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# The Bioethical Implications of Genetic Screening Programs for Rare Diseases

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# The Bioethical Implications of Genetic Screening Programs for Rare Diseases

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by

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*Introduction*

Humanity is preoccupied with extending life. There are supplements, exercises, diets and retreats that cater to this goal. Film, television, and novels explore how we might one day become immortal, or go extinct. When novel infectious diseases develop, humanity declares a world health emergency and countries across the globe unite to prevent its progression. In the United States, millions of dollars are committed to analyzing mortality and morbidity data so that public health officials can propose solutions to the one impending problem we all share - death. There is rarely protest to these measures, undertaken to protect humanity from early deaths.[1]

The leading causes of death in the United States have been heart disease and cancer for many years.[2] In 2016 and 2017, the number of individuals who died from either condition tripled that of the next most common cause of death.[2] Physicians regularly attribute heart disease and cancer to lifestyle choices, including diet, smoking, alcohol consumption, and exercise.[3-4] Individuals can also be predisposed to both conditions through certain genetic mutations, which increase their risk of disease development.[3-4] However, the role that distinct genetic disease plays in the leading causes of death is rarely discussed.

Hereditary hemochromatosis (HH) is a genetic disease that causes both heart disease and cancer, despite often being ignored in the diagnosis of both conditions. In fact, of the ten most common causes of death in 2016 and 2017, HH is associated with an increased risk of almost half of the listed conditions.[2-5] Despite the association of this disease with common fatal complications, HH is also severely underdiagnosed.[5-6] This is the result of a lack of physician and patient familiarity with the disease. For many years, HH was only identified as an unusual characteristic of autopsies; the role that it played during life was unknown.[5] Although it is the

most common genetic disease in people of Caucasian descent (it may be present in 10-15% of some populations), it is rarely considered when doctors are presented with its early symptoms.[7] This lack of appropriate diagnosis results in unnecessary and unrecognized mortality, which could easily be prevented with appropriate screening protocol and improved education.

HH remains severely underdiagnosed despite the clear benefit of early diagnosis and treatment. There are currently no established screening programs for HH anywhere in the world. Although several European countries have previously attempted to justify screening programs, none of them have been successful. This analysis outlines the major risks and benefits of such a screening program in the United States using the foundational principles of medical bioethics - autonomy, justice, beneficence, and nonmaleficence. Each fundamental principle is introduced generally, then applied more specifically to a potential HH screening program.

Before the analysis can begin, the term "genetic testing" needs to be defined. A genetic test is an analysis of a human sample - typically DNA - used to detect certain heritable diseases for clinical purposes.[8-10] There are three varieties of genetic testing: diagnostic, predictive, and carrier.[11] Diagnostic testing identifies a current disease state - for example, current prenatal and newborn genetic screening.[11] Predictive testing confirms the presence of a genetic mutation that will result in a disorder with delayed onset, typically in individuals with a positive family history.[10-11] Carrier testing determines if an individual, typically with no family history, has a certain genetic trait, which may affect progeny.[10-11] Currently, HH testing is almost exclusively diagnostic. An effective HH screening program will also serve as predictive and carrier testing.

What follows is a brief introduction to HH, which will be critical to the understanding of the remainder of this analysis.

*Hereditary hemochromatosis (HH)*

HH is a genetic disease characterized by unusually efficient dietary iron absorption.[12-13] Essentially, the body absorbs more iron than it can use. This excess iron progressively accumulates throughout the body, especially in organs and joints.[7, 13] The resulting condition - massive iron overload - leads to serious health concerns, including organ failure and death.[7, 12]

HH is caused by certain genetic mutations. The most commonly expressed mutation is HFE C282Y, a mutation on chromosome six.[5, 7, 14] There are additional mutations, including H63D, which are common in the gene pool but expressed at much lower levels.[14] Although the mechanism of the mutated HFE protein remains somewhat unclear, recent research suggests it regulates hepatic production of hepcidin, a key iron-regulatory hormone.[5, 13, 15] Hepcidin binds ferroportin, the sole protein responsible for transporting iron across cellular membranes.[5, 15] In a normal individual, when the duodenum absorbs sufficient iron, hepcidin binds to ferroportin and halts additional iron uptake.[15] In individuals with HH, hepatic production of hepcidin is decreased, so the critical hepcidin-ferroportin binding does not sufficiently occur.[16] The result is an excess of intra- and extracellular iron. Biochemically, this can be observed through elevated serum ferritin and transferrin saturation.[5]

Iron is a necessary element for healthy human life. However, in excess - such as in the blood of HH patients - it is toxic. Excess free iron produces reactive oxygen species and abnormal iron forms, which are known to cause organ damage and alter hepatic mitochondrial function.[5] In particular, abnormal iron forms are associated with disturbance of the metabolism of other metals, including zinc.[5] Parenchymal cells appear particularly sensitive to these effects, but under high enough iron concentrations, all cells begin to suffer detrimental effects.[5]

Disease progression in HH patients varies widely, and is heavily dependent on the point in the individual's life at which they are diagnosed. For some, the disease is secondarily identified in screenings for other conditions, and symptoms never present.[17] However, other patients die from complications of the disease without ever being diagnosed. This apparent discrepancy is the result of incomplete penetrance: although many individuals have the genetic mutation for HH, not all of those individuals will express symptoms of the disease.[18]

HH typically begins with chronic fatigue and joint pain.[5] As the disease progresses, osteoporosis, frequent bacterial and viral infections, and melanoderma are common.[5] Late stages of the disease are characterized by the most severe symptoms, which include cardiac disturbances (including rhythm abnormalities, cardiomyopathies, and cardiac failure), liver cirrhosis and cancer, rheumatoid arthritis, and diabetes mellitus.[5, 6, 19] Without monitoring and treatment, HH patients often die as a result of these disease complications.

The early symptoms of HH are easily attributed to other conditions, including stress. As a result, HH is rarely diagnosed early in its progression based off symptoms alone.[5-6] By the time the disease reaches its most severe stages, the complications are typically attributed to other well-known factors, such as lifestyle and predisposition mutations.

This chronic issue of misdiagnosis is particularly devastating because the disease is easily treatable. HH treatment requires phlebotomy, or periodic removal of venous blood.[5] Phlebotomy is extremely effective, safe, and cheap. Additionally, blood from HH phlebotomy can be used to save lives via transfusion with very few exceptions.[5] Most individuals who begin phlebotomy therapy early in life report never experiencing the severe complications associated with the disease; members of this group who do experience complications almost exclusively develop

mild arthropathies.[5] Treatment can begin in most HH patients at age sixteen, and maintenance only requires a few phlebotomy sessions each year and annual laboratory testing.[5] In the United States, the cost of phlebotomy varies widely by geographic location, but in most urban areas there are free blood donation centers that can be utilized by HH patients. For patients who do not respond well to phlebotomy, there are also a variety of effective iron chelating pharmaceuticals, although these are frequently associated with severe side effects.[5] Affected individuals are also continuously monitored on an annual basis once treatment is established as effective and safe.

HH diagnosis is simple. Genetic analysis at any point in an individual's life will reveal the presence of the mutations that cause HH. Biochemical tests - specifically serum ferritin and transferrin saturation - can be highly suggestive of the disease, but are only accurate predictors once disease progression has begun, and must be confirmed with genetic testing.[5] Therefore, the simplest method for detecting HH is genetic testing early in life. This will allow individuals to begin treatment as early as possible, massively reducing their risk of developing fatal complications. With all of this in mind, HH appears to be an obvious choice for newborn genetic screening. However, as mentioned above, there are a variety of bioethical issues that have prevented the development of a genetic screening program for HH and similar conditions.

*Autonomy*

Medical autonomy refers to a patient's right to make all of their own decisions - without fear of coercion or coaxing - with regards to their personal healthcare.[20] Theoretically, all medical decisions should be voluntary and made under the conditions of informed consent, and all medical content - biological samples, test results, and diagnoses - should be protected, private and confidential.

Before continuing, the term informed consent needs to be defined. A major issue in the medical world is variations on this definition, which results in patient decisions being made based on an insufficient level of understanding. Informed consent insinuates that the patient has been educated and completely understands the risks, benefits, efficacy, and alternatives of a proposed procedure or test.[1] Informed consent with respect to genetic testing also requires that the patient understand the disorder(s) being tested for - including disease severity, treatability, and variability - and how genetic samples will be stored, disposed of, and/or used after the test.[1] If there are any intentions to use the sample for extraneous tests, this must be shared with the patient, and the patient must give informed consent for those tests as well.[1]

In particular, extraneous testing of samples without informed consent is frequently cited as a deterrent to genetic testing. Currently, there are minimal restrictions on how newborn genetics samples can be stored and used after initial testing.[1] Often, the remainder of these samples are used to test new laboratory methods and collect population health data. Although it is unlikely that this extra use of samples will be stopped - and frankly, it would not be beneficial in the long run to eliminate this additional use of newborn samples - certain standards can be upheld to protect patient autonomy. For example, it is typically required that samples be

anonymized, and that the subsequent use not be anticipated at the time of sample collection.[1] Should the use have been anticipated, informed consent would have been required. Enforcement of these standards and continuous employment of informed consent can effectively eliminate this as an issue in genetic screening programs.

Autonomy is by no means absolute - there are various circumstances in which a patient's right to autonomy may be overridden in their own best interest, or in the best interest of society as a whole. In certain situations the patient is not capable of informed consent. In these instances, designated surrogates - typically family members acting in the patient's best interest - may instead give consent.[21-22] However, occasionally even the decisions of said surrogates may be overridden to prevent severe harm to the patient.[1] In instances in which the treatment or test is relatively low risk, and a child is at risk of immediate danger, even parent refusal of treatment can be ignored.[1] This was confirmed by a ruling from the U.S. Supreme Court in response to a Jehovah's Witness families denying life-saving blood transfusions to fatally ill children: "while parents are free to make martyrs of themselves, they are not free to make martyrs of their children".[1]

In the instance of early genetic testing, the patient - a newborn - is incapable of informed consent. Typically, the newborn's parents or legal guardians are his or her designated surrogates, and are therefore capable of making a decision about screening. Based on previous limits to surrogate control of autonomy, it might be argued that issues such as genetic screening should not be controlled by surrogates, but instead by some universal ethical board. However, an argument will be made later in this analysis to preserve patient autonomy and the right to choose genetic screening, as it in general improves participation rates and overall patient satisfaction.

One of the major issues associated with medical autonomy is the right to privacy. Privacy is a condition of limited access to a person and/or information regarding them.[1] In the medical world, privacy requires confidentiality, or the assurance that certain sensitive information - such as the results of genetic testing - will be protected.[1] Such protections insinuate that access to said information will be controlled by the patient or an authorized surrogate.

In reality, this is not always upheld. A major concern associated with genetic testing relates to the education of family members who may also be affected by a heritable disease. A patient may not wish to contact or disclose genetic information to certain family members, even though this may not be in the relatives' best interest. This often puts physicians in a difficult ethical situation. Studies have shown that a significant percentage of physicians will disclose - against a patient's request - genetic information to relatives if they feel that the relatives are in immediate danger.[1] Although the study does not disclose which genetic diseases in particular were analyzed, it can be inferred that most of them were conditions with diagnoses that were traditionally considered life-changing and untreatable - for example, Huntington's Disease. HH has no such stigma, largely due to the fact that it is so simple to treat. Therefore, although the issue of privacy is still relevant to HH screening, it is less of a concern than it would be in screening for untreatable, stigmatized conditions. Further, if all newborns are tested, there will be reduced concern about informing family members (as they will already be informed by testing of their own newborn, should they have one).

As a whole, privacy and confidentiality are concerned with who has access to sensitive information, and how that access is awarded.[23] In the context of genetic screening, these concepts are of paramount importance. Genetic information is directly related to an individual's identity,

and it is understandably disconcerting to believe that such information is available to random strangers. As an extension of such concerns, a variety of moral and legal principles, including federal and state laws, have been designed to protect patient autonomy and privacy.[1]

Despite these protections, absolute protection of privacy and confidentiality is near impossible as a result of modern technology. For example, in the context of one hospital visit, anywhere from dozens to hundreds of staff may have access to a patient's private medical records.[24] After the visit, that number only increases as information is passed on to primary care physicians and specialists, insurance companies, and public health organizations. Although it may be impossible to provide absolute autonomy and privacy, that does not mean improvements cannot be made to limit the number of individuals with access to sensitive information - such as genetic testing results - and give the patient as much power as possible over result distribution. Although this is a pressing bioethical issue, it applies to all medical testing and records, and is therefore beyond the scope of this analysis - if individuals are willing to undergo routine medical visits and testing, they are already exposing themselves to these issues.

As genetic screening becomes more commonplace, public health officials will face increasing pressure to disclose genetic test results.[10-11] However, this privacy violation comes at the benefit of medical research and public health programs; it can be used to inform physicians and researchers on how better to treat a variety of diseases, and how to distribute funding and resources.[8]

At the heart of autonomy is the right to choose.[25] Patients deserve the opportunity to decide what tests and procedures they will undergo, how their genetic material will be used, and who it will be shared with. However, certain circumstances require the limitation of autonomy in

the best interest of society. Although autonomy cannot be absolute, it can be preserved. At the end of the day, an understanding of one's genetic status with respect to heritable diseases is necessary to fully exercise autonomy. However, even that decision - whether or not exercise full autonomy - can also be protected.

Prior efforts to institute mandatory genetic screening for HH in Europe have failed for a variety of reasons. It is possible that one is this clear violation to the fundamental principle of autonomy: a mandatory screening program insinuates that patients will have no choice. In reality, studies have shown that designating a screening program as mandatory does not significantly increase the percent of individuals who participate.[1] The general public will look more favorably on a well-funded voluntary screening program, offered in conjunction with the United States mandatory newborn screening panel, which preserves their surrogate autonomy and right to informed consent. It is likely that more people will choose to participate - once they understand the risks associated with the disease - than would take part in a mandated screening program. To maximize protection of patient autonomy, any HH screening program should be optional, and operate under the full guidelines of confidentiality, privacy, and informed consent.

*Justice*

Medical justice refers to the overall fairness of medical practices and policies. Ideally, the burdens and benefits of medicine will be distributed equally among all groups in society.[20] Every individual has an equal right to access basic social goods, including medical diagnosis and treatment.[11] However, unequal distribution of resources - including individual circumstances such as socio-economic status, race, and geographic location - can reduce access to these social goods. Discrimination and stigmatization as a consequence of genetic predisposition can further reduce an individual's ability to access medical treatment.

In order to effectively utilize the right to the basic social good of medical treatment, an individual needs to understand his or her predisposition to genetic disorders and the appropriate treatment options.[11] In essence, this suggests that individuals must undergo screening to have full access to medical justice and its resources. As other bioethical issues prohibit mandatory screening, let us instead settle on the fact that the option to undergo screening is necessary for the fulfillment of medical justice.

Discrimination is a prominent concern in the context of medical justice and genetic testing. Historically, individuals with chronic or mental illness were involuntarily sterilized in the United States.[11] Although this process has long since been abolished, underlying fear that it will return - or that it continues to occur without widespread knowledge - prevails. On a less extreme level, modern discrimination is feared from employers, insurance companies, law enforcement officials and society..[1, 10-11] To avoid said discrimination, a variety of protective measures have been instituted over the past several decades. All medical practices, procedures and policies should conform to existing laws.[20] If existing laws do not support the best interest of patients, it

is the responsibility of physicians to instigate policy change that will further the patients' best interests according to the American Medical Association's Code of Medical Ethics.

Fear of discrimination in employment revolves around the belief that employers may choose not to employ individuals predisposed to conditions that will require regular and expensive treatment. Every year, the cost of providing health insurance for employees increases.[10] Predisposed employees will likely require more sick time benefits, and their ability to do their job may decrease if they are genetically predisposed to certain debilitating conditions.[11] All of these notions suggest that employers have a strong financial incentive to preferentially employ healthy individuals without predisposition to genetic disease. However, employment is about an employee's ability to fulfill a set of required tasks, and if an individual is capable of fulfilling said tasks - irrelevant of their genetic predisposition - they should not be discriminated against in hiring and firing decisions. To combat the concern of employment discrimination, the Equal Employment Opportunity Commission was established in 1995 so that employees experiencing discrimination on the basis of genetic predisposition could sue their employers.

Discrimination on the basis of genetic testing amongst insurance carriers would likely include required testing for some or all known genetic conditions and altered coverage, benefits and premiums dependent on the results.[11] Prior surveys suggest that many individuals already believe that insurance companies frequently discriminate against individuals with pre-existing conditions.[11] These hypothetical increased healthcare costs violate the fundamental principle of medical justice not only because they are discriminatory, but also because they reduce the individual's ability to access the universal social good of medical care. To combat the concern of

insurance discrimination, the United States established various programs, including: HIPPA, the Affordable Care Act (ACA), and the Genetifc Information Nondiscrimination Act (GINA). The ACA prohibits discrimination by insurance carriers on the basis of pre-existing conditions. GINA protects almost all individuals from genetic discrimination by both employers and insurers - members of the military are the only exception.

Law enforcement officials may also discriminate on the basis of genetic predisposition. However, this is perhaps the ideal circumstance for genetic discrimination: stored genetic data can be used to identify criminals with nearly 100% certainty.[10] DNA banks, originally intended for use in identifying deceased members of the military, can also be used to identify cold case criminals.[1, 10]

Finally, discrimination on a social level is also a concern with respect to genetic testig and medical justice. Family members (including parents of infants), friends, potential spouses, and other members of society may discriminate against individuals with known genetic predispositions. This relates to the critical protection of patient autonomy and privacy; patients have the right to control who, within society, is aware of their particular genetic predispositions.

In the specific case of HH, many of these concerns are insignificant. Individuals with HH who begin an inexpensive and effective treatment protocol early in life are extremely unlikely to experience debilitating complications, so well-informed employers and insurance companies are unlikely to discriminate. The use of genetic information for discrimination by law-enforcement and society, while somewhat difficult with respect to patient autonomy and privacy, is not a significant source of negative discrimination either. All in all, it appears that discrimination is not a pressing issue when considering a screening program for HH.

On a related note, many groups have also encountered stigmatization on the basis of genetic predisposition. Inherent to genetic diseases is their increased prevalence amongst certain social groups.[10] In some situations, said social groups feel stigmatized because they are targeted for genetic testing. In extreme situations, minority groups may see recommendations to abort affected fetuses or abstain from reproduction when affected by certain heritable conditions as a form of genocide.[1] Again, HH is an easily treatable and extremely common (as far as rare disease go) condition, so these issues are altogether moot.

A major concern in medical justice is the fair distribution of scarce resources, especially in the presence of competing needs.[1, 20] In the context of genetic testing, scarce resources include genetic specialists, testing facilities, and treatment centers. Trained genetic specialists are particularly rare outside of large urban areas. Primary care physicians often order genetic tests and interpret them without sufficient training because it is faster and cheaper than sending patients to genetic specialists.[11] However, this can result in incorrect interpretation of results and undue worry for patients and their families.

Following diagnosis with a treatable genetic disease, it is expected that patients and their families will pursue predictive and carrier testing of relatives and appropriate treatment programs. In the United States, many states financially support screening programs, but do not necessarily support coordinated treatment programs.[1] As a result, some families feel that genetic testing is irrelevant because treatment is not financially an option, and in fact only serves to stigmatize their family. The treatment and constant monitoring necessary to prevent fatal damage for many heritable diseases is expensive, and it makes some parents feel incapable of raising their children.[10] This prompts other ethical questions - should parents who cannot afford to treat

their children be required to give up said children? Should they be forcibly sterilized so that they do not have more children who they cannot treat?

All of these are pressing ethical concerns, but they are somewhat irrelevant in the context of HH. As mentioned in the disease summary, treatment for HH is - in most US regions - free and extremely effective. Assuming early diagnosis and regular blood donation, it is possible to live a completely normal life without severe complications or medical debt. In fact, in the long term it is cheaper to begin treatment early in life because patients will not incur medical costs related to the severe, late-stage complications of untreated HH. Overall, with respect to the bioethical principle of medical justice, HH appears to be an excellent opportunity to increase medical justice by making more affected individuals aware of their condition and the resources available to them, assuming that the entire population is also fully and accurately educated.

*Beneficence*

Medical beneficence refers to the intent of doing good for a patient.[20] In other words, all decisions that medical providers make should be in the best interest of the patient. This requires that medical providers be prepared, experienced, and qualified. At times it can be difficult to determine what will bring about the greatest good for a patient; health is a complicated concept that incorporates lifespan (mortality) and quality of life (morbidity).[21]

The critical extension of beneficence with respect to genetic testing is that screening must result in an improvement in the patient's life. This requires that a treatment be readily available, and early intervention should result in reduced mortality and/or morbidity.[22] There are hundreds of genetic predispositions that cannot be treated, so testing for them may only introduce unnecessary stress into the patient's life. However, HH is easily treatable, and the treatment is typically neither painful nor challenging to obtain.

Related to this is the question of when to inform parents and children of carrier or predisposition status. Although it is currently common practice for parents to receive the results of genetic testing (i.e. newborn screening) as soon as they are available, it may also be possible to delay receipt of results until the child is old enough to comprehend them.[1] For untreatable diseases, it may eventually also be possible to delay receipt of results until adulthood, as being informed earlier has no bearing on mortality or morbidity.[1] In the case of HH, it is easy to justify delaying release of screening results until later in life, as treatment does not begin until age sixteen. Therefore, informing patients and their families at a later point in time - say, when the patient is fifteen - will still provide the family adequate time to prepare for and treat the disease. For many individuals, understanding genetic predispositions actually relieves stress. It allows the

individuals to plan accordingly - financially and reproductively.[9] At the end of the day, medical beneficence is about increasing lifespan and improving quality of life; the impact of knowing about a genetic disease may or may not relieve stress, depending on the individual and their circumstances.[25] This is why the protection of autonomy is so critical.

Medical beneficence also suggests that the primary motivation of genetic testing should be to improve the patient's life, not the lives of the patient's relatives. For this reason, the Institute of Medicine determined that newborn screening is only appropriate for treatable conditions.[11] Otherwise, parents might agree to newborn screening solely for the purpose of planning future pregnancies, which does not benefit affected infants.[11]

Additionally, genetic testing can improve medical research and public health efforts. Sharing data to improve population-health studies can better inform treatment plans, allocation of resources, and emphasis during physician education.[8] In particular, genetic testing at an early age may allow patients to be tracked over the duration of their lives, providing more information on disease progression and the physical, emotional, and social impact of genetic testing.[1] Of particular interest is how genetic testing will impact reproductive decisions, which requires tracking from newborn genetic testing through reproductive age.[1]

Overall, the benefit of screening for HH is obvious - it saves lives. However, the ideal timing of screening and receipt of results is somewhat less clear. Early genetic testing - typically performed on newborns with a heel-stick blood test - is the only currently successful genetic screening program. In diseases such as HH, in which the results are not needed until the patient is approximately sixteen, testing could be delayed. However, prior investigation has suggested that families are less likely to bring older children and teenagers back into a medical office for

genetic screening, and the children themselves are more likely to refuse testing based on unrelated issues, including a dislike of needles. Altogether, it is far simpler - and less expensive - to simply test for HH and other late development conditions at the same time as newborn genetic screening, which is already required and enforced by the United States.

*Non-maleficence*

Medical nonmaleficence requires that a procedure do no harm to the patient or other members of society.[20] This requires an appreciation for the physical and emotional states of all affected individuals, and an understanding of the future implications and possible complications of the disease and any proposed treatments. If no treatment options are available, diagnosis may exclusively promote discrimination and psychological distress. Hence, untreatable diseases are rarely considered good options for early genetic testing.

If appropriate education and counseling is not provided to parents and children diagnosed with genetic conditions, unnecessary distress may also ensue.[1] For example, many non-medical professionals do not understand the concept of genetic disease carriers. If a child is identified in infancy as a carrier, parents may stigmatize the child, which can negate the benefit conferred by understanding the family history of genetic disease.[1] A major contributor to this issue is the fact that primary care physicians are often the medical professionals ordering and interpreting genetic tests.[11] In reality, understanding genetic testing is extremely complicated, and genetic specialists should be involved at every step to maximize medical nonmaleficence. However, this conflicts with medical justice, as not all groups will have access to said genetic specialists. A potential intermediate solution is improving education of primary care physicians with respect to genetic testing, which will improve the accuracy of their interpretations.

Clear interpretation and communication of genetic results is particularly important because affected individuals may view themselves as “defective” or “damaged”.[1] This can affect the emotional state of the individual and their family. In the case of childhood diagnosis, uneducated parents may inappropriately stigmatize affect children, leading to fewer financial

resources and social support for those children.[1] This is important even with respect to diseases such as HH, which have minimal detrimental effects when treated. If physicians and patients are not clearly educated about the disease and its treatment, they may experience unnecessary psychological suffering.

On the technical side of genetic testing, there is great concern over false results. In general, the issue is not false negatives (individuals who have the mutation but were not identified), but instead is false positives (individuals who do not have the mutation but were identified). False positives can result in confusion and lifelong anxiety for both patients and their families, especially if the results are not clearly explained or confirmed.[1] With respect to HH, the treatment is minimally painful and beneficial to society, so even individuals identified by way of false positive test results should be minimally affected.

Genetic testing may also reveal unusual family dynamics. Typically, this occurs when children are adopted or the biological father is not the spouse of the biological mother.[1, 22] In autosomal recessive diseases such as HH, both biological parents must carry at least one mutant copy of the gene for the child to inherit the disease. If one of the child's parents does not test positive for the gene, it is highly unlikely that that parent is biologically related to the child. This can be disruptive to both children and parents. A potential solution to this issue is delaying release of the test results and/or not requiring parents of affected children to be tested. However, this does not eliminate the possibility that the child may find out about their alternative family status at a time prior to when they might otherwise find out.

Overall, there is minimal concern that HH genetic screening will result in additional physical or emotional duress that is not already applied to these families as a result of the

mandated United States newborn screening program. By making the screening of additional diseases voluntary and improving educational programs, families sensitive to emotional distress as a result of disease diagnosis can decide for themselves if screening is the best option for their family.

*Conclusion*

Genetic disease is often a silent killer. In the case of HH, that does not need to be true. Although genetic screening is a complex bioethical issue, HH appears to be an ideal candidate. By establishing a screening protocol that encourages voluntary choice after thorough education and informed consent, along with working to establish and enforce additional privacy protection standards, a HH screening program will satisfy patient autonomy. By educating additional genetic specialists and all social groups - physicians and patients - the program will satisfy medical justice. Based on the ease and effectiveness of the treatment, an HH screening program will easily satisfy beneficence. And finally, assuming a voluntary program, it will also satisfy nonmaleficence by giving individuals the choice to protect their emotional state, if that is of major concern to them.

One major improvement in the medical system that needs to occur with or prior to establishment of this program is increased educational measures geared towards both patients and physicians. Awareness is critical for patients to understand why diagnosis is necessary, how to receive treatment and make the most of resources, and how to support family members as they undergo the screening process. Similarly, if physicians are unaware of the dangers that a disease poses, they are not capable of protecting their patients effectively, which leaves them vulnerable to legal consequences.[1] Although informed consent will become increasingly challenging as more disorders are tested for simultaneously, it is absolutely critical that the time and resources are taken to ensure that it is preserved. It is very possible that part of this increasingly complex process will be an option to delay receipt of testing results, which will give families time to further research and understand the implications of their diagnosis status.

By screening for HH, we have the opportunity to massively reduce mortality and morbidity in the United States, and possibly across the globe. Although versions of an HH screening protocol have been proposed and denied across Europe, the United States is often considered a leader in innovative medicine and prevention techniques. An established, successful screening protocol in the United States will set a strong standard for other countries to follow. Ideally, in the next decade, screening programs for HH and many other genetic diseases will be established globally so that affected individuals can begin receiving the treatment that they need and deserve.

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