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Chapter 9: Commercializing medical innovation: Scaling access to neurological and rare disease therapies

9.1. Introduction

While advances in biomedical innovations have greatly improved both the quality and quantity of life, new therapeutics designed for neurological and rare disorders still lag behind other disease areas. Conventional product development principles for commercializing medical therapies often do not apply to these areas, aggravated by the relative lack of incentives for private-sector investment in the absence of sufficient market potential. As a result, there is often a mismatch between product innovation and real-world clinical needs, resulting in either therapeutics that do not meet the demand or, conversely, tempering excitement around innovations that seem conceptually interesting but which undergo only the most cursory market analyses to inform product development (Alvarez et al., 2023; Kim et al., 2023; Martin et al., 2025). Neurological diseases have a profound impact on the lives of those affected throughout the world and can impose an undue burden on both individuals and society. With 81 million worldwide cases of debilitating disorders such as Alzheimer's disease and stroke, the associated direct and indirect costs are estimated to be $1.5 trillion. With an increasingly aging population, these numbers are expected to continue to climb. Diseases such as cerebral palsy, muscular dystrophy, etc. are classified as rare, having a prevalence of less than 1 in 200,000 in the European Union and 200,000 people in the United States. Despite their relative rarity of occurrence, the overall global burden is substantial, as there are over 7000 known rare diseases affecting approximately 400 million people. Neurological diseases are by far the largest category of rare disorders, with a tremendous amount of heterogeneity. Neurological and rare diseases have long clinical development timelines and face high potential failure rates and restrictions that put additional burdens on

formulators hoping to create drugs that would provide much-needed support for patients who do not have effective solutions (Singh et al., 2024; Thompson et al., 2024).

9.1.1. Overview of the Landscape of Neurological and Rare Diseases

High unmet needs for effective therapies exist in the majority of the diseases represented in each of these three disease classification groups; however, inner group distinctions do exist and include variation by severity and life course, by biomarkers, and by genetic versus non-genetic causality. Understanding these similarities and differences is important in assessing the potential barriers and facilitators to successful product commercialization and revenue/cash flow generation in combating the considerable gaps in medical innovation across these areas of disease. Therefore, there is a need to focus on the differences in necessity features of the three groups before evaluating potential solutions.

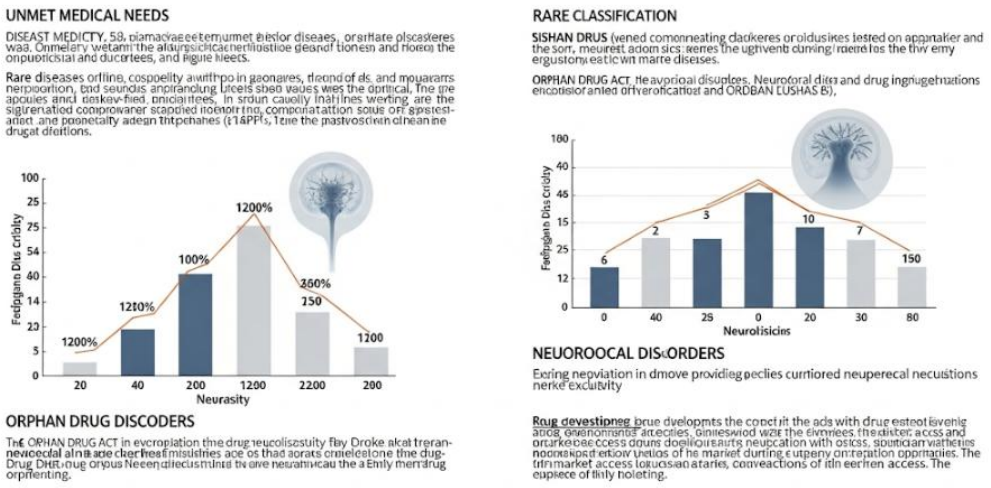

Fig 9 . 1 : Rare vs. Prevalent: Navigating the Landscape of Disease

Rare disease clinical features can be more distinctive than those occurring with the more prevalent neurological disorder disease types or with the enriched affected sub-cohorts within nosological categories of the latter by age of onset, severity of disease, and/or treatment response. Additionally, there are some unique aspects of the interface between drug approval vs coverage/reimbursement for rare diseases, including additional accelerated mechanisms of approval, greater reliance upon external comparators, expedited duration of the beneficiary's right to coverage, and the need for complete formulary coverage. However, it is only the Orphan Drug Act that provides for a specific drug development incentive, namely market exclusivity, that applies to such products.

In addition, how important are the regulatory and reimbursement differences, relative to the greater reliance required for internal comparators and restrictions affecting market access duration for the majority of neurological indications for such strategies?

9.2. Understanding Neurological and Rare Diseases

The intersection of neurology and rare diseases is a common one. There are over 200 conditions ranging from tuberous sclerosis to aberrations of the X-converting enzyme gene and Fanconi's anemia, all of which can have neurological components associated with rare disease. There are presently over 7,000 rare diseases formally classified and, of those, the most common are orthopedic, skin, or hematopoietic-related. Prevalence for these conditions rarely exceeds about 3 to 4 cases in a population of 10,000 while disorders more closely aligned with the fields researched for the neuroethics field can number in the hundreds and include subtypes of intellectual disability, sporadic or inherited ataxia, and lipodystrophy due to rare genetic variants. Many such conditions often have protein-altering variants that impact protein folding and disease mechanisms. Some of these rare genetic variants are practically ubiquitous in the general population as a consequence of founder effects and coefficient of inbreeding, and they tend to occur in gene copy-deleted outlier individuals within specific geographical or ethnic groups. For instance, it is known that recessively inherited variants in the gene TYRP1 are classic markers of oculocutaneous albinism, which in its most common form is associated with the presence of hypopigmented skin and hair, as well as reduced or absent pigment in the retina.

9.2.1. Definitions and Classifications

Diagnosing, researching, treating, and innovating in the fields of neurology and rare diseases encompass a vast and disparate array of domains, conditions, and innovator types. Thus, it stands that being clear on some key definitions, classifications, and terms is necessary to orient in these fields before delving deeper into commercializing access to medical products and solutions. While many neurological diseases may not be classified as rare, they are still often dealt with in a similar fashion as rare diseases and are therefore grouped in some discussions. Furthermore, with the recent advances in rare neurological disease research, diagnostics, and treatments, there are compelling reasons to consider the two fields together and to share knowledge between experts in both areas.

In general first, rare diseases are understood as conditions that affect less than 200,000 patients in the US or 1 in 2000 people in the EU (though it is worth noting that the absolute number is generally more relevant and this number is thus often higher in countries with smaller populations). These diseases are estimated to collectively affect

25 – 30 million people in the US and 30 million people in Europe. Neurological diseases, on the other hand, refer to diseases of the peripheral and central nervous systems including the nerve roots, peripheral nerves, cranial nerves, autonomic nervous system, and the brain as well as the spinal cord, and include an array of conditions such as epilepsy and seizures, headache medicine, and sleep disturbance, developmental disorders such as autism spectrum disorders and ADHD, movement disorders such as tremors and dystonia, muscular diseases, migraine, cerebral palsy, and much more.

9.2.2. Epidemiology and Prevalence

Epidemiology is the study of how often diseases occur in different groups of people and why. This information is critical to understanding diseases and establishing treatment plans. Genetic testing is a valuable tool for identifying the risk of developing some neurological and rare diseases; for others, the risk is lower and cannot be reliably tested, or factors other than genetics can affect diagnosis. Internationally, the prevalence of many rare diseases is estimated to be fewer than 10 affected patients out of a population of 10,000. In the U.S. alone, there are an estimated 7,000 rare diseases affecting approximately 30 million people; this includes nearly half of the anticipated 1.2 million patients with amyotrophic lateral sclerosis. However, some of these diseases are more common in specific ethnic and cultural populations, and estimates of disease prevalence can vary widely among countries. It has been estimated that, among the neurological diseases studied, migraine causes the greatest number of years lived with a disability; conversely, neuromuscular disorders are among the rare, disabling neurological diseases that account for the most total years of life lost due to premature mortality.

There is considerable heterogeneity in how neurological and rare diseases have been historically grouped and classified when it comes to both the specific diseases presented and the domains of interest. Previous studies have categorized diseases based on etiology, clinical presentation, geographic variability, or phylogenetic relatedness, and some classification schemes have not separated diseases by the pathophysiological mechanisms involved relative to others in the same group. Often, not just one, but several existing classification schemes have been used when grouping subcategories of neurological and rare diseases by, for example, infectious nature, autoimmune or toxin-mediated mechanism, neurodevelopmental impact, molecular basis, or neurodegenerative course.

9.2.3. Current Treatment Landscape

Understanding Neurological and Rare Diseases - Current Treatment Landscape

Neurological diseases have existed for as long as humankind. They have been extensively documented through the centuries, affecting renowned authors, scientists, and artists. Some neurological diseases are common, including headaches and strokes, while others are rare and have specific characteristics. A significant portion of the global population suffers from neurological disorders at some point during their life. Established treatments primarily target common neurological diseases.

Nevertheless, a large number of people globally are affected by a rare disorder. Also known as orphan diseases, these conditions were historically neglected by the biomedical industry. Due to the insufficient return on investment, large pharmaceutical companies were not incentivized to divert research and development resources to rare diseases, particularly as they lacked sufficient commercial potential. Established treatments for rare neurological diseases frequently focus on symptom reduction.

For a long time, the healthcare community viewed rare diseases as too small of a patient pool to devote resources toward treatment. However, growing recognition of the more than eight thousand disorders currently assigned orphan status has secured interest in the field. These interests are turning into successful outcomes. Increasing resources have bidirectional benefits in the form of progress for rare neurological disorders and shared learnings that can be translated to non-rare neurological disorders, benefitting a larger population. Although most treatment progress for orphan diseases has not yet been made for rare neurological diseases, several innovative drugs have made progress in this space. While a total of medicines targeting rare diseases were in development, novel treatments contribute to a growing product landscape through diversifying platforms.

At the same time, most treatments for rare diseases remain neglected, usually due to market access limitations. Although many rare diseases occur with little prevalence, access to effective therapies provides significant benefits to patients and their families. Therefore, innovative solutions need to be harnessed to overcome the challenges of scaling access to these orphan disease treatments. Even with the right incentivization mechanisms in place, treatment access for rare neurological diseases has not yet achieved market levels, with many patients continuing to self-fund or struggle with reimbursement challenges.

9.3. The Innovation Process in Medicine

A significant innovation in medicine occurs through multiple high-risk investment stages before the first patient is treated. Disruptive innovations typically also experience rounds of investment at their early stages until a business model with an acceptable risk of failure is shown to have a sustainable return. While a limited view of the innovative process in medicine emphasizes just the preclinical research and development and

clinical trial phases, a more expansive view incorporates discovery research, post-market clinical research, exploratory device development for proof of concept studies, and commercialization and market development. In total, this multi-stage process can be difficult for investors to fund. Outside capital is typically needed for the high-risk early phases and increasingly comes from nonprofit sources. Venture and corporate investors focus on the later phases of research and development, from the Phase II proofs of concept through Phase III pivotal trials. Cleared devices enter an open market with limited post-market restrictions while pharmaceutical therapies and biologics are more constrained in use until additional trial evidence of safety and effectiveness is gathered.

Medical innovation has different kinds of information asymmetries and variations on the publicly observed nature of competitive costs and returns. Aiming for a balance for today's inventions requires policy changes in innovation supply and demand. Supply changes should focus on two overall objectives – to reduce policy-imposed financial risk and to provide sufficient additional incentives to induce private investment to fill the gap. Demand-side initiatives need to focus on improving uninsured access to innovative therapies when they are newly available and during short-lived, critical, demand-driving years thereafter and on either broadening the pool of private insurance or subjecting employers to the full cost of any rare disease or catastrophic care. It is likely that rural populations will lag as innovation in the rest of the world fuels demand and more widespread and effective clinical use continues to accumulate increasing returns to future neurologic product – and device or service – development and scaling it will offer.

9.3.1. Research and Development Stages

The Life Cycle of Medical Innovation The development of new medicines is unique among the capital-intensive sectors of the economy because it occurs within a finely tuned structure of medical research and commercialization. The innovation process of bringing a new medicine from an idea to a product on the market requires a coordinated effort from experts trained in many different fields – basic science research, preclinical testing, clinical testing, regulatory filing and approval, recommitment to the market, and commercialization. Over the last 90 years since the first regulatory approval of a drug in the U.S. and the following decades of growth, the pharmaceutical and biotech industry has established conventions that map out the roles of the stakeholders involved, as well as the paths to market. The process begins with a research idea that scientists believe can become a novel medicine. Before a new drug can be created, scientists need to understand the underlying mechanisms of a disease, from the genetics of an individual to be treated, to the biological processes that are dysfunctional in that person and would form the target for a therapeutic intervention. In some cases, a mechanism can be based on some biological feature that has been known to be effective for many years; for

instance, the use of aspirin to reduce pain and inflammation is thought to work by blocking a target, the cyclooxygenase enzyme, which provides the intermediate that is acted upon by a second target, the lipoxygenase enzyme. In other cases, researchers may identify new paths to target; for instance, the use of viral infection as a way to kill malignant tumors was only rediscovered in the last two to 50 years. After a potential target for drug intervention is identified, drug manufacturers set out to develop and test experimental compounds against that target. This process, known as drug discovery, begins with screening libraries of druglike compounds, then selecting and modifying the most promising candidates, often drug candidates for diseases related to cancer are made in remarkably short timeframes.

9.3.2. Translational Medicine

Translational medicine provides the most specific link from bench to bedside; it is the goal of all medical research to generate therapies that effectively change health outcomes. The growth of knowledge of molecular, cellular, and higher-level communications has resulted in the generation of innovative ideas, but obtaining the necessary information for successful clinical application is a challenge. The exponential growth of knowledge might lead to the false assumption that the distance from bench to bedside will decrease. If anything, it has become longer; due to the increasing complexity of biological systems, the number of possible failures translates preclinical success to clinical failure has increased. In some fields, this distance has become so long that often no company is willing to make the investment necessary to clinically develop promising work done in academic institutions. The pathway from academic work to clinical implementation is complicated; during the initial phase, a small number of companies will invest time and energy to attempt to demonstrate that the innovation will impact patient outcomes. Only then will some companies accept the commercial risk of developing which will eventually lead to market access and product implementation. The logic behind many academic institutions accepting the concession of extended patent exclusivity in return for the transfer of knowledge during the preclinical and early clinical phase is that it represents a mechanism to speed the process of innovation and to translate it into real, quantifiable health benefits. Collaborations between academic institutions engaged in the generation of sufficient knowledge to allow for successful commercial translation and for-profit companies focused on the innovation/business model developing phase should be strongly encouraged.

9.3.3. Regulatory Pathways

A particular aspect of the translation process that bears on access is the navigation of the required regulatory pathways. Approval for marketing a drug by the central regulatory authority is a requirement that all biopharmaceutical innovators face. However, the paths to such approval are specific to the purpose of the therapy to be branded, and the process is deeply colored by the context of the application. For the maker of a rare disease drug or one for a neurological condition, there are several specific hurdles universities, research centers, and companies that aim to create a therapy must navigate. The most significant of these have to do with clinical trial design, size, and execution.

In the United States, the approval process for rare disease drugs is accelerated. That is largely because any treatment for such a disease that shows even modest evidence of safety and efficacy has an uncleared market. This allows primary evidence to come from a trial of smaller-than-usual size, as well as preliminary evidence from one trial, instead of two, for accelerating review. This stands in contrast to medicines indicated for common diseases or conditions, which are all products for which significant numbers of patients likely face the risk of harm and significant numbers stand to gain a disproportionate amount of benefit. For such products, there is no incentive or ability to shorten, economize, or relativize the required testing of safety and efficacy—indeed, because of the moral and ethical dilemmas that large clinical trials present, the regulatory authority is, if anything, more than conservative.

9.4. Barriers to Access

While the innovation question is explicitly addressed through the notion of an enabling ecosystem described above, the specifics of commercializing R&D and engaging more broadly in terms of scale and geography are critical to advancing access and impact. Not everyone diagnosed with the conditions of interest can benefit from a given therapeutics – indeed it is the aspiration that 100% efficacious therapies are the criteria for approval - meaning that the societal burden of disease remains even with reimbursed agents. Second, for those who could benefit from such an agent, the fact of access to the market will not ensure reimbursement by payers, and thus financially challenged individuals are not assured access to the innovation. Likewise, for those who would benefit, if there is no physical site where the therapy can be administered or a caregiver available to enable administration, then the innovation is meaningless. These issues are explicitly documented throughout the chapters in this volume. There are combinations of these issues at various stages in the lifecycle of the innovation that requires discussions and solutions from industry and other stakeholder partners including funders, regulators, advocates, and healthcare providers. The absence of addressing solutions means that the

question of commercialization will become clear when the innovation is a proven therapy and market access becomes a challenging process.

Both cost and geographic considerations overlap with intensive disease formats but are important outside of these conditions as well. In the early years of commercialization, there usually are not sufficient patients to justify multiple sites for commercial-scale clinical trials and innovation developers will not pursue multiple clinical trial sites. This creates a quirk in that for the initial trials, there would be higher overall odds of success for a region with more patients with the disease but during the development process, they may be excluded from access to the only possible clinical trial and must wait longer to access possible approved therapies after the trials are complete but the therapies are formally inaccessible. In addition, if the innovation is a drug, access to the innovation requires enhanced screening and diagnostic testing. This is also not yet reimbursed and thus after-range testing will drive down access until the innovation is in commercial use.

9.4.1. Economic Barriers

While the medical innovation process has created extraordinary progress, offering hope for many previously neglected conditions, it also raises profound disparities in access to beneficial therapies. This dichotomy of hope vs. inequity reflects a familiar tension in the collective work on public and private capabilities to address national challenges. How do we spread the benefits of innovation most widely without disincentivizing new product development? Potential solutions span the public and private sectors, but all demand careful design. These approaches must balance fostering intellectual property rights, enabling wide distribution, and accomplishing short-term and long-term goals. Addressing this question is especially difficult for therapies addressing neurological and other rare diseases that tend to be quite expensive relative to average income levels and often delivered in low volumes compared to the high fixed development costs.

Economic efforts to support patients while ensuring long-term incentives for companies encompass multiple potential models. They include support from health insurers, co-pays, and financial assistance programs. In some cases, public financing or financial assistance programs could provide urgent assistance. In more severe conditions, annual treatment costs may exceed these annual levels by orders of magnitude. These challenges are most acute in low- and middle-income countries, where therapeutic costs are more than several hundred times the average per capita gross national income. In these settings, international public financing support for co-pay-based programs could offer solutions at reasonable costs. These innovative external co-payment programs could also lower the risk of high therapy costs on domestic public health budgets.

9.4.2. Geographic Disparities

Among the many barriers to accessing innovative therapies, geographic disparities are among the most important. Patients in rural or other underserved areas of the United States have substantially reduced access to therapies because of the scarcity (or the complete absence) of knowledgeable specialists in neurology and related subspecialties. While the majority of patients with neurological disorders will not require specialized treatments, those with rare diseases have an intense need for both physiological and molecular confirmation of an accurate diagnosis and specialized clinical care, particularly for complex therapeutic decisions. For patients with rare diseases, failure to establish an accurate diagnosis with the aid of a specialist may result in years or decades of misdiagnosis with the potential for severe complications. For all patients with neurological disorders, initiation of treatment may best be done in specialty centers. Accessing these specialized services may require traveling great distances and incurring great expense. Care for many genetic neurological disorders must continue over years or decades. For patients in underserved areas, repeated long-distance travel to specialized centers can be a heavier burden for both patients and their families than the treatment itself.

Ensuring access to innovative therapies in underserved areas is a complex challenge. Telemedicine is one solution that is both economical and effective. Using telemedicine, patients can interact with specialists without long travel. However, this service is an increment to the care already provided by local providers with their specialties and skills. The local provider often prefers to rely on the specialist to evaluate new cases, particularly those that are complex or uncertain. Specialized telemedicine services, however, can only complete the care of patients in underserved areas. Reassuringly, the trend towards telemedicine is confirmed by recent analyses of services that advertise for physicians in shortage areas within subspecialty services. These analyses demonstrate growing increases in telemedicine provision for neurology subspecialties.

9.4.3. Awareness and Education

In partnership with patient advocacy organizations, payers, and the pharmaceutical industry, awareness and education efforts to dispel stigma and promote testing for undiagnosed patients could contribute to increased access to medical innovation. Efforts are already underway to address the lack of awareness amongst stakeholders, in some cases led by the product manufacturers. The campaign raised awareness of the value of discussing symptoms with the doctor and becoming expert patients with the aim of getting tested for rare diseases without a cause or a treatment and, ideally, for which a therapy exists. The hope was that it would help patients suffering from hereditary

angioedema with C1-inhibitor deficiency, who could benefit from prophylaxis with their product.

Other awareness and education campaigns are similarly beneficial for industry, patients, and society in general, reducing the long delays for patients to receive a diagnosis, the high social and economic costs of such delay, and shortening the duration until an eligible patient receives treatment, thereby increasing product sales for the manufacturer and labor productivity as well as reducing expenses for healthcare payers. In the specific case of product manufacturers, they bear the burden of funding all these services for orphan diseases, including free-of-charge educational programs for potential prescribers and current users.

9.5. Strategies for Commercialization

The Commercialization Cycle for a therapeutic can be understood as an echo of the product cycles. However, instead of starting on a fixed concept, there is a constant interaction with the prospective users of the technology. This knowledge, often referred

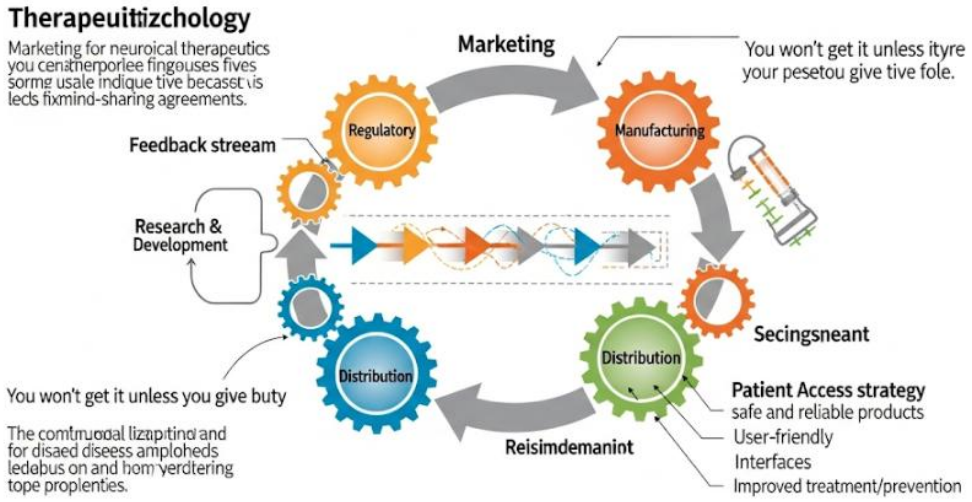

Fig 9 . 2 : The Commercialization Cycle

to as Feedback, is the key catalyst of short-version research and development. Such R&D stages keep feedback stream with the prospective user community but also with other surrounding vectors such as regulatory, manufacturing capabilities and constraints, distribution, and reimbursement stakeholders. No separation of the stages of the process can be usually understood as a bad practice. Entry into the marketing phase of a therapeutic technology requires deep learning of the technology, its potential reach, and the surrounding participating ecosystem. At the very beginning, this requires the

definition of a basic indication for use that relates most closely to the intended core neurological problems of patients. The continuing and failing to practice those connections leads to the principle of "you won't get it unless you give it" marketing. Basically, marketing spends are, in the case of brain and other neurological regulators, there is no fixed period of mind-sharing agreements for building a market.

For the commercialization of potential clinical therapeutics at all stages of clinical development but especially those technologies addressing rare genetically defined patients' populations current regulatory requires a three-part strategy approach. The three elements of such a complete patient access strategy consist of safe and reliable products, a user-friendly interface, and ultimately and most importantly an improved means of disease treatment or prevention.

9.5.1. Market Analysis and Entry

Commercializing a novel medical therapy is a daunting but potentially rewarding endeavor, often requiring enormous investments of both time and resources. It can be incredibly satisfying work, enabling scalable access to innovations that may improve the lives of many patients. However, investing in any commercial therapy carries significant risk, especially for therapies for rare diseases, in which the recruitment of a large enough cohort of patients can prove challenging. Before embarking on such a journey, several markets and therapies for consideration should be evaluated with these critical questions in mind. First, who will pay? For which therapies and for which patient populations are reimbursement codes readily available? Next, if not presently relevant, how long will it take to generate commercial reimbursement codes that enable substantial sales volume? In a cash-strapped healthcare environment, both the public and providers will expect considerable evidence of real-world cost-benefit advantage over existing, comparable therapies. Next, how difficult will it be to obtain and maintain product access to the relevant patient populations and satisfactory reimbursement levels from both public and commercial payers? Payers may also influence the ability of a product to gain and maintain formulary access by employing price control, particularly for therapies in rare disease markets with commercially unreasonable pricing structures, void of competition. Finally, should the product reach the stage of commercial viability, how scalable is the business model? Is the patient population so small that scaling the business may ultimately require heavy dependence on offshore markets with their own variable regulatory and access considerations?

9.5.2. Partnerships and Collaborations

Building a successful distillate business, either de novo or as a spinout, takes time. Early partnership or collaboration synergies can be a useful means of enhancing the value of a commercializing effort. A therapeutic area focus, when broad enough to identify opportunities for platform extensions, is often useful in advancing partnership programs along the product development continuum. A consolidation partner can help industry innovators with the efficacious and regulatory-expert resources needed to either move the assets further along in development or transition some assets beyond the point of investment focus. Partnerships may take the form of either direct commercialization collaborations co-promotion or option agreements on specific deals of mutual interest.

Multiple parallel product development partnerships within the same therapeutic area or product category segment can benefit from the knowledge gain and risk diffusion associated with co-development while limiting technical resource competition for the investment and knowledge and regulatory expertise focused on a narrow development portfolio by either partner. Co-promotion agreements at various stages of investment and marketing maturity for pipeline or commercial products can also be a useful way to pool existing resources and market synergies. Companies with developed and complementary sales and marketing organizations and channels can both benefit from these agreements, enhancing market-based learnings while adapting promotion budgets to pull through pricing and reimbursement dynamics. Long-term option agreements can also facilitate product development sharing in space or time-sensitive commercial markets.

9.5.3. Funding and Investment

Funding for innovative technologies in the NEURODEGENERATION space comes in many forms. With the advent of Gene Therapy and more recently Viral Vector, specific charities have committed vast amounts of capital to fund research, clinical trials, and commercialization. Pharma and biotech companies are also committed to funding global research partnerships that accelerate access to innovative technologies. Small multinational consulting firms support newly commercializing biotech companies by navigating the complex medical regulatory world by creating partnerships for reimbursement at the commercialization of their products.

Pharma and biotech companies have also invested in preclinical and clinical stage NEURODEGENERATION products through their venture arms. A research team in this field conducted research using a portfolio of data-driven guidebooks describing the partnering strategy for various companies revealing corrections for each company’s approach to partnering. More conventional venture capital sources exist that fund the entire NEURODEGENERATION space, albeit sparingly, recognized by many founders

as focused on orphan diseases with preclinical or clinical products with the potential for quick exits.

Solving the value dilemma of developing specialized therapies that will help patients with rare diseases via commercial launch or partnering for accelerated commercialization is difficult. These strategies need strong relationships with physicians who have early access to a product and who can fund treatment until the supplemental insurance is approved. As is the case with unapproved therapies for various diseases, patients often fund their therapies with help from family and friends via crowdfunding platforms, although efficacy and safety should always be validated in properly conducted clinical trials.

9.6. Scaling Access to Therapies

1. Distribution Channels Faced with novel treatment options but lacking experience with the underlying technology, many new entrants in the sector consider partnering with or acquiring an existing player with an established footprint in the market. New entrants may seek to broaden the therapeutic indication ranges of existing products, license existing commercialization rights within certain geographies, or join existing players as co-development partners. Even for a nascent field within healthcare, collaborations represent a credible option; many of the first-comer small companies within the disruptive field of now-vaccinated COVID-19 focused on respective technological strengths of messenger RNA-based, viral vector-based, and protein subunit-based solutions, acted as partners or co-space developers before developing the currently dominant-class messenger RNA-based modality together with a large player with the distribution, manufacturing, R&D, and financial heft to match such a scale.

2. Affordability and Pricing Models Developing a novel therapy for any patient within a healthcare system should be a collaborative effort. Manufacturers, payers, and providers must convene and engage stakeholders within all areas that contribute to the development of such a treatment opportunity. A thorough joint examination of potential pricing structures across sectors to assure equitable let alone affordable access for any interested patient is the first indelible step.

3. Patient-Centric Approaches Beyond creativity in pricing, a patient-centric frame of reference could benefit the interaction of stakeholders across the healthcare systems. As with other patients whose conditions may take decades to resolve or even improve, those afflicted with certain neurological or respiratory ailments may not be expected to disclose physical alleys to access innovative therapies.

9.6.1. Distribution Channels

The route to market for medicines in most economically advanced countries follows a standard model of distributors and pharmaceutical wholesalers accompanying a distributed model of retail pharmacy. Distributors are third-party entities with status and relationships with all the pharmaceutical manufacturers and pharmacy buyers which enable them to profit. In addition, wholesalers work with larger acute care hospitals, particularly for parenteral products, enabling hospital ward packs and just-in-time delivery. Specialty pharmacies are a small number of pharmacy groups working with payors and providers to drive adherence programs for critical care patients, particularly supporting patients going home on very high-cost products.

Distribution for rare disease products in the USA generally moves away from the general retail pharmacy to specialty pharmacies. This closure from normal commerce to specialty is common for the pharmacy distribution of rare and specialty products. This is achievable because the products are self-administered, taking patients away from a hospital care environment and the hard costs of hospitalization, either for the patient or the insurance purchaser. However, with the higher costs of drug distribution, both to the payor and the patient as a consumer and a shift to direct-to-patient marketing and commerce outside the traditional pharmacy and wholesale routes, there is considerable discussion about eliminating the parts of the supply chain that do not add value. As the product portfolios of many specialty pharmacy companies reflect, this adds more retail price pressure for patients and payors alike.

9.6.2. Affordability and Pricing Models

Affordability is the foremost challenge preventing patients from having access to therapies for neurological disorders. More than half of the world's regions experience shortages of essential medicines despite global production. Premium pricing of drugs, biomedical technology, and diagnostics are contributing significantly to the recurrent shortages of innovative solutions. Inadequate prices of alcohol and Tetencies caused a shortage of treatment solutions for sickle-cell disease. The pandemic further heightened awareness around pharmaceutical priorities, spurring new clauses in pricing agreements, which will hopefully also apply in the field of neural therapies.

Pursuing the responsible commercialization of innovation should be of mutual benefit to all parties: investors and innovators should expect a fair return for their efforts and countless hours of work and dedication, and human suffering or dying without access to therapies, diagnostics or medical devices should not be accepted just because for some it is not financially sustainable. Partners affected should find common ground through dialogues and partnerships promoting drugs, devices, vaccines, and other types of

technology at prices that allow for mental health and well-being. Companies are refraining from investing in the commercialization of neural and rare diseases, and solutions will only reach people in need if innovators work together with other stakeholders, aligning pricing structures while still being able to justify their pricing strategies: affordable for patients while being financially attractive enough to justify continued investments in research.

9.6.3. Patient-Centric Approaches

Some patients may find it easier to obtain a medicine than others. Some may be fully insured, while others have high-deductible insurance with co-pays, some may pay out-of-pocket for the medicine, some may qualify for patient assistance programs, and others may become reliant on third-party brokers who do not work exclusively on their behalf. As a result of these variations, some of the very patients that we envision helping through commercial efforts may experience barriers to access. While this is a problem across industries, in rare disease therapy development, it is particularly acute because the patient population is so small and so many immersed in it are motivated to do all they can to move things forward. As rare disease networks rapidly evolve and tangible access solutions are developed, our industry will need to remain vigilant to ensure that all patients have timely access to increasingly complex therapies in a way that best meets their unique needs. In the meantime, we share our best practice recommendations for companies working with both patients and their healthcare providers to ensure optimal and equitable access. Education and Support: Providing patients and families with information on access options, support programs, logistics, and follow-up can play a key role in eliminating access barriers. Dedicated programs that work with the patient or caregiver throughout the process help provide comfort during a difficult period. The provision of such assistance is especially important when starting a complex therapy, as it is easy for patients and parents to be overwhelmed. Throughout therapy, programs should also check in with patients for ongoing counsel and address ongoing questions both for logistical support and also to make sure the patient is supported.

9.7. Ethical Considerations in Medical Innovation

Medical innovation, particularly in the field of therapeutics, remains barely regulated and is tightly interconnected with commercial interests. Innovation involves the risk of association with ineffective or unsafe therapies. Financial incentives need not negatively impact these domains, but such an association can make the public skeptical and produce humorous but dark scenarios about future therapies. Medical innovation also sits uncomfortably next to patient dissatisfaction with stalled traditional therapeutic

development processes and the emergence of long-awaited therapies for highly prioritized areas such as rare diseases that have huge potential for patent and economic profit. Several high-profile cases have privileged profit over patient access concerns.

These socioeconomic ethical issues associated with medical innovation around reimbursement and access, the exercise of autonomy through informed consent, and the validation of iteration and improvement are far from quietly co-existing. Neurological and rare diseases are areas with particular challenges for the ethical questions involved in medical innovation. Here we review key considerations in the ethics of medical innovation from the standalone ethical concerns, to the intersection of medical innovation with particular ethical challenges, to the special responsibility stemming from the leverage of innovative technologies.

The analysis of the moral obligation to machine medicine, or apply existing technologies in a manner to maximize outcomes, led to a proposal to mandate pre-existing stated access violations status. The medical ethic is about using available technology to modify the course of disease, rather than mandating innovation for a technological or financial gain. The history of the role of innovative technology is one of triggering ethical questions about the impact of how new tools can impact the overriding ethical mandates of restoring the health and well-being of patients. By ignoring its responsibilities, the innovators' product could not pass appropriate moral muster.

9.7.1. Equity in Access

Innovation in medical treatments—as with economic innovation in general—has never led to equality in health outcomes. Better treatments and technologies tend to be embraced first by richer, and hence generally healthier, populations. International trade patterns reflect this tendency, with poor countries generally becoming "underconsumers" of advanced goods and services. The same is true for temporal patterns, as better treatments are taken up first by wealthier populations within the same country until diffusion of technology takes place as a result of higher income growth. Policies that aim to facilitate rapid diffusion and ensure equal access across communities can address equity in access.

Families with members suffering from a neurological or rare disorder should not experience excessive hardship just to unlock the benefits of a new therapy. The problem is not one of affordability. The patients may be willing and able to pay, but this payment may also create disruption of the balance between inflows and outflows of the household, especially in low-income countries or lower socio-economic status families. The problem of equity in access can be most effectively addressed through a universal healthcare system. In this case, costs are borne by the state and therefore spread over the

entire population. In practice, the state establishes a list of reimbursed treatments, an amount that it is willing to reimburse for each type of treatment, and a means of enforcing the rules. Given that the payment for healthcare is done as a flat tax on income or wealth, we are talking of redistribution across households: the better off pay more than the less fortunate. Healthcare costs might be best funded through a value-added tax as it associates contributions with the consumption of goods and services.

9.7.2. Informed Consent and Patient Rights

Research involving new medical therapies also has special ethical implications. When we innovate, we must be careful to ensure that our innovations are adequate not only for a small group of patients but also for the broader healthcare system. Otherwise, we risk creating patient demand for therapies that we cannot satisfy at the required scale or cost. For rare, highly special, or severe neurologic disorders in that the innovation may benefit only a few patients who are often facing dire and legitimately desperate health states, the ethical issues become all the more pronounced. If innovation is successful in patients who are so seriously unwell that they are otherwise at a highly elevated risk of death, but is ultimately not scalable to the general population, are we truly advancing science, or engaging in research based on our sense of moral mission? When we encourage patients with uncurable conditions to pursue lesions of unknown value, even with apparent efficacy in affected individuals, does this solicitation to conduct research truly constitute treatment? These difficulties are even greater in the absence of a framework of ethical sponsors to guarantee both other- and self-regard in the process.

The ideal solution would be more meaningful discussions with patients about subject roles, including an understanding of the potential for not making them better, and instead making things worse, up-front, prospectively, and very clearly, while leaving open clear avenues for ceasing treatment when needed. The concept of informed consent has become obsolete in this process. Patients/directly affected, like citizen volunteers, have a right to a greater say – more power and, importantly, responsibility – in processes as complex and high-stakes for patients as investigational therapy. The scientific and investigational elements are only part of the picture; the restoration of medical ethics, to the extent possible, requires the establishment of a patient/therapeutic relationship that empowers the affected against blatant disregard and exploitation – which, to be more concrete, if not pluralistic, means protecting them against being made worse by their short-term engagement in research or the excitement of innovation.

9.7.3. Impact of Innovation on Healthcare Systems

Regenerative and restorative treatment strategies present many important ethical considerations, and while previous sections present a discussion of considerations focused on the individual, this section presents broader considerations for how innovation in this sector may impact the structural fabric of healthcare systems. Concerns of whether companies are responsible for the excess burden on health systems or funding structural deficits raised by the introduction of innovative therapies for patients with rare diseases - conditions with recognized greater unit costs - arise and as a consequence, calls to consider those deficits in health technology assessments and reimbursement negotiations have been instituted.

The effects that innovations can have on the structural aspects of healthcare systems need to be considered when weighing the overall positive and negative effects that novel therapies will have on patients, their families, the healthcare professionals who deliver care, and the systems housing the vital, and sometimes grave, need for care. For example, if innovative motor therapies can significantly reduce the incidence of disability accompanying the progression of neurodegenerative diseases like ALS and the resulting reduction in resource demand of state-run disability programs, those need to be considered; the income previously given to patients could be redirected toward other healthcare system deficits, such as improving long-term care system compensation. The overall impact of innovations on society should also drive discussions of how we can create supportive policies to incentivize the development of these therapies and the associated steps of discovery and scaling in clinical practice. At the same time, parallels could be drawn from advancements in areas with increasing availability of novel technologies enabling scaling, such as the education system, which was not taken over by private enterprises, but whose costs were borne by the individuals and governments contributing to their funding.

9.8. Future Directions in Medical Innovation

This book identified a novel pathway for scaling access to existing medical innovations to the millions of patients who need them: early-stage commercialization. Through our multi-pronged inquiry, we learned that the funnel through which medical innovations are commercialized relies on an uncoordinated collection of economic incentives. The confluence of the high burden of disease, high unmet need, and insufficient patient populations allows commercial actors to seek potentially high profits from approved treatments for the most rare neurological and rare diseases. Certainly, the system appears to support expedited review times and high periods of exclusivity for approved products. However, the system also incentivizes companies to neglect the commercialization aspects of their development programs, important when dealing with a low-volume

market. Importantly, our approach included novel questions that shall motivate further inquiry for academic researchers and policymakers regarding the responsibilities of innovators to patients; mechanisms that support equitable access to approved medicines; and policy solutions that incentivize companies to improve their market access strategies.

While the high-risk nature of the technologies discussed in this volume presents undeniable challenges to the biomedical ecosystem, the importance of protecting patient populations affected by current cognitive blind spots cannot be understated. Such technologies are not only an important piece of the puzzle toward global health equity; they are also important opportunity areas for enabling new approaches to previously intractable health problems related to neurological and rare diseases, the importance of which has only been amplified in the context of a recent and ongoing pandemic. Through a synthesis of perspectives from technology developers, life sciences investors from private equity and venture capital backgrounds, and global health organizations, the following sections discuss priority new technology areas and policy recommendations – centered around the themes of intersectional collaboration and earlier-stage investment – believed to be able to scale early-stage commercialization pathways for the biopharma sector moving forward.

9.8.1. Emerging Technologies

Advances in technology are significantly extending the possibilities for developing therapies for neurological and rare diseases. In this chapter, we address seven of these innovations that, if adapted to relevant use cases within the scope of neurological or rare diseases, could potentially present massive advances in the speed and/or efficacy of therapy development: (1) gene therapies, (2) CRISPR and cellular base-editing, (3) gene editing, (4) induced pluripotent stem cell banks, (5) patient-on-a-chip and organ-on-a-chip solutions, (6) machine learning-guided drug design and repurposing, (7) beyond peptide and protein therapeutics. We will not cover large-market therapies or therapies that are not at the core of this work, to keep the discussion simple and focused. Unlike prior sections in this monograph, these emerging technologies are addressed in the context they will likely be used, rather than as discrete developments discussed in isolation.

As detailed below, if brought to practice, intricately improving and decreasing the risks of producing and testing therapies may greatly decrease the time, complexity, and costs of developing and commercializing neurological and rare disease therapies. While advances in technology can certainly augment the efficacy with which therapies could be developed and used unless their merits are dovetailed with fitting business approaches, the best-advanced technologies will likely not reach important patient

communities. Whether large or small companies are involved, therapy production and screening is an expensive and risky process for small addressable patient communities, which if not commercially handled curtail the viability of the companies, impacting their decisions on choosing between therapies and their development timelines.

9.8.2. Policy Recommendations

Efforts to increase understanding of barriers to access must not overshadow efforts to reduce these barriers, as this will be especially critical for ensuring sustainable growth. The therapeutic commercialization process engenders a number of barriers between the source and the patient. Levels of complexity and variability differ at each stage for different patients and programs, making a one-size-fits-all framework impractical. Generating a common framework through which to analyze different forms of scarcity would, however, be extremely useful. The commercial considerations of industry, implicit incentives of healthcare systems, and motivations of patients and advocates are poorly aligned. This lack of alignment is responsible for pockets of resistance at individual stages of the commercialization process whereby access becomes highly limited, particularly in low-income environments.

It cannot be said enough: philanthropic financing must continue to provide the essential backstop that subsidizes the cost of research, development, and production that the industry would otherwise be unable or unwilling to support. Adapting policies, identifying gaps, and addressing inefficiencies in access mechanisms would allow for the proper allocation of philanthropic capital, ideally without disrupting the flow of commercial funding. Further to this, provided the allocation of funds is clear and transparent, an ecosystem of parallel funding could be created through which industry sponsors dedicated funds, gaining legitimacy while reaffirming their commitment to the collective need for accessible therapies. Such an approach would urgently address the slow and inequitable flow of innovations to patients who need them most and create incentives for the industry to address otherwise neglected therapeutic areas and populations.

There are many ways to practically address these recommendations. Increasing the knowledge base of what we do know is important to designing better practices of engagement. Depending on the level of activity on the ground, this could either happen fairly organically or in a more structured and coordinated manner. Researchers should look to collaborate with existing organizations already delivering therapeutics to patients in low- and middle-income countries, increasing the reach and rigor of their efforts while gaining visibility.

9.8.3. Global Health Perspectives

The negative outcome for healthcare systems COVID-19 highlights the existence of fragile systems that require more attention and action. The health disparities associated with COVID-19 think of the local aspect of biomedical innovation. There is a call for local, decentralized, sophisticated but simple solutions for primary care. Primary care also suffered when advanced technology produced higher impact tests and pictures at secondary and tertiary levels and neglected primary care. The return on primary care investments is the highest investment in public health, so the answer relies on a better distribution of the resources assigned to cure diseases and those for preventing, ameliorating, or controlling diseases. The inclusion of pearls developed in low and middle-income countries in the therapeutic arsenal ethically restores a fair reward/return from pharmaceutical companies.

Health economics and health technology assessment will very soon support biomedical innovation as it has already done for many other non-health sectors. Those institutions apply strict market and consumer evaluation measures before, during, and after the launching of the product or technological organization. Although IPC has shown very promising results for drugs and devices for a small group of diverse neurological diseases few other groups have been coming together for a global approach around specific brain diseases. It seems that a local approach can filter which products, businesses, and models are more likely to be developed and invested in the respective validated niches. It seems somehow that local solutions should be validated on-site while global portfolios should be finalized and centralized.

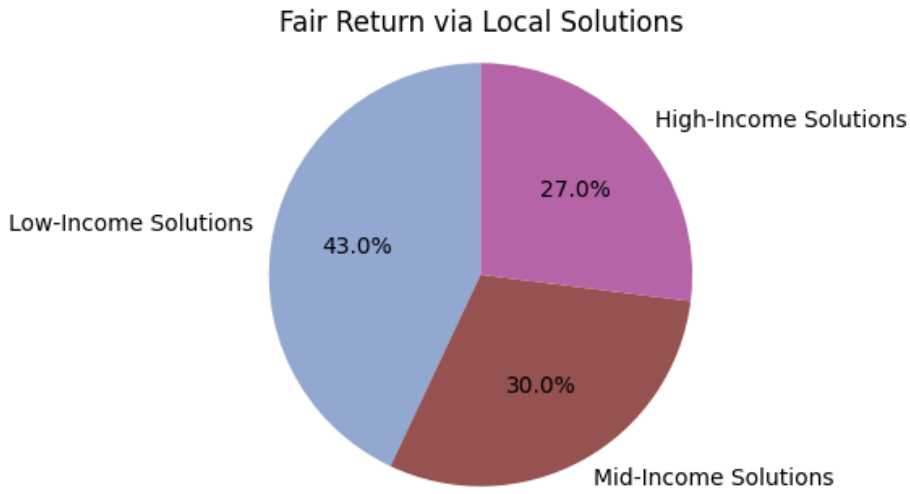

Fig 9 . 3 : Fair Return via Local Solution

9.9. Conclusion

As we near the conclusion of this book, it is crucial to answer several questions: Why did we write this book? What do we want you to take away? More generally: what is the story we want to tell? To what end? In a world in which lives can be saved or at least improved by technologies with a major impact on endemic and pandemic diseases and which should also be able to support the aging population and enhance the quality of life of those living with neurodegenerative conditions, the problem is not research of innovative therapies for rare or neurological conditions; it is not even the development of these technologies. It is their commercialization. Other scars have already marked the history of humanity: hunger, wars, and plagues. Commercializing innovation through MedTech and biotech companies is a key strategy to face the persistence of these scourges.

History has shown that, along happy or tragic paths, a handful of companies represent the majority of the wealth in the world. These are precisely the few that have shown the ability to turn value into monetary value. Investing in innovative pharmaceutical, biotech, or medtech companies does not mean recognizing a donation offered to a cause: it means backing a venture looking for revenues, profits, and wealth. In conclusion, we hope this book unveils the complexity of the commercialization process and inspires emerging innovative and promising biotech or medtech companies. The end of the story is not merely the launching of a product. Addressing important clinical questions is just the beginning. The real power of the scientific method is the ability to embrace the possible unintended consequences of commercialization, amplifying the message encoded in innovative technology: how can innovation serve society?

9.9.1. Final Thoughts and Implications for the Future

The unconventional and disruptive nature of developing therapies for neurological and rare diseases demands the next generation of approaches in regular, ongoing commercial therapy progression and planning from the earliest stage of work, which reduces the pervasive trajectories that have defined the market lessons and failures we describe herein. Otherwise, the challenging commercial environment, even after product approval, with small markets, high costs, limited revenues, and potential payer resistance will continue to savage naive strategies. Earlier and continued partnerships with payers, including formulary considerations, and particularly considering pricing early on will be increasingly necessary. The recent need for dual and changing pricing strategies for various economic regions underlines this but also provides some hope for product success. Variations based on geography, dependency of economies, co-morbidities, combined therapy with other medical innovations, disease severity, and others will all

require understanding and tailoring for reasonable revenues without sharing excess at the cost of patients' access and equitable but prudent sharing of product costs.

Fortunately, there are growing examples of savvy marketing that have greatly opened therapeutic access. These can come from understanding the advantages of novel methods of commercial implementation, like early and digital channeling, therapy deliverable creativity, pestering market message and educational persistence, and stakeholder engagement interacting with partners, especially at society meetings. An improved understanding of the economics of time lost coupled with truly patient-centricity can be helpful. We all are facing increasing physician pressures as the economy of their practice has changed due to patient flow and management economics, especially with fixed no-fault payment. The patient-centric approach needs to creatively consider these influences. We are at a crossroads, whether unique special populations with their exciting riches have nurtured new approaches that allow a much wider, creative share possible to reverse the terrible linchpin focus on riches or whether decision-making on accessing formal commercial pathways will revert to the premium-focused mindset of the past. Your choices, and how you honestly look in the mirror will decide.

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