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# Strategic Portfolio Prioritization in the Age of Gene and Cell Therapy

- As the possibilities of gene and cell therapy move from breakthroughs in the lab to commercial realities, biotechnology and pharmaceutical companies are tasked with identifying the next set of opportunities to grow their portfolio
- Triangle Insights recommends a 3-pronged approach to portfolio strategy that involves the careful consideration of each potential opportunity across its commercial potential, development risks and resources required, and strategic fit for the company
- It is the balance of these three factors that ensures a comprehensive mix of programs that is positioned for sustainable growth

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## Introduction

Gene and cell therapies are rapidly moving from possibilities in the lab to realities in the clinic. As biotechnology and pharmaceutical companies are confronted with deciding which opportunities to pursue, numerous strategic considerations emerge. Leaders who were previously focused on demonstrating the viability of remarkable, but uncertain innovations now face a new question: How should the portfolio be structured to best align to the company's strategic objectives? Given the variety of opportunities made possible by these platforms, the options for product development can appear nearly endless.

Strategic portfolio prioritization requires a clear articulation of the company's goals, evaluation of the market landscape, and a sober assessment of the organization's ability to transition medicine from the laboratory to production. As companies prioritize their next wave of gene or cell therapy assets, considerations for each potential program should be made along three key dimensions: commercial potential, development risk and resource requirements, and strategic fit.

Balancing these three strategic considerations will enable companies of all sizes to achieve clarity in portfolio prioritization.

***Figure 1: Key Areas for Consideration in Strategic Portfolio Prioritization for Gene and Cell Therapy Applications***

| 1 Commercial Potential | 2 Development Risk and Resource Requirements | 3 Strategic Fit |
|---|---|---|
| *By assessing potential opportunities through diligent identification of the addressable population, unmet need, existing and future competition, and evolving treatment paradigms, companies can focus their bets on programs most likely to achieve commercial success.* | *Through evaluation of the technical, clinical, and scale-up feasibility of an asset, manufacturers will be able to avoid or mitigate challenges to commercialization.* | *A clear understanding of a company's established goals, existing capabilities, access to capital, and risk tolerance provides a framework to understand the strategic fit of an asset within a broader pipeline.* |

## Commercial Potential

As novel approaches with incredible potential to treat patients with severe disease burden, gene and cell therapies offer a new frontier of opportunity. However, characterizing these opportunities can present significant challenges. Teams face many unknowns associated with pioneering entry within nascent markets or disrupting mature markets with a transformative technology. An evaluation framework that enables thoughtful consideration of the target patient population, standard of care, level of competition, and value proposition of the therapy is essential.

Zolgensma, Novartis's recently approved gene therapy for spinal muscular atrophy (SMA), is a model example of the potential for cell and gene therapies to address a debilitating condition. Yet, beyond a surface-level recognition of Zolgensma's target indication and transformative potential, a host of factors must be considered to understand the potential market opportunity. One such factor is the size of the **addressable patient population** that can be served with the therapeutic in development. In the case of SMA, an autosomal recessive monogenic disease, the entire prevalent population can be addressed with a single gene addition approach. On the other hand, in cases where a condition can be caused by multiple genes (e.g. retinitis pigmentosa), or, particularly for genome editing, in cases where the condition can be caused by multiple mutations in the same gene, the therapeutic approach may only address a specific subset of the population. In these cases, additional factors may then limit the pool of addressable patients. For Zolgensma, FDA approval has initially been granted for the treatment of all SMA types but only in newborns and toddlers. Teams responsible for portfolio strategy must assure they have identified the true addressable patient population to ensure they are building an accurate perception of the available opportunity.

*Figure 2: Examples of the Complexity Associated with Estimating the Addressable Patient Population for a Gene Therapy*

| | Lower Complexity | Higher Complexity |
|---|---|---|
| **Addressable Patient Population** | • Autosomal recessive genetic diseases, caused by a single gene, that can be addressed with a gene addition approach (regardless of mutation) | • Genetic conditions caused by mutations in one of several genes<br>• Genetic conditions caused by multiple mutations in the same gene |

Cell and gene therapies may present paradigm-shifting value propositions for nearly any indication, but the extent to which the standard of care is improved upon can notably impact the opportunity size. Conditions where treatment options are wholly unavailable or aimed only at symptom-relief would enable any effective cell or gene therapy to represent a strong value proposition. On the other hand, if the condition is currently adequately treated by chronic management strategies, a **curative gene therapy may provide value, but the value may be associated with patient convenience/compliance by providing a far lower frequency of administration**. Accounting for these two unique scenarios, a relatively lower value proposition as presented in the latter example may result in lower market penetration but still correspond to an attractive total opportunity if associated with a condition with a larger total patient population.

*Figure 3: Examples of How the Value Proposition of a Gene Therapy Factors into Potential Commercial Opportunity*

| | Potentially Lower Value Proposition | Potentially Higher Value Proposition |
|---|---|---|
| **Technology Value Proposition** | • Convenience/compliance benefit: (e.g. constitutive monoclonal antibody (mAb) production in indication with conventional mAbs available) | • Unique efficacy benefit: Effective therapy for conditions with high unmet need that cannot be addressed with conventional technology |

Beyond condition-specific considerations, **competition** will become an increasing consideration as more companies enter the gene and cell therapy space. Competitors with similar platform technologies will have to differentiate effectively in order to maximize the available opportunities. Whether it be through selection of a specific gene target, optimization of the transgene delivered, development of a superior vector, or targeting of a particular cellular marker, the final key to success is the defense against the threat of other gene and cell therapies.

## Development Risk and Resource Requirements

Compared with conventional drug development, additional considerations must be made for the development risk and resource requirements for gene and cell therapies. These factors include:

- Technical feasibility
- Clinical and regulatory uncertainty
- Market access uncertainty
- Manufacturing and scale up complexities

These factors must be considered compared with the overall opportunity in order to maximize value of the portfolio.

One of the first considerations toward this end may be in the **technical feasibility** of the therapeutic approach for the condition of interest. In situations where the genetic mutation(s) results in a protein deficiency, a relatively straightforward gene addition strategy may be applied. For more complex scenarios, such as conditions where mutations lead to dysfunctional proteins, protein aggregates, or another altered state, an effective therapy

may require an approach that both suppresses a mutated allele and increases the production of the normal copy. Even gene addition strategies can be associated with further complexity, for example, when the size of the endogenous gene exceeds the packaging capacity of the vector. In these cases, development of alternative strategies such as miniature versions of the original gene (e.g. Pfizer's mini-dystrophin and Sarepta's micro-dystrophin candidates for Duchenne Muscular Dystrophy) or dual vectors may be required.

Technical feasibility extends beyond the therapeutic itself and into its interactions with complex biological systems. In their current state, most gene therapy technologies are permanent (in the case of integrating vectors or genome editing) or constitutively active (in the case of non-integrating vectors). For some conditions, this level of durability without the ability to fine-tune or inactivate expression could potentially have unintended long-term consequences. To overcome these additional technical complexities, considerable investment in R&D capabilities and development time may be required.

Since consistent and persistent efficacy and safety are expected from cell and gene therapies, a thorough grasp of the biological barriers to delivery and subsequent physiological consequences is paramount to defining the potential of a program in consideration. While approved agents such as Luxturna and Zolgensma achieve relatively consistent, concentrated delivery in a localized region, success of approaches that require broader administration (e.g. intravenous) may depend on achieving a fine balance between sufficient delivery to the target site while evading the immune system or avoiding potential off-target effects. Further, while some conditions can be addressed by a wide range of gene expression levels and may not require expression from a particular physiological target (such as in hemophilias A and B), others may demand broad cellular transduction at a specific site of action (such as in many liver-specific diseases, CNS disorders, or cardiomyopathies). Finally, toxicity challenges observed with CAR-T therapies highlight that the therapeutic window for complex products cannot be explained by delivery and therapeutic expression alone. With each of these factors in mind, **the technical features of an asset become inextricably linked to decision-making around indication prioritization**.

***Figure 4: Examples of the Differences in Technical Complexities that should be Considered for Gene and Cell Therapies***

| | Lower Potential Complexity | Higher Potential Complexity |
|---|---|---|
| **Therapeutic Approach** | • Straightforward gene addition, within size limits of vector | • Combination approaches (e.g. gene knockdown + gene addition)<br>• Addition of larger genes<br>• Tunable gene expression |
| **Delivery** | • Localized delivery for local expression | • Systemic delivery |
| **Transduction Efficiency and Expression Levels** | • Low levels of expression can achieve a therapeutic effect<br>• Expression from a specific physiological target not required | • Broad expression required in a specific subset of cells, tissue, or organ<br>• Narrow therapeutic window |

Beyond an asset's therapeutic potential, a clear understanding of the clinical, regulatory, and managed care environments must be considered ahead of committing substantial resource investment. On the regulatory front, teams must be prepared for oscillations between enthusiastic encouragement and returns to caution from decision-makers. Already, the National Institutes of Health (NIH) is repurposing the Recombinant DNA Advisory Committee (RAC) to expand beyond human gene transfer, while the FDA has developed a broad series of guidance literature over the past two years focusing on regenerative medicine product development. Understanding new avenues for expedited development and approval that may be tied to disease epidemiology, as in the case of "regenerative medicine advanced therapy (RMAT)" designation, can have a profound effect on the commercial opportunity of an asset. Likewise, as regulators expand in number and scope, ensuring robust communication across regulatory channels will be key to mitigating risk. In turn, **increased scrutiny from regulators (as well as payers) may be expected moving forward, and**

**this may pose greater challenges for manufacturers to meet increasingly robust performance expectations**. In the same way that companion diagnostics and validated biomarkers have refined target patient populations and lent confidence toward pricing and reimbursement, the consistency and durability of outcomes in gene and cell therapies may define market access decision-making moving forward.

Development risk and resource allocation within product manufacturing and distribution must be considered also. Several manufacturing models have been proposed (e.g., point-of-care, distributed, centralized), with decision-making varying based on product requirements, in-house capabilities, and the availability of third-party developers, manufacturers, and distributors. Consistency of sourcing and processing become even more critical when developing complex biologics as "on-demand" products, where their functionality within patients fundamentally drives their performance. Furthermore, scalability is often limited, and places increased pressure upon both in-house capabilities and contract services to meet clinical and commercial batch demands. Manufacturers of off-the-shelf viral vectors and CAR-T therapies have felt this scarcity firsthand, experiencing longer development timelines and a more complicated growth strategy compared to conventional therapeutics. Effective innovators in the gene and cell therapy spaces will plan for each of these demands, and leverage a comprehensive indication prioritization with an expedited clinical and regulatory strategy that takes into account manufacturing as well as technical limitations.

## Strategic Fit

Gene and cell therapy business models may require portfolio strategies that differ from those designed for conventional technologies. Individual companies must consider current and desired capabilities while potentially readying for a partnership to advance development programs.

**Strategic objectives within a gene or cell therapy business model should be informed by current human resource, technical and financial capabilities. These considerations likely contribute to the marked variation in portfolio development strategy observed across companies in the gene and cell therapy space.** A large pharmaceutical company considering the addition of a new gene or cell therapy technology may have a more macro strategic objective, such as building a brand within a technology or therapeutic area. The Novartis acquisition of AveXis for $8.7 B in 2018, for example, expanded Novartis' position as a gene therapy and neuroscience leader. Conversely, smaller biotech companies are more commonly focused on the advancement of a specific technology platform, such as a novel viral vector for enhanced delivery or uptake in specific tissues. A near-term strategic objective for such a company may be to successfully validate the preclinical technology in the clinic.

Once the strategic objectives have been defined, a gene therapy company must take into account the specific mechanics required to drive the transformation of their current capabilities. **Core to this consideration is the concept of risk mitigation; companies must construct a strategy that incorporates the internal appetite for risk at each stage of development.** Larger companies with greater resources may choose to acquire multiple high-risk, high-reward preclinical platforms with the hopes that some will be able to advance their portfolio. Early-stage platform companies, however, must first validate their platform by purposefully pursuing indications where a high degree of confidence can be placed in the proof-of-concept and/or where a clear value proposition over the current standard of care is evident. Unlike conventional therapeutics, long-term commercial outcomes and the benefit of hindsight do not yet exist in the gene and cell therapy space, thus necessitating a meticulous process for portfolio expansion that is driven by clearly defined short and long-term goals.

Gaining credibility and trust from potential partners or investors throughout the development process can also be critical to a company's success and should be considered alongside the strategic objectives of the portfolio. For an early-stage company, academic partnerships may be valuable because they facilitate both the testing of novel technologies and orthogonal expansion of existing platforms, thus supporting a more diverse portfolio for long-term growth. Additionally, an academic partnership can provide valuable preclinical models and data, leveraging capabilities that may otherwise be outsourced, to validate the platform to investors and partners. Larger pharmaceutical companies, in contrast, may aim to establish credibility within a therapeutic area or component of commercialization. Manufacturing capabilities, for instance, are of particular concern for these types of therapies. Therefore, larger companies may develop expertise in a therapeutic area to establish trust in the industry before purchasing clinically validated assets that will benefit from their commercialization infrastructure.

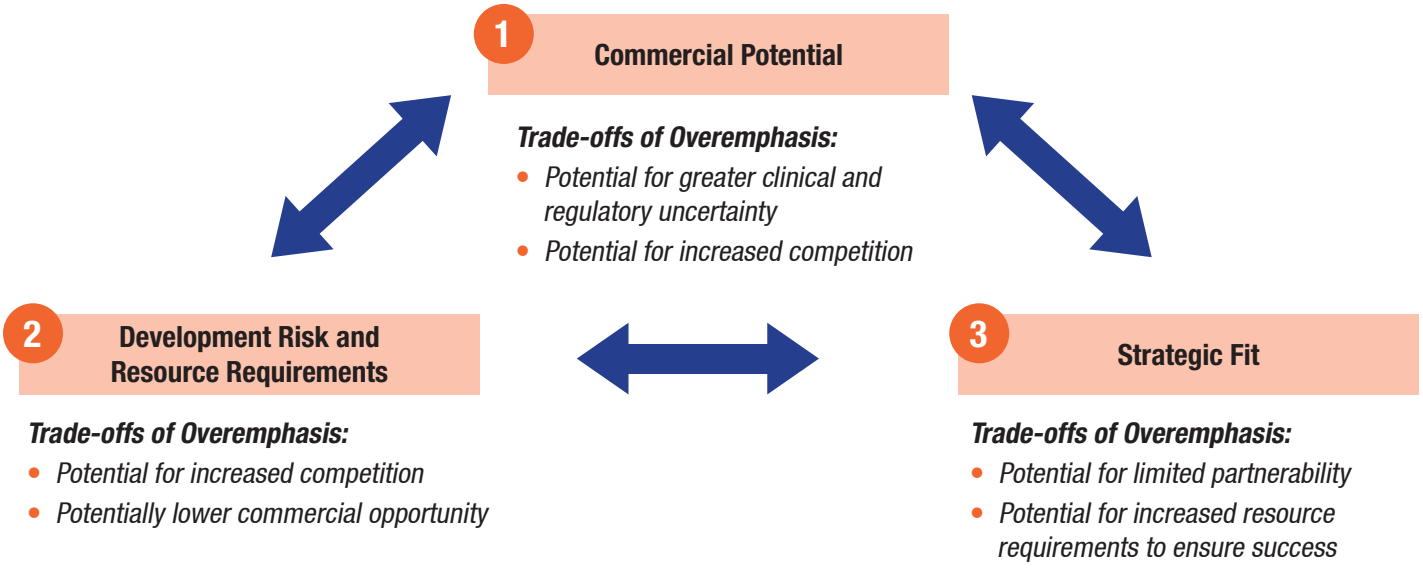
## Closing Thoughts

The novelty of cell and gene therapies introduces several scientific, regulatory, and strategic considerations that must be carefully balanced for any biotech or pharmaceutical company to be successful. Though the individual goals and benchmarks will differ depending on a company's size, market position, and strategic objectives, portfolio strategy should almost always be driven by a combination of considerations for opportunity size, risk and resource requirements, and strategic fit.

While the commercial potential of an opportunity in consideration is often a key driver in whether the program should be pursued, this must be balanced with the development risk and resources required to ensure clinical and commercial success. Opportunities with seemingly large commercial potential but with unchartered clinical or regulatory pathways could result in additional upfront resources required to conduct exploratory trials or protracted studies powered to achieve significant differences in functional outcomes. Furthermore, opportunities with higher commercial potential may also attract other gene and cell therapy competitors. Companies focusing solely on the technical capabilities of their technology may lack the required expertise or resources to navigate the ever-shifting regulatory landscape. As such, even with a potentially revolutionary product, those therapies may never achieve the critical clinical milestones that allow for approval and commercial success. In contrast, an overemphasis on mitigating development risk may result in a portfolio focus in areas with higher competition (and thus potentially lower commercial opportunity), since these spaces may represent easier proof-of-concept programs for other gene and cell therapy companies as well.

Both the commercial potential and risk/resource profile of a potential portfolio program should be balanced by how the potential asset aligns with the strategic objectives of the company. A lack of focus towards strategic fit may result in unsuccessful development due to limited or misaligned internal capabilities and resources. On the other hand, overemphasis of esoteric internal initiatives may limit potential partnership opportunities that could dramatically propel a cell or gene therapy's path towards becoming a commercial product. For larger companies, a single focus on a specific objective, such as seeking a position as a market leader in a prioritized indication or technology, without considering other factors, may result in overpaying for assets that have a limited technical foundation or require considerable back-end support to achieve profitability.

***Figure 5: A Comprehensive Approach: Balancing Commercial Potential, Development Risk and Resource Requirements, and Strategic Fit to Achieve a Sustainable Portfolio for Near-Term and Long-Term Development***



The recent examples of Luxturna and Zolgensma highlight the difficulty of being a frontrunner in the gene and cell therapy landscape, as both products have initially struggled to meet revenue and value projections, despite offering transformative treatment options for patients with debilitating conditions. Pricing, reimbursement, and other associated challenges for these novel therapies should serve as a cautionary tale on the realities imposed by the current healthcare system that, at present, contrast with the high expectations associated with these therapies in general. While there may be nuances associated with population sizes (e.g. rare vs. non-rare) or the adequacy of current treatment options, these challenges will likely exist for any novel gene or cell therapy, at least for the foreseeable future.

The exciting scientific achievements of gene and cell therapy carry with them a promise of groundbreaking medical advancements and lucrative potential products across any number of different therapeutic areas. However, with new discoveries comes the requirement of new thinking in commercialization and development as traditional business models may not prove effective. Applying a portfolio strategy that balance commercial potential, risk and resource requirements, and strategic fit is critical to realizing long-term, sustainable success with these platforms.

## About Triangle Insights Group

Headquartered in Research Triangle Park, Triangle Insights Group, LLC is a strategy consulting firm providing guidance on the most critical business issues to leaders in life sciences organizations. The firm's approach combines deep knowledge of the industry across therapeutic areas and functional groups, with a dedication to creativity and disciplined critical thinking. Recommendations from Triangle Insights Group are original, relevant to the industry environment, and supported by rigorous analytics. Clients of Triangle Insights Group include large pharmaceutical companies, emerging biotechnology firms, diagnostics manufacturers, medical device companies, and private equity investors.

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Has thirteen years of pharmaceutical and consulting experience. Gautam focuses on providing strategic guidance to clients within life sciences organizations. His recent engagements have involved commercial assessment, indication prioritization, white-space strategy, commercial model design and in-licensing/ out-licensing support.

Gautam has provided strategic advice to a wide range of clients, spanning Top-5 pharmaceutical manufacturers, emerging biotechnology manufacturers, bio-pharmaceutical investors, and service providers to bio-pharmaceutical companies. He has spoken at several industry conferences (LES, CED, EBD, BIO-Windhover, CHLA, Banff Venture Forum) and has published a peer-reviewed article on deal timing.

His previous employers have included GlaxoSmithKline, Boston Consulting Group and Campbell Alliance, where he was a Senior Practice Executive and led business/corporate development efforts for the central region. Gautam received his M.B.A. from the Fuqua School of Business at Duke. He holds an M.S. and a B.S. in Bio-Statistics from UNC-Chapel Hill.

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Chris has worked as a Senior Practice Executive with Campbell Alliance where he led the company's Business/Corporate Development efforts for the NY and NJ region. His recent management consulting experience has centered on corporate strategy and market opportunity assessments for life science companies and investors.

While at GlaxoSmithKline, Chris's scientific accomplishments led to multiple patent authorships and peer-reviewed publications, as well as discoveries resulting in over $30 million in company cost savings. In business development roles, Chris was responsible for corporate strategy and reviewing in-licensing and out-licensing opportunities. Chris earned an M.B.A. from the University of North Carolina Kenan-Flagler Business School as a member of Beta Gamma Sigma academic honor society. He has an M.S. from the University of Buffalo and a B.S. in Biochemistry from the University of Rochester.

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Recent by-lined articles have appeared in Pharmaceutical Executive, InVivo, Nature Biotech, RPM Report, and Scrip. In addition, Ben's case studies on the pharmaceutical industry have been used in graduate business programs.

Ben is the chairman of the Life Sciences Sector of the Licensing Executive Society. He has also been a member of the program committee for the BIO International Convention. Prior to the founding of Triangle Insights Group, Ben was the leader of the Business Development Practice at Campbell Alliance and a partner in the Strategy practice at Oliver Wyman (formerly Mercer Management Consulting/Strategic Planning Associates). Ben earned an M.B.A. from the Stanford Graduate School of Business and a B.S. from Duke University.

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Barrett's previous management consulting positions in the life sciences industry were with Campbell Alliance and Boston Healthcare Associates. He also founded an independent life sciences consulting firm prior to the founding of Triangle Insights.

His background also includes client-side experience within the pharmaceutical industry. For plasma manufacturer Grifols Therapeutics (previously Talecris), Barrett led market intelligence for the pulmonary franchise including Prolastin-C, an orphan drug indicated for alpha-1 antitrypsin deficiency. Barrett received his M.B.A. from the Tuck School of Business at Dartmouth College. He holds a B.A. from the University of Virginia. He has been a lecturer at several life science industry conferences.