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Drug development for neglected ultra-rare diseases of no commercial interest: Challenges and opportunities

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Ultra-rare diseases, particularly those that affect a few hundred patients worldwide, are of little commercial interest to the pharmaceutical industry. Patient-led organizations have made remarkable progress in funding the early-stage, academic development of therapies for such neglected ultra-rare conditions. But the long and difficult path to translate most academic proof-of-concept studies into approved medicines means that very few therapies ever reach patients. Here, we discuss some of the roadblocks to the development of therapeutics for conditions of limited commercial interest and propose ways to overcome these obstacles.

Keywords: ultra-rare disease; philanthropy; patient advocacy

Introduction

Rare and ultra-rare diseases are commonly defined, somewhat arbitrarily, on the basis of their incidence and prevalence. Ultra-rare diseases have been defined as conditions that affect fewer than 1 in 50 000 people, which equates to approximately 7000 people in the United States.(p1) Owing to its operational nature, this definition lacks enough granularity to acknowledge the wide variety of conditions that fall under this umbrella, some of which might affect only tens of people worldwide.

Several authors have proposed new terms such as nano-rare, micro-rare, and hyper-rare to consider diseases with extremely low prevalence.(p2),(p3) Although these terms are useful, here we will use 'neglected ultra-rare diseases' to specifically refer to conditions so uncommon that they are of little or no interest to the pharmaceutical industry.

We acknowledge that this definition is also arbitrary, but argue that it is helpful, because it already points to the lack of investment as an obvious obstacle to the development of therapies for this patient population, a point that we elaborate on below. In fact, early-stage venture investors, who often are the first link in the chain towards the commercialization of an academic discovery, are seldom interested in conditions that affect fewer than 2000 people in the United States, let alone globally (Figure 1).

Patient-led organizations lead the charge but need guidance

The typical journey for a patient newly diagnosed with an ultra-rare disease, many of which have a genetic basis, frequently starts with joining (or even founding) a patient-led organization to support academic research aimed at curing the disease in question. The contribution of these organizations to drug discovery and, more broadly, to creating a new research and development ecosystem around neglected ultra-rare diseases cannot be overestimated.(p4),(p5) Indeed, patient-led organizations fund a lot of the initial research that is necessary before launching a proper drug-discovery campaign, such as understanding the disease mechanism, developing cellular and animal models, creating biorepositories and patient registries, and funding natural-history studies.

An early challenge that patient-led organizations consistently face is assembling the right team of clinicians and scientists to tackle the disease of interest. Often, there is only a handful of

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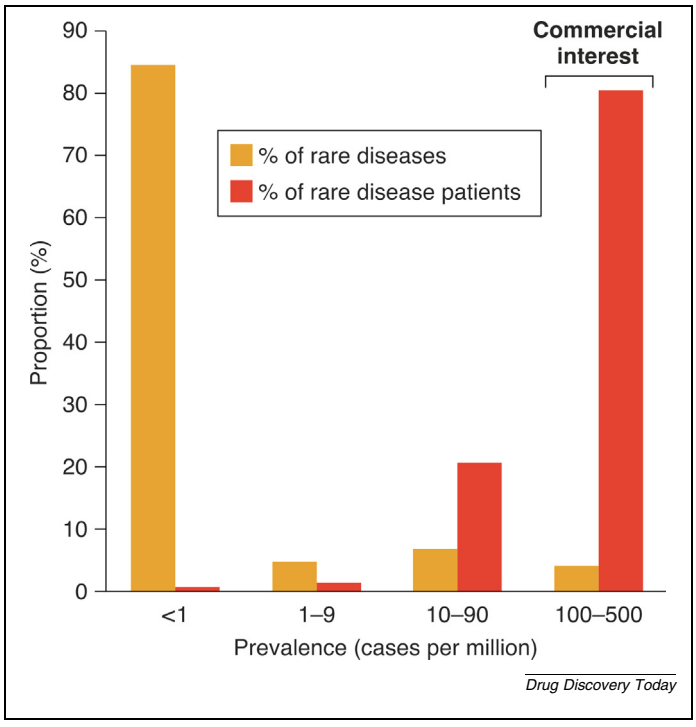

FIGURE 1

Most rare diseases are of no commercial interest. According to an analysis of the Orphanet database,[p23] >80% of rare diseases affect <1 patient per million people, accounting for ~0.5% of the total number of patients living with a rare disease. At the other end of the spectrum, ~4% of rare diseases affect 100–500 patients per million people, accounting for >80% of the total number rare-disease patients, enough to attract the interest of the pharmaceutical industry.

experts worldwide who are familiar with a given ultra-rare disease, and it is simply too hard to attract new researchers to study these conditions. More relevant to our discussion is the fact that, out of this small number of scientists, very few will have drug-discovery experience. This means that key decisions that must be made before launching a drug-development program – choosing the most appropriate therapeutic modality, selecting the right mutation to model in the mouse, and so on – are often incompatible with the attributes that a company would prioritize to maximize the chances of an approval. This limitation markedly reduces the usefulness of academic projects to finding cures.

Even in cases in which an academic group makes the right decisions, the lack of drug-discovery expertise is often problematic if the team does not have the skills necessary to assemble a strong development plan to advance the project towards a first-in-human study. In other words, an academic group might have obtained compelling proof of principle that a given therapeutic modality works in an animal model of an ultra-rare disease, but that is as far as these scientists are able to take the project. In the case of diseases of commercial interest, projects that reach this stage might be licensed to a company. But for a neglected ultra-rare disease, it is very difficult to attract the interest of professionals with the right expertise to navigate the preclinical development of a therapy.

Some organizations, such as the RTW Foundation, Rare-X (a research program of Global Genes), and Odylia Therapeutics, provide patient-led organizations and their scientists with advice on drug-discovery strategies, sometimes on a philanthropic basis. But there remains an urgent need for additional resources and expertise to help guide the projects funded by people living with neglected ultra-rare conditions in the direction of the clinic.

Academic institutions: Sources of innovation and frustration

Almost invariably, research on ultra-rare conditions starts at universities and academic medical centers. Although the interests and priorities of a patient-led organization are often fully aligned with those of the clinicians and scientists working on the disease in question, problems often begin when money exchanges hands.

For patient-led organizations, the whole purpose of funding research is to develop a therapy. These organizations typically understand that bringing medicines to the clinic is very costly and that a commercial organization needs to be involved to make it happen. Academic institutions, in turn, want to protect and commercialize the inventions of their faculty. But in the case of neglected ultra-rare diseases, this conventional model is unhelpful and represents another obstacle to the development of therapeutics.

First, in the case of neglected ultra-rare diseases, the idea that delivering a therapy to patients requires the creation of a start-up company or licensing an asset to a multinational company is in many cases not true. For example, an investigator-initiated clinical trial might be a faster route to patients, particularly for conditions that affect only a few dozens of patients worldwide. We elaborate on this idea below.

Second, academic institutions often fail to acknowledge that the ultra-rare diseases in question are of no commercial interest: the probability of making money from these academic innovations is very low. Technology-transfer offices should not lose sight of this fact and adopt instead a more nuanced approach when negotiating a sponsored-research agreement with a patient-led organization. Adding onerous terms to an agreement for the sake of protecting an innovation that will not result in financial gains is another way in which the deck is stacked against patient-advocacy groups.

This does not mean that academic institutions must not secure any rights on these innovations, but that they should understand under what conditions their intellectual property (IP) might result on a return on investment. Let's consider the simplest scenario: obtaining approval for a drug for a pediatric ultra-rare disease can result in securing a Priority Review Voucher (PRV) from the US Food & Drug Administration (FDA). US Congress created the PRV program in 2007 to encourage the discovery of drugs for neglected tropical diseases and, in 2012, the FDA expanded its use to spur the development of therapies for rare pediatric conditions. Crucially, PRVs can be sold to pharmaceutical companies interested in the expedited review of a commercial product. In the marketplace, these vouchers routinely command price tags higher than US$100 million.[p6]

The existence of PRVs has led an increasing number of patient-led organizations to launch drug-discovery programs and to even create start-up companies. Their goal is to use the

income from selling a PRV to recoup the up-front expenses that they incurred upon during the development of the therapy, and to defray some of the costs for the manufacturing and distribution of the medicine to their patient population. Academic institutions might argue that they are entitled to a fraction of this income, but then they should claim their share only upon approval of the drug, granting the patient-led organization all the rights they need to develop the therapeutic.

Although the renewal of the PRV program by the US government has not been granted and its reauthorization is currently uncertain, the sale of PRVs represents only one example of how patient-led organizations are trying to fund the development of therapies for neglected ultra-rare diseases. There are other models (Box 1), and each of them might require a different type of agreement. The important point, however, is that academic institutions must acknowledge that innovations around ultra-rare conditions might not generate a financial return on investment, but could generate a social return.

Box 1 Commercialization models for neglected ultra-rare diseases.

Generating revenue through the sale of a Priority Review Voucher is a popular idea in the ultra-rare-disease space, but it is by no means the only model.

The reason why ultra-rare diseases are of no commercial interest is because patient populations are too small to generate a profit. However, some organizations believe that neglected ultra-rare diseases might be more common than we think, but are markedly underdiagnosed. If this is the case, the argument goes, then a traditional commercial model based on sales might be suitable for therapies for these conditions, because once a therapy exists, more patients will be identified. Mahzi Therapeutics, for example, has launched several drug-discovery programs for ultra-rare neurodevelopmental conditions that might be more prevalent than currently believed.

Another commercialization model for ultra-rare therapies involves the validation of a platform technology. If a company invents a new therapeutic, a new delivery system, a new vector for gene therapy, or any innovation that might work across several diseases, a strategy to obtain fast access to the market is to test the technology in an ultra-rare population of patients. A recent example is the approval of pozelimab-bbfg for the treatment of CD55-deficient protein-losing enteropathy, also known as CHAPLE disease.[p21] This monoclonal antibody, developed by Regeneron Pharmaceuticals, blocks the activity of complement factor 5 and has clinical potential in several commercially attractive immunological conditions, but it was first approved to treat a condition that affects fewer than 10 people in the United States.

In the context of academic innovation and intellectual-property protection, technology-transfer offices need to think with extra granularity about neglected ultra-rare diseases, because as these examples show, not every discovery has the same potential to result in financial gain.

We want to stress that we are not proposing that innovations in neglected ultra-rare diseases should be exempt from IP protection. This protection is necessary to prevent others from commercializing an ultra-rare therapy that might ultimately benefit a large patient population (Box 1). What we are suggesting is that technology-transfer offices ought to think about advances in neglected ultra-rare diseases differently from the way they manage their portfolio of inventions that have commercial potential. In fact, it is even possible to consider a model whereby the ownership of the IP around neglected ultra-rare diseases could be shared between the academic institution where the research took place and the patient-led organization that funded the work.

First-in-human studies: One size does not fit all

In the previous section, we questioned the assumption that developing a therapy for a neglected ultra-rare disease requires the creation of a start-up company or the involvement of a commercial entity. There are certainly advantages to founding a company, and we already alluded to, for example, the need for the right expertise to guide an academic proof-of-concept study through the development and regulatory pathways, as well as access to the financial resources to conduct clinical trials. But if we analyze the experience of organizations that have taken alternative approaches, we realize immediately that there are other paths to success.

Let's start by considering diseases that affect, say, fewer than 100 people in the world. Thanks to advances in genome sequencing and the work of organizations such as the Undiagnosed Diseases Network, more and more of these extraordinarily rare conditions are being uncovered. Because they have the smallest patient populations and, therefore, the least commercial potential, these conditions are simply unable to attract the investment required for the preclinical and clinical work necessary for the regulatory approval of a therapy.

Paradoxically, an increasing number of patients with these exceedingly rare diseases are already being treated through so-called investigator-initiated trials (IITs). These are clinical studies in which a physician scientist is the sponsor of the trial, conceiving the research, developing the protocol, and taking responsibility for its execution. IITs are commonly launched to test whether a drug that is already in clinical use is also effective in a small population of patients with a condition different from the one that led to the approval of the medicine. However, these trials have also been authorized to test new therapeutics, and this has led to the treatment of a growing population of patients living with diseases that, in some cases, have only recently been discovered. The efforts of organizations such as the n-Lorem Foundation,[p7] the N = 1 Collaborative,[p8] and the International Rare Diseases Research Consortium[p9] to develop antisense oligonucleotides to treat individual patients, and of several academic medical centers to develop gene and cell therapies for small patient populations, provide inspiring examples of the power of this strategy.

An important feature of IITs is that they can remain open for a long time, recruiting new patients as they are identified. Because of this feature, we would argue that, for organizations focused on conditions with vanishingly small patient populations,

embarking on the creation of a company to navigate the traditional drug-development pathway does not pay off. Instead, investing in the capabilities and expertise required to launch an IIT that can then remain open for as long as possible might be a more efficient way to deploy capital. If the therapy is efficacious, then any additional financial resources of the patient-led organization can be destined towards drug manufacturing and to support patient travel to the site where the trial is conducted.

We acknowledge that the above model might only work for exceedingly rare conditions. The disease might affect a population of patients larger or smaller than the arbitrary 100 people that we mentioned above but, at some point, an IIT can no longer be the right approach to develop therapies for neglected ultra-rare diseases. Similarly, this model might be better suited to modalities such as gene therapy, which requires a single trip to the trial site for administration of the virus, than to antisense oligonucleotides, which must be administered to the patient with a certain periodicity. Moreover, some organizations do not entertain IITs because of concerns about equitable access to treatment and the perception of a 'pay to play' relationship between patients and the medical center conducting the trial. Considering these limitations, what options exist for patient populations for which the IIT model is inadequate? Could an IIT pave the way towards an approved therapy?

As it turns out, IITs are not intended to lead to regulatory approval. In other words, even if the therapy is effective, the sponsor of the IIT cannot take these data to a regulatory agency and request approval of the treatment. So, a patient-led organization working to develop an ultra-rare therapy cannot start with an IIT and decide halfway through the study that it will become a conventional pivotal trial. Conducting an IIT can save some development time by, say, identifying biomarkers of clinical response or helping to stratify patients, but it is not meant to be a shortcut to approval.

Although there are legitimate reasons for this regulatory framework, we would argue that the lack of a pathway for an IIT to result in a drug approval is another obstacle to the development of therapies for neglected ultra-rare diseases. If we agree that these conditions are of no commercial interest, it should be possible for regulatory authorities to outline a path for the approval of efficacious and safe drugs tested in IITs, provided that this path is beyond the reach of commercial entities. Furthermore, we believe that removing this regulatory barrier would be an important incentive to attract philanthropic capital to neglected ultra-rare diseases. As we discuss below, this type of funding has an important role to play in this space.

We want to emphasize that we are not advocating for the approval of substandard therapeutic products by cutting corners. Outlining a pathway to the approval of a drug on the basis of IIT data will require careful discussion among all the stakeholders to make sure that it is fit for purpose. Our goal here is to draw attention to this problem and, hopefully, to catalyze this overdue discussion. Indeed, the time could be ripe to start this conversation, because neglected ultra-rare diseases are becoming a fertile ground for advances in regulatory science, as we discuss next.

Winds of change in regulatory science

IITs might not be a viable strategy for many neglected ultra-rare conditions, but this has not deterred patient-led organizations from exploring other alternatives to the development of a therapy. Indeed, there are organizations that have decided to walk the full regulatory pathway by creating what can be described as 'non-profit start-up companies'. Among them, Elpida Therapeutics is a well-known example within the ultra-rare-disease community. Founded by Terry Pirovolakis to develop gene therapy for Spastic Paraplegia 50 (SPG50), a neurological condition that affects his son Michael, Elpida is a 'social-purpose corporation' that has attracted substantial resources towards the clinical development of therapeutics for neglected ultra-rare diseases.

In brief, Elpida raises capital from various funders in the form of grants or loans and solicits in-kind contributions from contract research organizations. With these resources, the organization is building a pipeline of five gene-therapy projects, including one for SPG50, that have been chosen with stringent criteria aimed at maximizing their probability of clinical success. They expect each drug approval to result in a PRV, which the company would then sell to pay off the loans and fund future gene-therapy programs.

Elpida has not crossed the finish line with any of their assets yet, but their SPG50 program is already in clinical development. Regardless, this organization has already made a great impact by bringing a new perspective on drug discovery for neglected ultra-rare diseases. But perhaps more importantly, Elpida has also led the way in terms of making the FDA acutely aware of the regulatory challenges associated with incredibly small populations of patients and, therefore, limited financial resources (Box 2).

Box 2 Regulatory challenges for neglected ultra-rare diseases.
A therapy for a disease that affects, say, 200 people in the world should not receive the same regulatory scrutiny as a therapy for a common disease. Although everyone agrees that safety considerations must remain front and center for any new therapeutic, regulatory agencies are beginning to pay more attention to the challenges associated with neglected ultra-rare conditions. These are some of the regulatory questions that have come to the fore:

(1) When are toxicological studies in non-human primates necessary? If a viral vector for gene therapy has been safely used in the clinic to deliver a variety of genes and the only difference in the new therapeutic is the payload, an argument can be made that studies in non-human primates might not be necessary if there is safety evidence for the new therapy from another species. This question is even more pressing in the case of new therapeutic modalities such as gene editing, in which the guide RNAs for repairing different mutations might differ by a single nucleotide.[p22] It would be excessive to require a new set of studies in non-human primates for every new gene-editing product that is the same in all respects to a previously approved therapy except for the guide RNA.

(2) What kind of first-in-human trial could lead to an approval? If only 200 patients worldwide are known to live with the condition in question, how many of them need to be part of a trial before it can be regarded as pivotal? Would it be necessary to include a placebo arm? In the case of an antisense oligonucleotide, a crossover trial design might address this question, but what about gene therapy?
(3) Can surrogate biomarkers be used to establish the efficacy of a therapy? For most ultra-rare diseases, natural history studies simply do not exist. It might therefore be difficult to choose an appropriate end point to measure the efficacy of a therapeutic within the duration of a trial. However, molecular biomarkers such as protein expression or enzymatic activity are often measurable in samples from patients. It should therefore be possible to grant conditional approval of a therapeutic on the basis of these biomarkers, provided that long-term patient follow-up takes place.
(4) How much of the therapeutic product needs to be retained for quality control? Regulatory agencies often require developers to retain drug product for stability testing, comparability studies, and other assays. The amount of drug product that is used for this purpose is always much smaller than the size of vial intended for dosing patients. However, all vials must be identically filled, which results in substantial waste of a drug that could otherwise reach the clinic. In the case of neglected ultra-rare diseases, the challenges around manufacturing and distribution that we discuss in this article render such a waste unconscionable, making it urgent to revise regulatory requirements on this front.

Although several of the regulatory questions that neglected ultra-rare diseases pose remain to be categorically answered, the Elpida experience has attracted renewed interest in these problems and underscored the need for innovative solutions. Moreover, this focus on regulatory issues dovetails with two other important initiatives in the gene-therapy space: Platform Vector Gene Therapy,[p10] a program of the US National Institutes of Health (NIH) to speed up the development of gene therapy for rare diseases through the standardization of platforms and protocols to avoid starting from scratch every time a new program is launched, and the Bespoke Gene Therapy Consortium,[p11] an initiative led by the Foundation for the NIH to foster the development of gene therapies for conditions of no commercial interest. Both initiatives have incorporated FDA input from the beginning, further highlighting the willingness of regulatory agencies to address the concerns of the ultra-rare-disease community.

Manufacturing and distribution: One bridge too far

A therapeutic for a neglected ultra-rare disease might receive regulatory approval or be effective in an IIT, but this does not mean that the therapy will be readily available to patients. For that to happen, the drug must be manufactured under conditions suitable for use in humans and distributed to the medical center where it will be administered. The supply chain that is necessary for this part of the process is complex and expensive, and this results in medicines that can cost several million US dollars per patient.

The price of drugs, particularly 'curative' treatments such as gene therapy, represents an ongoing challenge that continues to attract a lot of attention.[p12] Here, however, we want to focus on the fact that, because ultra-rare patient populations are so small, the manufacturing and distribution of therapies is simply not cost-effective. Because of these economic factors, there are examples of companies that have discontinued the production of approved therapies that could save patients' lives.

There are several initiatives to address manufacturing and distribution challenges for the benefit of patients living with neglected ultra-rare diseases. Perhaps the most striking example is the work of Fondazione Telethon in Italy.[p13] This organization funded the work that led to the development of gene therapy for severe combined immunodeficiency caused by adenosine deaminase mutations (ADA-SCID). After regulatory approval, Orchard Therapeutics marketed and distributed the therapy until 2022, when the company decided to stop producing it. To make sure that patients continued receiving the medicine, Fondazione Telethon engaged with Orchard Therapeutics and with European regulators to arrange the transfer of the marketing authorization to the foundation. In other words, Fondazione Telethon decided to become the organization responsible for manufacturing and delivering the gene therapy, a gargantuan task that required a huge investment in capabilities and expertise. Remarkably, the transfer was completed in 2023, and Italian ADA-SCID patients continue to benefit from access to this treatment.

Alas, access for patients from other European nations remains complicated, owing to reimbursement restrictions.[p13] In other words, the lack of a commercialization network charged with negotiating the price and reimbursement of the ADA-SCID therapy in each European country restricts access to the medicine outside of Italy. So, the supply chain that we alluded to above and the need for a commercialization network are two factors that impede achieving economies of scale for ultra-rare therapeutics.

Recent initiatives on both sides of the Atlantic are exploring ways to overcome these obstacles. In Europe, the Access to Gene Therapies for Rare Disease (AGORA) Consortium,[p14] of which Fondazione Telethon is a member, aims to create a sustainable non-profit mechanism to provide access to clinically effective gene therapies that are not commercially viable. In the United States, the Pediatric Advanced Medicines Biotech[p15] aims to support the development of ultra-rare and other pediatric therapies by reducing manufacturing costs and exploring new business models for drug discovery.

One thing that both initiatives have in common is the idea that solving these problems will require substantial financial support from governments and philanthropic organizations, and we could not agree more. In fact, we would go one step further and argue that neglected ultra-rare diseases offer an opportunity for national governments or international bodies such as the European Union to create manufacturing facilities for advanced therapeutics to meet the needs of their citizens living with ultra-rare conditions. As an increasing number of ultra-rare therapies move to patients through IITs and other mechanisms, a non-profit

national or international manufacturing center could be a way to produce small batches of all of those therapies and achieve the economies of scale that we mentioned above.

In this regard, this idea might be particularly viable in the Middle East, where some ultra-rare diseases have a comparatively high prevalence owing to consanguineous marriages. Because some countries in the region have the capital and the appetite for innovation that are necessary to kickstart a project of this nature, the Middle East could become a leader in exploring solutions to the manufacturing and distribution dilemmas that plague neglected ultra-rare diseases worldwide.

Furthermore, the work that the World Health Organization (WHO) has undertaken in the space of infectious diseases illustrates the feasibility of the above idea. After the COVID-19 pandemic, the WHO launched the mRNA Technology Transfer Programme with the aim to contribute to the manufacturing capacity of low- and middle-income countries for the development and production of mRNA-based vaccines.[p16] The success of this initiative has led to its expansion to advance the development of mRNA vaccines against influenza (https://www.who.int/news/item/29-07-2024-new-initiative-launched-to-advance-mrna-vaccine-development-against-human-avian-influenza-(h5n1)).

Alongside government backing, philanthropic support can certainly help address the above manufacturing and distribution challenges, but we believe that this type of capital is indispensable for multiple steps in the development of therapies for neglected ultra-rare diseases, as we discuss next.

Mission capital and neglected ultra-rare diseases

We started this article alluding to the key role of patient-led organizations, which are invariably philanthropic. We also mentioned that their financial support often only stretches as far as proof-of-concept academic studies. Philanthropic organizations with deeper pockets can make a real difference by taking the lead from that point of the drug-discovery process onwards, handling lead optimization, clinical-candidate selection, safety and toxicology studies in non-human primates, and so on.

These stages of drug discovery are much more capital-intensive than the early-stage discovery work and, as we also indicated above, require expertise that is seldom available in academic settings. Philanthropic entities can therefore make a dual contribution to the development of ultra-rare therapies with financial and human capital, and there are examples of organizations that have taken up this challenge. In the United Kingdom, LifeArc is a self-funded research charity with extensive in-house drug-discovery expertise. LifeArc has made substantial investments in rare diseases, trying to close the gap between academic research and the clinic. Although their support does not specifically focus on diseases of no commercial interest, the strategy of LifeArc represents an excellent example of how philanthropic organizations can contribute both financially and with expertise to advance the development of ultra-rare medicines.

Another way in which philanthropic organizations can support the fight against neglected ultra-rare diseases is by providing oversight. Any drug-discovery project, in addition to money and expertise, requires oversight to guarantee its proper execution. In a start-up company, venture investors provide some of this oversight, and there is no reason why it should be different for the development of an ultra-rare therapy supported by venture philanthropy. In fact, the original definition of venture philanthropy encompassed both the deployment of capital to achieve a social goal and the discipline in execution that characterizes traditional venture investments.[p17]

Some disease foundations that practice venture philanthropy have adopted a narrow definition of this term that tends to emphasize the financial returns that are reinvested in the foundation's programs. But when applied to neglected ultra-rare diseases, venture philanthropy can capture more faithfully its original goal: financial support and oversight to achieve social benefits. In this regard, the term mission capital or impact investment is increasingly used in this context to differentiate it from other forms of venture philanthropy.

The main goal of mission capital is to make an impact through a philanthropic gift, and this is what makes this type of funding ideal for the development of ultra-rare therapies. Mission capital is less interested in supporting early-stage, academic research (what some donors dismissively call 'science projects') than in investing in a proper drug-development plan that aims to make a direct impact on patients.

In the United States, mission capital often resides in private, family foundations that provide tax benefits to their founders. We would argue that the ultra-rare-disease community needs to engage with these family foundations to communicate the challenges to develop therapies for their patients, present a compelling drug-discovery strategy, and impress on them that their support is indispensable to achieve the most impactful goal of all: saving lives.

The Buffalo Initiative is an emerging organization that has taken this idea to heart. This collective is building a platform for patient organizations, impact investors, researchers, and other stakeholders to contribute to the development of therapies for neglected ultra-rare neurological diseases. Crucially, they have adopted a portfolio approach, working on multiple diseases in parallel. This approach has several advantages. For investors, it allows them to increase their impact by simultaneously funding a diversified pool of projects, as opposed to making small contributions to individual disease foundations. For patient organizations, this approach allows them to share experiences across diseases and to achieve the economies of scale that we mentioned above in the context of manufacturing.

Financially, this portfolio approach is also advantageous, because it increases the number of 'shots on goal' to develop a successful drug and therefore the probability of generating income through the sale of PRVs or other means. In fact, the economist Andrew Lo has used financial-engineering techniques to show that a portfolio of ultra-rare disease projects could generate a return on investment, even if the only income is derived from PRVs (https://www.forbes.com/video/808637f7-bf0b-4975-a09f-02bff9a61739/new-financial-engineering-models-for-ultrarare-diseases–ai-frontiers-and-implications). This insight is tantalizing because it points to a way in which the development of ultra-rare therapies can become self-sustainable.

In summary, we see a fantastic opportunity to marry mission capital and its desire for impact with the urgent need to develop therapies for neglected ultra-rare conditions. This appetite for

generating social benefits dovetails with the ideas of the economist Mariana Mazzucato, who has argued that public investments that underpin innovation in the pharmaceutical industry should not only lead to private-sector gains.[p18] Instead, governments should ensure that the benefits of these investments are shared equitably with the public.

Concluding remarks

In his famous book *The Innovator's Dilemma*,[p19] Clayton Christensen wrote: "disruptive technologies typically are first commercialized in emerging or insignificant markets." Neglected ultra-rare diseases represent one such 'insignificant market', and throughout this article we have illustrated that they are indeed a hotbed of 'disruptive' innovation: regulatory innovation, business-model innovation, manufacturing innovation, and so on. We predict that new therapeutic modalities, new platforms, and other elements of the drug-discovery process will also be introduced to the clinic through the ultra-rare 'market'. So, even if saving the lives of patients living with neglected ultra-rare conditions was not a strong enough incentive to act now, devoting resources to this neglected space is bound to result in key advances that will influence the development of therapies for rare and even common disorders.

Speaking of rare diseases, as our understanding of disease grows, we increasingly appreciate that most of these conditions are not a single, monolithic entity, but rather consist of subtypes defined by specific molecular mechanisms. Mutations in different parts of the same gene, for example, often result in important phenotypic variability. More relevant to our discussion, some disease-causing mutations are so unusual that, within a given rare disease, they can be considered ultra-rare: a disease subtype neglected because it is of no commercial interest.

Take cystic fibrosis, for example. Although the advent of modulators of the cystic fibrosis transmembrane conductance regulator has been transformative for people living with this disease, there is a subpopulation of ultra-rare patients who do not respond to the available therapeutics.[p20] Similarly, some mutations in dystrophin, the protein affected in Duchenne's muscular dystrophy (DMD), are present in an ultra-rare fraction of patients who might not obtain enough benefit from the existing exon-skipping therapies.

We would argue that some of the lessons that the ultra-rare-disease community is learning as it tries to develop therapies are very relevant to these ultra-rare variants of rare diseases. Conversely, neglected ultra-rare diseases can learn a lot about clinical end points and regulatory strategy from rare diseases such as cystic fibrosis and DMD, for which approved drugs exist.

Drug development for neglected ultra-rare diseases is an extraordinarily active field fueled much more by passion than by commercial interest. For many people living with these conditions, finding a cure is literally a question of life or death. We want to conclude this article by expressing our admiration to all the patients and their families who have refused to accept that medical science can do nothing for them and have decided to devote their lives to finding cures for neglected ultra-rare conditions.

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Joseph A. Katakowski: Writing – review & editing. **Juan C. López:** Writing – review & editing, Writing – original draft.

Data availability

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