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Precision medicine and Friedreich ataxia: promoting equity, beneficence, and informed consent for novel gene therapies

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Abstract
Friedreich Ataxia (FA) is an incurable neurodegenerative disease with systemic consequences affecting vital organs including those of the central and peripheral nervous systems. This article will use FA as an example to explore some of the practical and ethical issues emerging in precision medicine for rare diseases. It will first describe the existing management strategies available for FA patients, before considering the potential impact of gene therapy trials on the prevention and treatment of disease symptoms. Finally, ethical considerations will be discussed, including equity of access and managing resource allocation dilemmas; balancing benefits, burdens and harms; and gaining informed consent for novel treatments.

Introduction

Friedreich Ataxia (FA) is an incurable neurodegenerative disease with systemic consequences affecting vital organs including those of the central and peripheral nervous systems [6]. Approximately one in 29,000 people are affected and while this classifies FA as a rare disease, it remains the most common form of hereditary ataxia with 1 in 85 Caucasians being disease carriers [18, 44]. First symptoms often present at the age of 5-25 years and become progressively worse. In early disease, patients suffer from an unsteady gait, and many become full-time wheelchair-users within ten years of diagnosis [33]. In later stages of the disease, severe symptoms including slurred speech, dysphagia, spasticity, and compromised vision ensue [10, 20, 44]. Approximately 60% of patients succumb to a premature death at 35 years or younger due to heart complications [33, 37, 39].

In 96-98% of cases, FA is caused by an autosomal recessive inheritance of a guanine-adenine-adenine (GAA) repeat expansion in intron 1 of the frataxin (FXN) gene [29, 33]. A minority of FA patients are compound heterozygotes for this mutation [13]. Healthy individuals normally carry up to 36 GAA repeats but people with FA are found to have more than double, typically 120 to 1700 repeats [7, 29]. The length of the GAA repeats is positively correlated to the severity of FA symptoms, with studies suggesting an inverse correlation between GAA expansion length and disease onset age, as well as a positive correlation between expansion size and disease progression [36]. The FXN gene codes for a ubiquitously expressed protein that is responsible for controlling iron transport and respiration in the mitochondria [33]. However, the GAA repeat expansion partially silences the FXN gene and reduces FXN protein levels. Consequently, iron accumulates in cells and tissues, triggering lipid peroxidation, oxidative stress, inflammation and cell death [6].

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This article will use FA as an example to explore some of the practical and ethical issues emerging in precision medicine for rare diseases. It will first describe the existing management strategies available for FA patients, before considering the potential impact of gene therapy trials on the prevention and treatment of disease symptoms. Finally, ethical considerations will be discussed, including equity of access and managing resource allocation dilemmas; balancing benefits, burdens and harms; and gaining informed consent for novel treatments. This paper adopts an applied principlist methodology due to its wide applicability to assessing both stakeholder-specific and population-wide ethical implications of novel treatment paradigms and its focus on universal principles with relevance across various cultures and age groups [1].

Existing and emerging treatments for FA

The sole clinically-approved FA drug, omaveloxolone, is only accessible to the patients over the age of 16 residing in the United States and countries within the European Union [3]. Furthermore, omaveloxolone primarily acts as an inducer of the Nrf2 oxidative stress pathway and it was not designed to restore normal levels of FXN [6, 32, 44]. The optimal treatment must be able to restore normal levels of FXN protein expression and/or reduce oxidative stress and inflammation while restoring mitochondrial function [6]. As the saying goes, "prevention is better than cure," thus recent research efforts have mostly focused on increasing levels of FXN gene expression in affected individuals, with the hope of halting the onset of the downstream pathological processes. This has led to investigations involving gene therapy to determine if it can offer a sustainable and safe option for FA patients. Due to the nature and typical onset pattern of FA, candidates for gene therapy are likely to include newborns or children, highlighting additional ethical complexity when seeking informed consent for experimentation.

Gene therapy has been approved for treatment of related ataxias involving different kinds of DNA repeats [25]. This form of therapy can be delivered into patients via viral and non-viral vectors [26]. While non-viral vectors have been shown to exert low immunotoxicity in patients, their efficacy in successfully entering cells and integrating the "corrected" gene into the host genome is questionable. This has shifted the focus to the use of viral vectors due to the infectious nature of viruses and their capacity to successfully transfect the host cells with their genetic material, in gene therapy [26]. Such vectors can sustain prolonged expression of the target gene delivered and while harmless antibodies in response to the viral vectors may develop over time, concerns surrounding irreversible systemic genetic modifications, immunotoxicity and increased cancer risk prevail; thus limiting the uptake of such trials [4, 26].

Some studies have used viral vectors to mediate the transplantation of haematopoietic stem and progenitor cells to deliver normal FXN proteins to the patient but the fear of host rejection and the toxicity of overexpressing the FXN gene also threatens the feasibility of this treatment [30, 34]. However, for Friedreich ataxia patients where there is no cure but only a single clinically-approved treatment exists for certain age groups and individuals in some countries, gene therapy is still seen as an attractive therapeutic option to stop the progression of this debilitating disease in order to maintain a relatively good quality of life [37]. A study investigated the perceptions of at least 133 participants (64% patient and 36% parent/caregiver) with regards to gene therapy. This study reported that there was general consensus that "the most severe patients with FA should be treated first" but participants were unsure if "children should be treated with gene therapy before adult patients"; and approximately 40 to 50% of the participants were willing to try the therapy immediately even if it is given at a more conservative "lower" dose and knowing the risks and possible side effects [37]. Many pre-clinical studies examining the prospects of viral vector-mediated gene therapy using animal models have been reviewed but to our knowledge, there is only one ongoing trial that uses an adeno-associated virus (AAV) to deliver gene therapy (i.e. LX2006) in patients with FA [22, 26, 35]. LX2006 directly targets the cardiac muscle cells via intravenous injections into the patient with the aim to transfer a normal functioning FXN gene to these cells that will increase mitochondrial FXN protein level which will sustain mitochondrial function and prevent apoptosis [22, 24]. However, only FA patients who demonstrated first symptoms younger than the age of 25, with FA cardiomyopathy and with satisfactory levels of antibodies are eligible for this trial. Hence, only a small subset of patients would be able to trial this gene therapy.

The use of genetically-modified organisms (GMO) or their constituents (e.g. viral vectors) in gene therapy poses a biological hazard and therefore there is a need for rigorous risk assessment and critical scrutiny in managing the administration of the said treatment and the removal of waste from the patient that may contain viral vector-based GMO (including in their feces) [43]. GMO-contaminated wastes introduced to the environment can impact agriculture, animal husbandry and biodiversity that may consequently generate food from sources with cumulative mutations over time that may have long-term health risks [38, 40]. Therefore, medical staff involved in providing gene therapy to patients will need to be trained to safely and legally handle GMO medicines, dispose of any waste materials including biological specimens from patients in a biosafety hazard container for subsequent decontamination, and engage in hygienic practices which

minimizes the risk of infection in the patient receiving the gene therapy [43]. This raises the question if patients will need to make alternative sanitary arrangements in relation to their excrement disposal at home or in public settings, which has been an active debate amongst clinicians. The majority of the viral particles from the patients are shed into their urine and feces which are removed via household and sewage water before entering the environment. One study assessed the impact of AAVs that have exited the patient's body on the natural environment [9]. It was comforting to learn that 90% of AAV-containing solid sewage (i.e. sludge) is degraded within 3 h of disposal and it was found that the half-life of the AAVs in water is seven days [9]. While the number of vector particles shed by a patient are reported to be relatively high, these amounts are too low to elicit a successful transduction, as confirmed by in vitro tests conducted by Pfizer, the pharmaceutical company [9]. This study concluded that viral particles shed in human waste do not remain stable and/or soluble once they enter a typical wastewater treatment facility to be treated and therefore do not present as a threat to the natural environment [9]. A simplified and risk-based regulation of medicinal GMOs need to be implemented to help significantly reduce the time required to deliver much needed life-saving medicines to FA patients without compromising patient safety or posing a potential risk to the environment.

Resource allocation dilemmas: ethical issues regarding equity of access to treatment

A major ethical issue regarding FA relates to equity of access to treatment and diagnosis. As noted above, access to omaveloxolone is currently limited according to geographic location, age, and financial status, with online distributors advertising the brand-named 50-mg pills at $360USD each ($32,477 for a box of 90) and noting there are no generic alternatives [8]. While some financial assistance options are listed, these are again restricted to citizens of certain countries with confirmed diagnoses who meet various other conditions. Likewise, gaining access to experimental drugs, including TAK-831 and CTI-1601, through clinical trials is only possible for patients meeting strict eligibility criteria [30]. Perlman [30] notes that at present, most patients with cerebellar ataxias are only able to receive medications and therapies that target the various symptoms that "complicate an ataxic illness," such as "tremor, myoclonus, dystonia, and rigidity…[s]pasticity, pain, fatigue, depression, sleep disturbances, cognitive decline, and bowel and bladder dysfunction, if they occur" (p. 1664). Accepting there will likely never be "one 'magic bullet'" that can address all these complications or "be approved as 'the cure' for ataxia," Perlman suggests there will instead "most likely be a 'cocktail' of agents, some disease-specific and some ataxia-specific, that will ultimately turn the neurodegenerative cerebellar disorders into treatable diseases" (p. 1663). However, cocktails are expensive, and pharmaceutical cocktails even more so, thereby significantly increasing the potential disparities between health outcomes for FA patients on socio-economic grounds. Like many chronic and incurable diseases, reliance on multiple medications for symptom management increases overall cost and therefore the treatment gap between patients covered by national or private insurances schemes and those who must privately fund their (or their child's) treatment. Families lacking financial resources in the latter category may not be able to afford all components of the current best practice "cocktail," thereby diminishing efficacy. A future curative option, whether it be pharmaceutical or achieved through gene therapy, would reduce these lifelong costs while contributing significant improvements to quality of life.

One of the reasons developing new FA treatments is so expensive is the condition is classified as rare, which in the EU means it manifests in less than five people per 10,000 population, and in the US means it affects less than 200,000 citizens in total [28]. This substantially increases the cost of conducting a statistically valid clinical trial as there are fewer patients in the clinical trial community and thus participants must be recruited across various geographical regions. Increased costs in research and development are then translated into higher costs when future treatments are approved, particularly when the total number of future consumers is also expected to be comparatively low. Palau [28] relates that the International Rare Diseases Research Consortium listed as one of its 2017-2027 goals that persons with rare diseases receive "accurate diagnosis, care, and available therapy, with 1 year of coming to medical attention" (p. 149). However, this author also notes that such a goal is dependent on expanding available genomic testing and genetic therapies, interventions that are only available in advanced facilities at considerable expense. Using LX2006 as an example, this gene therapy candidate carries both "rare pediatric disease" and "US orphan drug" designations [22]. This means that the US Food and Drug Administration [11] incentivizes drug development through granting certain tax credits, waiving user fees, and promoting the potential for a seven-year market exclusivity period following approval, in recognition of the limited market for a rare disease treatment [11]. Assuming some of the emerging gene therapies discussed previously in this paper become successful, benefiting from these also first requires individualized genomic profiling [28], which is financially out of reach for many individuals and families.

FA does not just demonstrate inequity in treatment access but also inequity in clinical outcomes even among

advantaged communities, due in large part to delayed diagnosis leading to irreversible cardiac damage. Hanson et al. [16] note up to 5% of FA patients initially present with severe cardiomyopathy without traditional neurological symptoms. However, early diagnosis and preventive care often rely on access to genetic testing, which may not always be available or financially possible [19]. Similarly, detection of cardiac dysfunction often depends on the use of high-resolution imaging techniques, while cerebellar atrophy can be visualized using magnetic resonance imaging (MRI) [5, 23]. In much of the world, access to these technologies is severely limited, and even in highly developed healthcare systems there are often out-of-pocket expenses.

From a global health equity perspective, it is particularly telling that although the epidemiology of FA in Caucasian populations is well described, the first genetically confirmed case in a West African family was reported as recently as 2021 [5]. The authors of the relevant case report note once genetic testing becomes more widely available to families in African nations, understanding of FA and its phenotypic variability may improve, concluding: "In addition, whole genome sequencing of cohorts in diverse populations may identify other disease-modifying variants that could be used as therapeutic targets." While such sequencing may not be necessary for individual diagnosis, these authors suggest the information will be essential for building more diverse profiles for FA beyond its typical manifestation among those of European descent. More complete data regarding FA's genetic epidemiology and global inheritance patterns is essential to further characterize the disease and develop new treatments. However, while increasing the diversity of research participants in trials of FA drugs and future gene therapies is necessary, as with all forms of precision medicine, there are widespread criticisms regarding the potential for knowledge gained from such studies to only benefit wealthier patients and populations. As Galasso [14] and Viaña [41] note, "downstream exclusivity" means the therapeutic products developed from medical research may be inaccessible to marginalized populations, or simply fail to confer any benefits due to being designed for other patients (typically those of European ancestry). If FA being rare among Caucasians is limiting drug development, this issue must be compounded further for non-Caucasian patients where disease manifestation is rarer still.

A further equity concern relates to the allocation of finite resources within the broader healthcare system. Both domestically and internationally, novel gene therapies represent a costly intervention and have demonstrated limited successes to date. From a resource allocation perspective, the high cost of these treatments (and their associated trials) also represent an opportunity cost for both privatized and socialized healthcare systems, where the costs of providing access to treatments for one patient group must necessarily be balanced against the needs of others. As discussed previously, there is also disagreement regarding whether children with FA should be given preference for new treatments compared to adults, or whether limited supplies should only be targeted to the most severe cases, which speak to both resource allocation and safety considerations. For FA, newborns and children are ideal candidates for gene therapy, especially given the trajectory of the disease and impact on life expectancy. However, children cannot consent to the risks of unproven gene therapies or the associated burdens of these interventions. These issues will now be considered further in terms of the need to balance the potential burdens and benefits of novel gene therapies.

Balancing benefits, burdens, and harms in novel gene therapy

A clear benefit of improving genetic testing and individualized therapies for FA relate to its status as an inherited condition. More accurate diagnostic processes for one patient necessarily impact other genetically related individuals at higher risk of the condition, while better therapies can reduce the negative effects of the disease for the whole family, even when only one member may be directly affected. Papadopoulou et al. [29] suggest that identifying and testing family members at risk of inherited neurological conditions can improve disease surveillance and management in cases where mutations are detected and avoid "needless anxiety" in cases where they are not. However, this highlights the potential of genetic testing to cause social harm, as some family members may not want to know that they are at increased risk of disease or likely to have carrier status, but have this knowledge forced upon them if another family member chooses to get tested. Even in cases where the actual increased risk is small, changes to an individual's perceived risk may still be distressing.

When whole genomic sequencing forms part of the approach to precision medicine the risks to family members' genetic privacy is also exacerbated. Berkman and Hull [2] suggest the "right not to know" regarding genetic testing is often justified by appealing to respect for decisional autonomy and a desire to protect patients from potentially harmful information (29). However, this has implications for offspring, particularly regarding the potential for early intervention in the case of FA. If any increased likelihood of disease is already known, other tests can be engaged earlier than would be applied symptomatically, thereby potentially avoiding some of the negative sequalae of FA, including cardiac damage. Arguments in ethics scholarship favoring waiting for pediatric patients to reach adulthood before offering genetic

testing for risk profiling may be less compelling in the case of FA, where disease symptoms often manifest in childhood and there are strategies available to slow disease progression. In cases where disease carriers have not yet reproduced, genetic testing will enable individuals to make informed decisions surrounding family planning and might also provide the opportunity to use prenatal or preimplantation genetic diagnosis to avoid disease transmission [29]. Prenatal diagnosis for FA has been reported in the literature since 1989, with its first use to provide information for a family with one already affected child [42]. The latter interventions only benefit patients in locations where such techniques are accessible and where they have legal and socio-cultural support.

Beyond genetic testing there are also safety considerations regarding proposed gene therapies for FA. Perlman [30] notes that although multiple trials using AAV vector-based gene replacement therapies are ongoing, the "[m]anagement of the anti-capsid and anti-transgene neuroinflammatory responses as it impacts safety and efficacy remains a challenge" (p. 1663). She notes gene editing using CRISPR-Cas9 and epigenetic approaches that can stimulate the normal expression of the FXN gene to transcribe the correct protein despite the mutation are also being explored [30]. CRISPR-Cas9 represents a valuable tool in gene therapies, allowing for addition, deletion, and alteration of sections of DNA, with Palau [28] claiming it has become the "most reliable system for gene editing" currently available (p. 148). Ormond et al. [27] note CRISPR-Cas9 could be used in FA either to delete the pathological triplet repeats and/or insert a functional gene, by splicing the genome at a particular point and exploiting the body's natural DNA repair mechanisms. To date, no such therapies are available and the successful development of such interventions would require significant experimentation with many potential risks. Gouw [15] notes there are four "scientific concerns" with such gene editing, summarizing these as "off-target effects, on-target effects, epigenetic effects, and chimerism," in addition to various "social justice concerns," focused on inequitable access to novel gene therapies due to socioeconomic differences (25). Off-target effects occur when the intervention misses the intended gene or region of DNA (potentially hitting other genes), while on-target effects refer to when the correct location is acted upon but there are unintended side-effects, such as large deletions, translocations, over-activation of target genes or activation of harmful genes [21]. A gene therapy for FA that compromised the function of FXN would fall into this category. Epigenetic alterations affect gene activation, deactivation, protein transcription and responses to the environment, without changing the DNA itself, while chimerism refers to when uptake of the gene modifications does not occur in all target cells, leading to a mixture of modified and unmodified genes in the patient. In all these cases, the possible outcomes range from having no effect, to reducing the efficacy of a treatment or natural process, to causing genes or their encoded proteins to develop hyperactive, toxic, or even lethal functions, to entirely knocking out a system that is essential for survival. As discussed previously, some GMO products used in gene therapies also pose a potential biological hazard to the community [43]. Finally, as noted above, when considering social justice concerns, equity issues are even more concerning when approached on a global scale. While CRISPR-Cas9 is generally considered a fast and cheap alternative to other genetic modification techniques, some argue this also makes it riskier, more difficult to regulate globally, and more likely to be abused by private entities [12]. Equitable distribution of CRISPR gene editing services is also unlikely to be achieved either within or across populations.

Informed consent: hope, hype, exploitation, and medical paternalism

A final ethical consideration to be discussed here relates to the challenges of gaining informed consent for novel gene therapies. As with all genetic analyses, any referral for FA testing should also include a referral to appropriate genetic counselling services and results should be communicated in a way that is sensitive and comprehensible [29]. Perlman [30] also reminds healthcare providers that even though FA has no cure, there is "always something [they] can do, even if it is just educating, listening, and having the conversation" about disease management (p. 1663). These are essential elements of patient care which help families interpret their risk, understand genetic inheritance patterns, and make informed decisions about testing, preventive interventions, and adaptive strategies to cope with disease symptoms; thus, bringing some level of comfort to patients and hope for the future [28]. However, given the substantial variance in symptom onset and severity, gaining informed consent for novel gene therapies remains a challenge. Potential use of GMOs in FA gene therapy may also lead to harsh demands on patients in terms of lifestyle modification, including the handling of waste products [43]. Hohenfeld et al. [18] note that FA patients often present in childhood or adolescence, and it would be reasonable to assume that those predicted to have the most severe symptoms would be most likely to pursue novel therapies, even if they carried substantial risks and costs. But with the heterogeneous nature of the condition and subsequent significant prognostic uncertainty in FA, these authors note it is often difficult to answer questions about disease progression, suggesting predictive modelling may assist in this area by "employing techniques of statistical learning." They identify loss of ambulation to be a particularly burdensome

symptom for many FA patients, claiming a predictive model could estimate the time interval to lost function for this and other faculties. As noted previously though, the data required for such analyses must first be sourced from somewhere, and in this case, it will be FA patient populations.

A major ethical concern with using individuals with FA for research is the risk of exploitation. Given the disease has no cure, patients and their families may be unduly influenced to participate in clinical trials, including for novel gene therapies. Macrae [23] notes orphan diseases are already responsible for accelerating drug development for various conditions, suggesting it is "feasible to consider active 'orphanization'" of certain symptoms of FA "to drive more efficient clinical trials" (680-1). The argument that certain people must be willing to take risks for the greater good of medical advancement falls into what Harris [17] refers to as "instrumentalization," that is, the use of individuals "as a means to the purposes of others" (355). Given the potential vulnerability of patients with an inherited neurological disease, it is vital that participation in clinical trials is a truly voluntary choice. This is further complicated when considering parents and guardians will often have to make decisions regarding treatment and trial involvement for minors, and they may have other children who stand to benefit from the results of one child's participation.

Ensuring fair distribution of the burdens and benefits of medical research is a basic justice requirement, as is preventing exploitation of vulnerable research populations. Nevertheless, FA patients and their families have the same rights to contribute to research as other citizens and it is equally important to avoid instances of medical paternalism limiting personal autonomy here. Plows and Boddington [31] note "biocitizenship" is a term applied to disease communities who use their collective force to pressure governments and other institutions to listen to concerns regarding "access, price, quality and availability of treatments and cures—in other words, *over increasing access to the fruits of biotechnology*" (121). As such, the right to be involved in the development of emerging FA treatments, including those involving precision medicine, is a biopolitical issue. Like many biocitizen groups, FA communities have a disease and/or genetic risk factor in common and may be motivated to agitate for regulatory changes that promote their interests.

Conclusion

Advances in precision medicine hold much promise for diagnostic and preventive medicine, with novel gene therapies remaining the focus in the generation of a panacea for rare inherited neurological disease such as FA. Nevertheless, there are significant safety concerns that need to be addressed and issues of vulnerability when it comes to participant recruitment for clinical trials. Given the risks and uncertainty surrounding these gene therapies, measures to enhance informed consent are needed. At the same time, equity issues need to be considered to ensure the outcomes of medical research reach all who would stand to benefit from them. As with all novel therapies, substantial research and implementation costs need to be balanced against competing needs in the healthcare sector, particularly under conditions of resource scarcity.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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References

1. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. 8th ed. Oxford: Oxford University Press; 2019.
2. Berkman BE, Hull SC. The right not to know in the genomic era: time to break from tradition? Am J Bioeth. 2014;14(3):28–31.
3. Biogen. 2024. Biogen received European Commission approval for Skyclarys® (omaveloxolone), the first therapy to treat Friedreich's ataxia. *Biogen* media release, February 12, 2024. https://investors.biogen.com/news-releases/news-release-details/biogen-received-european-commission-approval-skyclarysr
4. Chen W, Hu Y, Ju D. Gene therapy for neurodegenerative disorders: advances, insights and prospects. Acta Pharm Sin B. 2020;10:1347–59.
5. Cissé CAK, Cissé L, Ba HO, Samassékou O, Simaga A, Taméga A, Diarra S, Diallo SH, Coulibaly T, Diallo S, Yalcouyé A, Maiga AB, Keita M, Fischbeck KH, Traoré SF, Guinto CO, Landouré G, from the H3Africa Consortium. 2021. Friedreich ataxia in a family from Mali, West Africa/Friedreich ataxia in a Malian family. Clin Case Rep, 9(5), e04065.
6. Cook A, Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. Br Med Bull. 2017;124:19–30.
7. Cossée M, Schmitt M, Campuzano V, Reutenauer L, Moutou C, Mandel JL, Koenig M. Evolution of the Friedreich's ataxia trinucleotide repeat expansion: founder effect and premutations. Proc Natl Acad Sci U S A. 1997;94:7452–7.
8. Drugs.com. 2024. Skyclarys prices, coupons and patient assistance programs. https://www.drugs.com/price-guide/skyclarys
9. Fleischmann T. Assessing the environmental fate of rAAV in activated sludge and water: implications for environmental risk assessments and GMO regulatory frameworks. J Environ Manage. 2023;345:118754.

10. Folker J, Murdoch B, Cahill L, Delatycki M, Corben L, Vogel A. Dysarthria in Friedreich's ataxia: a perceptual analysis. Folia Phoniatr Logop. 2010;62:97–103.
11. Food and Drug Administration (FDA). 2022. Medical products for rare diseases and conditions. https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions
12. Furrow BR. The CRISPR-Cas9 tool of gene editing: cheaper, faster. Riskier? Annals Health L. 2017;26(2):33–51.
13. Galea CA, Huq A, Lockhart PJ, Tai G, Corben LA, Yiu EM, Gurrin LC, Lynch DR, Gelband S, Durr A, Pousset F, Parkinson M, Labrum R, Giunti P, Perlman SL, Delatycki MB, Evans-Galea MV. Compound heterozygous FXN mutations and clinical outcome in friedreich ataxia. Ann Neurol. 2016;79:485–95.
14. Galasso I. Precision medicine for whom? Public health outputs from Genomics England and all of us to make up for upstream and downstream exclusion. Am J Bioeth. 2024;24(3):71–85.
15. Gouw AM. CRISPR challenges and opportunities for space travel. In: Szocik K, editor. Human Enhancements for space missions: Lunar, Martian, and future missions to the outer planets. Switzerland: Springer Nature; 2020. pp. 19–34.
16. Hanson E, Sheldon M, Pacheco B, Alkubeysi M, Raizada V. Heart disease in Friedreich's ataxia. World J Cardiol. 2019;11(1):1–12.
17. Harris J. Goodbye Dolly? The ethics of human cloning. J Med Ethics. 1997;23:353–60.
18. Hohenfeld C, Terstiege U, Dogan I, Giunti P, Parkinson MH, Mariotti C, Nanetti L, Fichera M, Durr A, Ewenczyk C, Boesch S, Nachbauer W, Klopstock T, Stendel C, Rodríguez de Rivera Garrido, Schöls FJ, Hayer L, Klockgether SN, Giordano T, Didszun I, Rai C, Pandolfo M, Rauhut M, Schulz H, J. B., Reetz K. 2022. Prediction of the disease course in Friedreich ataxia. *Nature Scientific Reports*, 22, 19173.
19. Jensen MK, Bundgaard H. Cardiomyopathy in Friedreich ataxia: exemplifying the challenges faced by cardiologists in the management of rare diseases. Circulation. 2012;125(13):1591–3.
20. Keage MJ, Delatycki MB, Gupta I, Corben LA, Vogel AP. Dysphagia Friedreich Ataxia Dysphagia. 2017;32:626–35.
21. Lee H, Kim J-S. Unexpected CRISPR on-target effects. Nat Biotechnol. 2018;36:703–4.
22. Lexeo Therapeutics. 2024. Friedreich's ataxia: LX20006. *Lexeotx.com*. https://www.lexeotx.com/programs/cardiac-programs/friedreichs-ataxia/
23. Macrae CA. Rare diseases inform myocardial phenotypes for precision medicine. J Card Fail. 2018;24(10):680–1.
24. Mayo Clinic. 2024. Gene therapy for cardiomyopathy associated with Friedreich's ataxia. *Mayo Clinic Clinical Trials* database. https://www.mayo.edu/research/clinical-trials/cls-20542201
25. Novartis. 2020. Novartis provides update on AVXS-101 Intrathecal Clinical Development Program. *Novartis* news, September 23, 2020. https://www.novartis.com/news/media-releases/novartis-provides-update-avxs-101-intrathecal-clinical-development-program
26. Ocana-Santero G, Díaz-nido J, Herranz-Martín S. 2021. Future Prospects of Gene Therapy for Friedreich's Ataxia. Int J Mol Sci, 22.
27. Ormond KE, Mortlock DP, Scholes DT, Bombard Y, Brody LC, Faucett WA, Garrison NA, Hercher L, Isasi R, Middleton A, Musunuru K, Shriner D, Virani A, Young CE. Human germline genome editing. Am J Hum Genet. 2017;101(2):167–76.
28. Palau F. Pediatric genomics and precision medicine in childhood. In: Faintuch J, Faintuch S, editors. Precision Medicine for investigators, practitioners and providers. Cambridge M. A.: Academic; 2020. pp. 143–52.
29. Papadopoulou E, Pepe G, Konitsiotis S, Chondrogiorgi M, Grigoriadis N, Kimiskidis VK, Tsivgoulis G, Mitsikostas DD, Chroni E, Domouzoglou E, Tsaousis G, Nasioulas G. The evolution of comprehensive genetic analysis in neurology: implications for precision medicine. J Neurol Sci. 2023;447:120609.
30. Perlman SL. Update on the treatment of ataxia: medication and emerging therapies. Neurotherapeutics. 2020;17:1660–4.
31. Plows A, Boddington P. Troubles with biocitizenship? Genomics Soc Policy. 2006;2(3):115–35.
32. Profeta V, McIntyre K, Wells M, Park C, Lynch DR. Omaveloxolone: an activator of Nrf2 for the treatment of Friedreich ataxia. Expert Opin Investig Drugs. 2023;32:5–16.
33. Reetz K, Dogan I, Costa AS, Dafotakis M, Fedosov K, Giunti P, Parkinson MH, Sweeney MG, Mariotti C, Panzeri M, Nanetti L, Arpa J, Sanz-Gallego I, Durr A, Charles P, Boesch S, Nachbauer W, Klopstock T, Karin I, Depondt C, Hagen V, Schöls JM, Giordano L, Klockgether IA, Bürk T, Pandolfo K, M., Schulz JB. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational studies (EFACTS) cohort: a cross-sectional analysis of baseline data. Lancet Neurol. 2015;14:174–82.
34. Roberts R. 2021. Using CRISPR to defeat Friedreich's ataxia: A precision disease model and a novel cell therapy. *CRISPR Medicine News*, July 6, 2021. https://crisprmedicinenews.com/news/using-crispr-to-defeat-friedreichs-ataxia-a-precision-disease-model-and-a-novel-cell-therapy/
35. Sivakumar A, Cherqui S. Advantages and limitations of Gene Therapy and Gene Editing for Friedreich's Ataxia. Front Genome Ed. 2022;4:903139.
36. Tiberi J, Segatto M, Fiorenza MT, La Rosa P. 2023. Apparent Opportunities and Hidden Pitfalls: The Conflicting Results of Restoring NRF2-Regulated Redox Metabolism in Friedreich's Ataxia Pre-Clinical Models and Clinical Trials. *Biomedicines*, 11.
37. Trantham SJ, Coker MA, Norman S, Crowley E, Berthy J, Byrne BJ, Subramony S, LOU X, Corti M. Perspectives of the Friedreich ataxia community on gene therapy clinical trials. Mol Therapy - Methods Clin Dev. 2024;32:101179.
38. Tsatsakis AM, Nawaz MA, Tutelyan VA, Golokhvast KS, Kalantzi O-I, Chung DH, Kang SJ, Coleman MD, Tyshko N, Yang SH, Chung G. Impact on environment, ecosystem, diversity and health from culturing and using GMOs as feed and food. Food Chem Toxicol. 2017;107:108–21.
39. Tsou AY, Paulsen EK, Lagedrost SJ, Perlman SL, Mathews KD, Wilmot GR, Ravina B, Koeppen AH, Lynch DR. Mortality in Friedreich ataxia. J Neurol Sci. 2011;307:46–9.
40. Van Eenennaam AL. GMOs in animal agriculture: time to consider both costs and benefits in regulatory evaluations. J Anim Sci Biotechnol. 2013;4:37.
41. Viaña JNM. All from us or all with us: addressing precision medicine inequities requires inclusion of intersectionally minoritized populations as partners and project leaders. Am J Bioeth. 2024;24(3):111–4.
42. Wallis J, Shaw J, Wilkes D, Farrall M, Williamson R, Chamberlain S, Skare JC, Milunsky A. Prenatal diagnosis of Friedreich ataxia. Am J Med Genet. 1989;34(3):458–61.
43. Webb TL, Hong E. GMO Medicines and hospital pharmacy practice: a review. J Pharm Pract Res. 2021;51:203–10.
44. Yang W, Thompson B, Kwa FAA. Molecular approaches for the treatment and prevention of Friedreich's ataxia. Drug Discov Today. 2022;27:866–80.

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