankind relates to its own mortality and its drive to maintain itself.

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