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THERAPEUTIC DIGEST

GENE THERAPIES IN RARE DISEASE

IN COLLABORATION WITH thinkgen

SEPTEMBER 2021

Table of Contents

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GENE THERAPIES IN RARE DISEASE

Challenges Emerging Gene Therapies Face in Rare Disease Drug Development

Introduction

I'm sure most of you have seen the movie *Field of Dreams*, starring Kevin Costner as Ray Kinsella, an inexperienced, struggling farmer in Iowa. Early on in the movie, Kinsella hears a disembodied voice coming from his crops declaring, *"If you build it, he will come."* The "it" in this scenario is a baseball field and the "he" is Kinsella's father, who passed away some years prior. Kinsella does indeed build a baseball diamond; his father does comes back to play one last game of catch. If you have not seen the movie, I highly recommend it. It's a feel-good yarn about lost chances, following your dreams, and the intricacy of human choices.

This e-book is obviously not about *Field of Dreams*, but the movie is a useful analogy for when we think about the challenges the pharmaceutical industry faces when launching a gene therapy into a rare disease space. Costner's character took a giant leap of faith spending a large sum of money building a baseball field on top of his crops when financial ruin seemed a possibility. What if *it* was built but *he* never showed? What is more nuanced is how the movie revealed the profound complexities of how people behave unpredictably when they hope for a better, yet unknown future, particularly when their lives are rife with adversity.

We're seeing incredible advancements in the development of medicines to treat people living with rare diseases. Enormous sums of money are being spent investigating regenerative medicines, like gene therapy. Analysts estimate that the global cell and gene therapy market size will top nearly $58B by year 2028. [citation: PR Newswire, Sept 2021] Despite significant growth opportunities in disruptive technologies, there are numerous risks and unknowns associated with developing gene therapies for rare diseases. And the industry needs to ask itself one very important question: *if I build it, will they come?*

Understanding the Current Rare Disease Landscape

What is a rare disease? In the United States (US), it is defined as any condition affecting fewer than 200,000 people. In Europe, it is any disorder affecting fewer than 1 in 2,000 people. While the number of people living with a particular rare disorder may appear small, there are roughly 7,000 rare diseases that affect *400 million people globally*, the majority of whom are children. It's a sobering number.

The journey to a correct diagnosis is one of many battles a person living with a rare disease will fight. People wait on average 6 years between symptom onset and an accurate diagnosis, despite the routinization of expanded newborn screening and access to validated genetic testing. However, many rare diseases do not have any consistent diagnostic criteria and people may come upon a diagnosis simply because they see a healthcare provider who has some awareness of the disorder and knows how to test for it.

Once diagnosed, few have an approved therapy available to them. Most will rely on supportive care therapies that have been available for decades, such as corticosteroids. Even those who do qualify for a disease-modifying treatment, like Sarepta's Exondys 51 for Duchenne muscular dystrophy, may find that payer polices restrict access. Regardless, most individuals living with a rare disease will experience life-limiting debility and early mortality.

The need for more treatment options is obvious. And because nearly 80% of rare disorders are the result of a genetic variant, treatment innovation has begun focusing more on technologies that combat the disease at its source, like gene therapy.

Understanding Gene Therapy and Rare Disease Drug Development

What is gene therapy? It is important to understand what gene therapy is and is not. The FDA defines a gene therapy as a treatment that, "seeks to modify or manipulate the expression of a gene or to *alter the biological properties* of living cells for therapeutic use." [citation: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy] In other words, it's a treatment that will modify a person's genes to hopefully treat (or halt) their disease. It is the hope that gene therapies will transform the treatment of rare (and non-rare) diseases.

Gene therapy achieves this in a few different ways:

- Replacing a disease-causing gene with a healthy copy of the gene,
- Inactivating a disease-causing gene that is not functioning properly, or
- Introducing a new or modified gene.

Gene therapy is different from other forms of disruptive medical technology, such as genome editing, which is a technique that alters the DNA of an individual. Currently, no gene editing products exist outside of clinical research.

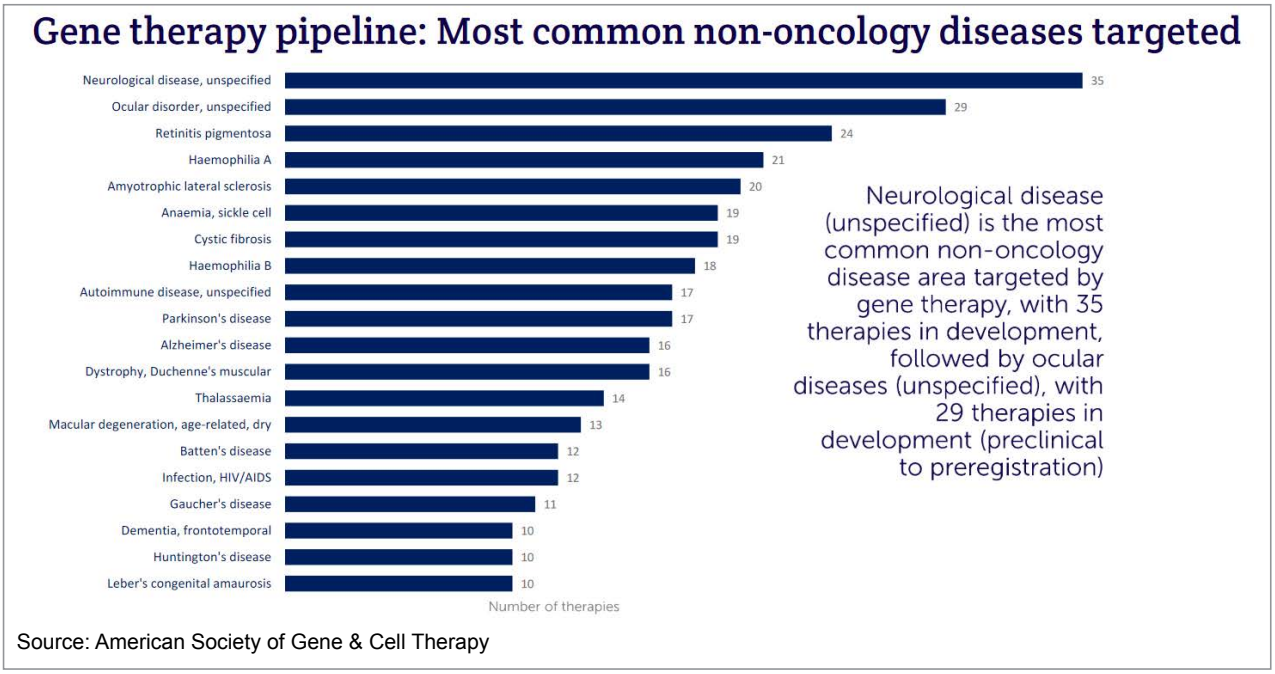
In 1983, the US Congress established the Office of Orphan Products Development – and the enactment of the Orphan Drug Act – to promote the development of products to treat "orphan" diseases in response to historically poor commercial investment in the research and development for rare diseases.

The US Orphan Drug Act provides benefits to drugs with Orphan Drug status to encourage drug-makers to develop new therapies for historically underserved diseases. Pharmaceutical companies are provided financial incentives through a seven-year period of market exclusivity for a drug approved to treat an orphan (or rare) disease, even if not under patent, and tax credits of up to 50 percent for research and development expenses. Therapeutics designated under the orphan status umbrella are also provided grants for clinical testing and assistance in how to frame protocols for investigations.

Despite these incentives, pharmaceutical companies face many hurdles in an attempt to bring new, rare disease treatments to market; many of these challenges are *particularly acute* in gene therapy clinical research.

Challenges for Any Rare Disease Drug Development	Challenges for Rare Disease Gene Therapy Development
Geographically dispersed, small populations make participant enrollment and retention challenging (now further exacerbated by a global pandemic).	Research and development (R&D) costs are growing significantly higher than the actual revenues over similar time periods.
Length of time between symptom onset and genetic diagnosis takes several years, during which people will lose function, resulting in exclusions from some clinical trials.	Current regulatory infrastructure is set up to evaluate and approve chronic treatments, even complex biologics like monoclonal antibodies, not potentially one-time gene therapies.
Heterogenous phenotypic expressions and a sub-optimal understanding of disease natural history make identifying meaningful and measurable clinical trial endpoints tricky, thereby challenging what treatment success looks like.	Strategic resource planning is incredibly complex due to small populations and high costs to set up a reliable and consistent treatment infrastructure.
Cultural differences and other difficult-to-measure obstacles may impact response to therapy	Low levels of awareness and poor understanding of the technology spanning across all stakeholders (providers, patients and families, payers), influences the type of evidence needed to make informed decisions.

Yet, the rare disease pipeline is on fire. The global rare disease market accounted for $161B in 2020 and is projected to soar above $500B by 2030. Gene therapy is anticipated to account for a sizeable slice of that pie with genetic medicines for a range of disorders, like sickle cell disease and several muscular dystrophies, within reach – sooner even, than some people anticipated. With more than a thousand gene therapies currently under investigation, most for various oncology disorders, Former FDA Commissioner, Scott Gottlieb predicted approval of 10 to 20 cell and gene therapies every year by 2025. [https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics]



The Gene Therapy Pioneers

Genetic medicine is no longer theoretical. There are a number of commercially-available gene therapies, including:

- **Luxturna**, manufactured by Spark Therapeutics (acquired by Roche, marketed by Novartis OUS), approved for the treatment of Leber congenital amaurosis (LCA), a rare inherited retinal disease that leads to blindness.
- **Zolgensma**, manufactured by Novartis, approved for the treatment of type 1 spinal muscular atrophy (SMA), a rare central nervous system disease that is the leading genetic cause of newborn mortality.

In 2017, Luxturna became the first gene therapy to receive FDA approval. The price tag for this one-time treatment is $850,000 (or $425,000 per eye). Zolgensma is currently the most expensive therapy in the world, commanding more than $2M per treatment.

In 2018, sales from Luxturna were nearly $27M. In 2019, sales rose to almost $44M. Staggering sums, yes, but compared to the $550M loss accumulated during development and lower-than-forecasted 2020 commercial sales, Roche reported that Luxturna failed to make it to its "growth drivers" list. Despite a remarkable observed clinical benefit in children who receive it, Zolgensma's sales in the US have stalled and 2021 revenue is being driven largely by sales in Europe. Novartis recently announced it would close one of its Zolgensma production plants, laying off 400 employees in the process.

Part of what we are seeing with Luxturna and Zolgensma are the aftershocks of payer coverage decisions that are more restrictive than FDA labeling or require prior authorizations and step edits, preventing some eligible people from receiving treatment. High price tags and unknowns around treatment durability require different reimbursement strategies. Insurers are considering several different payment models, such as outcomes-based models and value-based contracts, in an attempt to share some of the financial risk with the manufacturer.

> *"At launch, with these new gene therapies, it's unknown if the therapy will provide 5 years, 10 years, or a lifetime of benefit. In health where budgeting is done on an annual basis with a complex of insurers that hand off patients over time, these therapies create real problems."* (Lou Garrison, PhD, professor emeritus, The Comparative Health Outcomes, Policy, and Economics Institute, School of Pharmacy, University of Washington)

The COVID-19 pandemic has also created access restrictions. In Luxturna's case, the pandemic has limited the number of elective surgical procedures being done. (Yes, it is considered elective because while vision loss from LCA is progressive, is not fatal.) Zolgensma may be suffering from a similar fate, with a minority of healthcare providers and families reluctant to stop or switch from Spinraza (the current standard of care) to Zolgensma during a global health crisis.

This delay in access to gene therapy opens the door for other therapies. While some people may never receive Zolgensma, they may be candidates for Roche's new oral, small molecule Evrysdi, broadly indicated to treat children and adults living with SMA, gaining a foothold in an older population currently out of Zolgensma's reach.

Patient acceptance of a treatment with unknown risks is another significant hurdle. Many gene therapies are delivered using a viral vector, essentially a hollowed out version of a common cold virus. Because a gene that is inserted directly into a cell typically will not function, scientists use viruses as a delivery system because of how exceptional they are at penetrating cells.

Twenty-two years ago Jesse Gelsinger was the first person to die after participating in a clinical trial to test the safety of gene therapy for a rare disease called ornithine transcarbamylase (OTC) deficiency. Gelsinger experienced a severe immune response to the viral vector that was used, and passed several days later. Although the field rebounded, some members of the healthcare community and patients and their families continue to have serious concerns about how gene therapies are administered.

Additionally, most gene therapies are designed to be a one-time treatment, which could be associated with downstream, unexpected adverse events. I interviewed several parents for this publication who spoke about the *finality* of gene therapy. If you have a child on Spinraza or Brineura (indicated for Batten disease resulting from a CLN2 mutation) and do not like the outcomes or safety profile, you can choose to stop treatment. Once you receive a gene therapy, there is no way to remove it, you are stuck with it for the rest of your life. These unknowns around long-term safety have some families questioning if gene therapy is really the right path for their child.

As a result, people living with a rare disease (and their families) now have to make excruciatingly difficult decisions. Do you stop a treatment that is "working" in hopes that a gene therapy will work "better?" What if the gene therapy doesn't work as expected and you want to try another therapy, but payers won't cover it because of treatment history? Without long-term safety data about gene therapies, how do I know I won't trade one awful condition for another?

Finding answers you can trust is another obstacle. Many people will rely on their healthcare provider as one source of information, however the technology is transforming at lightning speed. Healthcare providers outside of clinical research may have trouble staying up-to-date, which impedes relaying timely, accurate information to patients and families.

Disability is Not a Bad Word

There is another element that influences treatment choice, something that is hard to quantify and even harder to explain to people outside of the Rare community. I recently interviewed Nadia Bodkin, co-founder of the Rare Advocacy Movement (RAM), the first network of professionals dedicated to protecting the interests of the global community of people living with rare conditions and their care partners. As someone living with three rare diseases, I was curious to learn what Nadia thought about gene therapy development for rare disorders. She immediately talked about the optimism people are experiencing, and of course the significant concerns they have around accessibility (e.g., will it be covered, can I afford it). She quickly pointed out, however, that there are deeper psychological processes happening when people make treatment decisions.

> *"If you go long enough in your body, you develop comfort with your body. And even if you qualify for a treatment, you may not accept it, because you've already accepted who are you. And people with options have real concerns that may prevent their acceptance of new gene therapies."* (Nadia Bodkin)

Resilience, which you can think of as the compensatory strategies that patients and their families develop in the face of adversity or trauma, is something that many people living with a rare disease (and their families) have in common. And depending on where you are on your journey and the road that's led you there will often dictate how you interpret quality of life and therapeutic benefit.

Several years ago, I had the opportunity to conduct in-person ethnographic interviews with several families who have a child with congenital hearing loss. Ethnography proved invaluable because we learned something that we had not learned previously in one-on-one interviews, specifically the schism in the well-established Deaf community. You can split the Deaf community in half: those who are pro-cochlear implants and those who are anti-cochlear implants. You may be wondering, who doesn't want to hear?

Ableism, or the discriminatory belief that an abled body is superior to a disabled body, often clouds our understanding of human behavior. In the scenario I just shared, able-bodied people may believe that deaf people will want cochlear implants because hearing is better than deafness. But hearing-impairment is not better or worse, it's just different. Instead of trying to fit into someone else's normal, some people in the Deaf community have embraced their "disability" and are spending their energy on making the world more deaf-accepting.

> *"If you view deafness as a cultural difference rather than an impairment to be cured, cochlear implants start to look less like an assistive device and more like an attempt to erase a minority group and assimilate its members into the mainstream." Chloe Kent, June 2021, Medical Device Network*

Interestingly, children who receive cochlear implants before 2 years of age reap more benefits (e.g., language development) than those who receive cochlear implants later in life. Cochlear implants are not a cure (same with gene therapy) and do not perfectly simulate full range of typical human hearing. Research has shown some adults who are fitted with an implant describe sounds as mechanical.

This limited window of perceived benefit may be a similar issue we see with existing and emerging gene therapies. Novartis is studying an intrathecal indication of Zolgensma in children 2-18 years with type 2 SMA, but early clinical data indicated that an adverse immune response against the AAV vector used to deliver the product is more prevalent in older populations, and the FDA halted the study. Though the clinical hold has been lifted, some portion of the population who may have benefited from Zolgensma has aged out of reach. Even if an adult is able to access the treatment, it is unclear how any gene therapy will improve their life. As one parent of a child with SMA type 1 child who received Zolgensma stated, *"All of these treatments are great, but none will bring back what was lost."*

The Rare Dichotomy

So there exists this duality in someone living with a rare disease: the seeker and the serene. Seekers, particularly those who are newly diagnosed, will spend an incredible amount of energy searching for a treatment that will improve their quality and quantity of life. Some of the parents I spoke with talked about being on a mission to do anything to help their child. To get them closer to "normal". One mother of an adult child with Rett syndrome who I interviewed remarked, *"When she [her daughter] was diagnosed, and that darkness you're in, there is so much confusion. It's extremely challenging. Hands down, the hardest part of my life. At that point if gene therapy were availability, I would have been all over it."*

The Serene, on the other hand, have found peace. Perhaps they are financially stable, have modified their home to accommodate their disability, are in a relationship or partnership. Some are relying on their religious beliefs to reach this place of acceptance. Regardless of the reason, they have chosen to spend their energy on maintaining their (or their child's) quality of life and planning for the future. You may be thinking that someone diagnosed with a devastating disease can't possibly fit into the Serene category, but you could be wrong.

> *"We are not depressed or angry at the world or God because my child isn't "normal." My husband and I have had a lot of time to practice this. This acceptance doesn't happen overnight. And it's hard to balance between making sure my daughter has what she needs while loving her as she is. It's not fair for me to put my own expectations on her. My daughter can't talk to us, but we know that we can do things to make her happy, and let her appreciate her time on Earth."* (Mother of a teenage daughter with Rett syndrome)

I also interviewed a mother of two young daughters living with Batten disease, a progressively fatal condition of the central nervous system. Both children receive Brineura, a bi-weekly enzyme replacement infusion. Treatment days are rough. They begin at 5am, with a one and half hour long car ride to an infusion center. This is followed by an eight-hour stay in the infusion center; two hours for the medication to thaw and a six hour infusion that includes unpleasant side effects, like nausea. When done, another long car ride home, hopefully arriving by 6pm. This routine is repeated weekly, alternating between children, so that this mom can give each daughter her full attention on their respective infusion day.

This mother is aware of the gene therapies currently being investigated for Batten disease, but she does not hold out much hope for her daughters. Although there are drawbacks to Brineura, she has seen positive results of treatment and would not stop it if she had to pick between Brineura or a new gene therapy (which could be a reality depending on payer coverage). *"We are living in an enzyme replacement world. If we have to pick, if insurance made us pick, I will stay with enzyme replacement. I don't want my girls to lose function for a gene therapy that may or may not work."*

So what do people living with rare diseases and their care partners want? It's a question I asked everyone I interviewed and there were very consistent responses. Better ways to communicate (if non-verbal). Reliable and accessible respite care. A centralized location to find the information they need as their/their child's disease progresses. Access to empathetic and well-educated healthcare providers. Purpose. Happiness. Joy.

Implications

What does all of this mean for the pharmaceutical industry? Testing the genome and using those results to identify a host of genetic errors resulted in the desire to "fix" those errors. And while gene therapy is exciting technology that offers abundant hope where before there was none, it would be incorrect to assume it's for everyone. Further, FDA approval and real world evidence of clinical benefit may not be enough to sway those people sitting on the fence.

Conversations evolve and needs change, therefore engagement strategies with rare disease stakeholders (people living with disorder and their families, healthcare providers, payers) should begin prior to clinical trial protocol design and continue beyond commercialization to ensure long-term success.

Engaging people early and often has the potential to result in clinical protocols that measure meaningful endpoints, improve clinical trial participation and retention, and identify the complex emotional factors behind treatment choice and how these intangibles have the potential to impact commercial forecasts. Also, barriers like delays in a timely genetic diagnosis resulting in loss of function while making peace with a life-limiting disease means drug-makers are likely competing for even smaller populations than perhaps they originally thought, at least initially. If you build it, some will come. And understanding who the "some" is will be critically important for near- and long-term commercial success.

Above all, continue to innovate. Continue to pursue viable solutions that benefit all stakeholders. But don't forget that providing people with the resources and support needed to live life with dignity remains a universal need in the Rare community.

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