

# UNLOCKING POTENTIAL CURES WITH CRISPR

## Indication Selection And Portfolio Strategy For CRISPR-Based Gene Editing Companies

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### HEALTH ADVANCES

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#### EXECUTIVE SUMMARY

- CRISPR-based gene editing technology is differentiated from other modalities, even traditional gene therapies, unlocking potential cures for a range of indications but also presenting unique developmental challenges
- Devising a portfolio strategy for CRISPR-based gene editing therapies requires considering the unique therapeutic potential but also the technical, clinical, and commercial complexities

In this whitepaper, Health Advances proposes a framework for indication selection and portfolio strategy for CRISPR-based gene editing companies:

- Suitable indications should have a compelling unmet need and strong scientific rationale for using a gene editing approach compared to other modalities
- Based on the level of competition and addressable market size, indications may fall into one of four categories:
  - “Platform validation”
  - “Value driver”
  - “White space”
  - “Holy grail”
- A balanced portfolio of CRISPR programs should align with the sponsor’s capabilities, near-term clinical and commercial goals, and long-term strategy

## INTRODUCTION

2020 saw the first ever dosing of CRISPR-based therapies in humans, with Editas and Intellia Therapeutics initiating Phase I trials in Leber's congenital amaurosis 10 and transthyretin amyloidosis, respectively. Clinical trials of CRISPR have been highly anticipated, given the excitement surrounding CRISPR and other promising gene editing technologies. Since its inception, CRISPR has been hailed as a cure for diseases ranging from blood disorders to neurodegenerative diseases to various forms of cancer (not to mention controlling malaria-spreading mosquitos!). Amid this hype, the casual observer may have been surprised to find out that the first human trials of CRISPR therapies were not conducted in large, well-known diseases but instead in rarer diseases with perhaps hundreds or thousands of Americans diagnosed each year. In fact, while the pipelines of CRISPR companies include higher prevalence indications such as cancer, sickle cell disease, and  $\beta$ -thalassemia, they also contain many other orphan diseases. Why did researchers choose such obscure diseases as their lead indications for a revolutionary gene editing technology? How should companies built around emerging gene-editing technologies compete against more mature modalities for gene therapy using vectors like AAV and lentivirus? And generally, how should companies think about their translational and portfolio strategies surrounding unproven but promising gene editing technologies like CRISPR?

## WHAT IS CRISPR GENE EDITING?

Researchers have possessed tools for modifying the genetic material of lab models such as bacteria, yeast and human cell lines since the 1970's. The discovery of the CRISPR system and the subsequent development of CRISPR-based gene-editing systems have generated substantial interest. Compared to predecessor gene-editing technologies like Zinc Finger Nucleases and TALENs, CRISPR tools have a greater ease of generating the desired DNA-modifying tool and higher levels of enzymatic activity in human cells. The main features of CRISPR-based research tools are the ability to a) modify a cell's DNA (such as cutting the DNA or altering its sequence) and b) precisely direct that modification to a specific region of the cell's genome<sup>1</sup>. Further bioengineering has also expanded the applications of the CRISPR system, as described in the sidebar.

## WHAT INDICATIONS DOES GENE EDITING UNLOCK?

*Key Takeaway: Gene editing tools are differentiated from other modalities, even traditional gene therapies, unlocking potential cures for a range of indications.*

Gene therapies represent an exciting advance over traditional therapies for chronic conditions, such as small molecules and biologics. While most drugs treat the symptoms of disease or attempt to restore balance to an

## CRISPR TOOLKIT GLOSSARY

### Gene Disruption

- CRISPR protein is directed to cut DNA, which is repaired by error-prone processes
- Results in nucleotide insertions or deletions that alter or destroy gene function

### Targeted Integration

- Both the CRISPR protein and template DNA are supplied to cells; after the genomic DNA is cut, the template may be preferentially integrated at the cut site
- Results in gene restoration (although error-prone repair may also occur)

### Regulation of Gene Expression

- CRISPR fusion proteins are recruited to specific genomic loci for transcriptional regulation
- Results in the activation or repression of transcription

### Base Editing







- Impaired CRISPR protein and associated enzymes make chemical changes in the nucleotide
- Results in targeted point mutations without cutting the DNA

### Prime Editing

- CRISPR proteins are programmed with a guide RNA that specifies target site and desired edits
- Can result in all point mutations, small insertions, and small deletions

imbalanced system, gene therapies could address the genetic root cause of the disease with just one or several doses, representing the potential to permanently cure the patient and eliminating the need for future therapy.

Traditional gene therapies use vectors – typically modified viruses – to deliver a functional copy of a gene to a patient’s cells. As such, traditional gene therapy is most appropriate for diseases in which a patient’s cells lack a functioning copy of a protein or sufficient levels of that protein’s production. There are still many barriers to widespread use of gene therapies, including safety concerns around viral vectors and a pricing model to equitably provide access to cures, and the first commercial applications of gene therapy have indeed been for narrowly defined patient populations with high unmet need (Figure 1). However, the limited proof points to date speak to the astounding potential of traditional gene therapies.

<b>Product</b>	 LUXTURNA® voretigene neparvovec-rzyl for subretinal injection	 zolgensma® (onasemnogene abeparvovec-xioi)	 KYMRIAH® (tisagenlecleucel) YESCARTA® (axicabtagene ciloleucel)
<b>Company</b>	 Spark THERAPEUTICS	 NOVARTIS	 NOVARTIS GILEAD
<b>Indication</b>	Leber Congenital Amaurosis, Retinal Dystrophies	Spinal Muscular Atrophy (Type 1)	R/R B-cell lymphomas
<b>Treatment Alternatives</b>	<ul style="list-style-type: none"> <li>No approved treatments prior to the gene therapy</li> </ul>	<ul style="list-style-type: none"> <li>Spinraza first approved treatment for SMA (2016)</li> </ul>	<ul style="list-style-type: none"> <li>5-year OS of 27% prior to approval of CAR-T's</li> </ul>
<b>Natural Course of Disease Development</b>	<ul style="list-style-type: none"> <li>Leads to complete blindness without intervention</li> </ul>	<ul style="list-style-type: none"> <li>Muscle weakness and atrophy</li> <li>Typically fatal by age 2</li> </ul>	<ul style="list-style-type: none"> <li>No effective alternative treatment options for late-line / refractory patients</li> </ul>
<b>Year of Approval</b>	2017	2019	2017
<b>List Price</b>	\$850K	\$2.1M	\$373K to \$475K

**Figure 1: Gene Therapy Drugs Overview**  
Source: Health Advances analysis, DataMonitor, company websites, Sehn 2015 Blood.

The unique capabilities of CRISPR-based gene editing tools further expand the arsenal of gene therapy technologies and consequently the range of indications that drug developers can address. While traditional gene therapies deliver synthetic genes to cells to restore function, gene editing aims to modify a cell’s existing DNA. Gene editing is thus capable of addressing the following types of genetic diseases:



### Removal of Harmful Genes

- The simplest form of gene editing is the inactivation of portion of a cell's DNA, which can address the subset of genetic diseases caused by the presence of a harmful or even deadly protein
  - This includes “autosomal dominant” diseases such as Huntington’s Disease, in which a toxic form of the Huntington protein is produced in a patient’s neurons, leading to neurodegeneration and eventually death
- In these instances, delivery of a healthy gene may not be sufficient to restore a cell’s function; instead, the toxic protein must be removed, potentially requiring gene editing approaches<sup>2</sup>



### Restoration of Damaged Genes

- Other diseases addressable by gene editing include instances where the repair of a mutated gene is more feasible or efficacious than attempting to deliver a wholly new gene to the cell via gene therapy
- The majority of human genetic diseases are caused by mutation of a single DNA base in the protein’s coding sequence or regulatory regions<sup>3</sup>
  - For example, most cases of cystic fibrosis are caused by the lack of just one amino acid building block (out of more than 1,400 total) in the CFTR protein
  - Researchers can use modified versions of the original CRISPR gene editing system to repair such mutations, representing the potential for a safer and more effective gene therapy for CF and other similar diseases<sup>4</sup>



### Modulation of Gene Expression

- Gene editing may also be used to unlock the hidden curative potential within a patient’s own cells
- For example, patients with sickle cell disease and beta thalassemia have mutations in the hemoglobin gene that lead to reduced function and disruptive symptoms such as vaso-occlusive crises
  - Clinical trials are underway in which gene editing is used to restore production of fetal hemoglobin, a version of the gene that is active during embryonic development but then silenced as humans develop
  - In treated patients, the production of fetal hemoglobin is sufficient to offset or even eliminate the disease symptoms<sup>5</sup>

## WHAT IS DIFFERENT ABOUT GENE EDITING PORTFOLIO STRATEGY?

*Key Takeaway: Devising a portfolio strategy for CRISPR-based gene editing therapies requires considering the unique therapeutic potential but also the technical, clinical, and commercial complexities.*

Aside from the unique therapeutic potential, CRISPR-based gene editing assets present some additional nuances for portfolio strategy compared to other modalities. These include the scalability of R&D, the approach to life cycle management, the greater need for technical and clinical validation, and the challenge of recruiting patients for clinical trials. Together, these factors underscore the need for gene editing companies to maintain a robust pipeline to improve the probability of success and sustain revenues over the long term.



### Scalability

- Gene editing therapies are often customized to address a very specific genetic mutation, and therefore the potential to distribute learnings and milestones between programs may be lower compared to other modalities
  - For example, due to the custom nature of each CRISPR program, it may be difficult or impossible to expand the indication of a therapy after its first approval, with each indication requiring a separate BLA
- Additionally, the translational research and delivery strategy for, e.g., an ocular therapy, may not transfer to programs in the ear, brain, or liver; likewise, the success of an ex vivo gene editing program may not assist the development of an in vivo program



### Life Cycle Management

- Much like traditional gene therapies, which can permanently cure a disease, gene editing assets have a shorter life cycle than traditional modalities
- Particularly for ultra-rare diseases, the pool of untreated patients may quickly shrink after only a few years on the market



### Required Investment

- Gene editing programs require a significant upfront investment
  - In addition to R&D and preclinical studies for the new modalities, many rare genetic disorders have never been studied in clinical trials
  - Thus, sponsors must first pioneer natural history studies and clinical trial design, meaning additional investment before running interventional clinical trials



### Patient Recruitment

- A gene editing sponsor's ability to recruit patients for clinical trials is key to its commercial success
  - For some indications, gene editing approaches must compete with other modalities, such as traditional gene therapy, RNA-based therapies, and biologics, to recruit patients
  - Even for rare diseases, where small populations of patients are managed by a handful of referral centers, sponsors may be in competition with other gene editing companies
  - In these situations, the timing of entry into the clinic and recruiting patients relative to competitors could be the difference between success and failure of the program.

## FRAMEWORK FOR GENE EDITING INDICATION SELECTION AND PORTFOLIO STRATEGY

### How Should CRISPR Companies Prioritize Indications?

*Key takeaway: When prioritizing indications to determine suitability for gene editing, unmet need and scientific rationale should be among the first considerations.*

**Unmet Need:** While all drug development programs aim to satisfy a compelling unmet need, this factor is especially important given the high cost as well as the elevated risk profile associated with gene therapy.

Gene therapies are among the most expensive drugs ever launched, with list prices approaching \$1MM per dose (Figure 1). A single dose of curative gene therapy may indeed cost less than a lifetime of chronic treatment, and manufacturers are exploring innovative funding models to improve patient access<sup>6</sup>. However, the high sticker

price means stakeholders – patients, physicians, and payers – will be expecting a substantial benefit in return. This means that the technology should address diseases in need of a therapy in the short-term.

Gene therapy is also considered a high-risk therapy compared to traditional modalities such as small molecules or biologics. This is in part due to both the potential immunogenicity of gene therapy vectors such as adenoviruses – which has led to fatal reactions in clinical trials<sup>7</sup> – and the risk of causing permanent genetic damage in a patient's cells<sup>8</sup>. Efforts to address these challenges are underway, but in the near-term, gene therapy will typically only be considered for patients with fatal or highly debilitating diseases that currently do not have effective therapies.

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**Scientific Rationale:** Among potential gene editing indications, sponsors should prioritize those that have a high mechanistic probability of success, a technical advantage relative to other modalities, and a higher feasibility of CRISPR drug delivery.

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**Amenability to CRISPR Gene Editing:** Much as some disease targets are considered 'undruggable' by small molecules, a genetic defect can be more or less amenable to CRISPR-based gene editing approaches. Based on a range of factors – some of which are poorly understood – some mutations can be more efficiently and predictably modified by CRISPR-based gene editing tools than others. An additional element of amenability to gene editing is the level of gene rescue required. For example, a mutation that results in the absence of protein might require a low level of successful gene correction in order to impact the disease phenotype. This may be the case for diseases resulting in blindness or deafness, as the brain has been shown to amplify audio or visual signals; or for organs such as the liver, where research has shown that cells that undergo corrective gene editing can increase in abundance relative to unedited cells. On the other hand, a much higher proportion of gene editing may be required to provide the intended therapeutic benefit for autosomal dominant diseases, as trace amounts of the mutant protein may still be toxic.

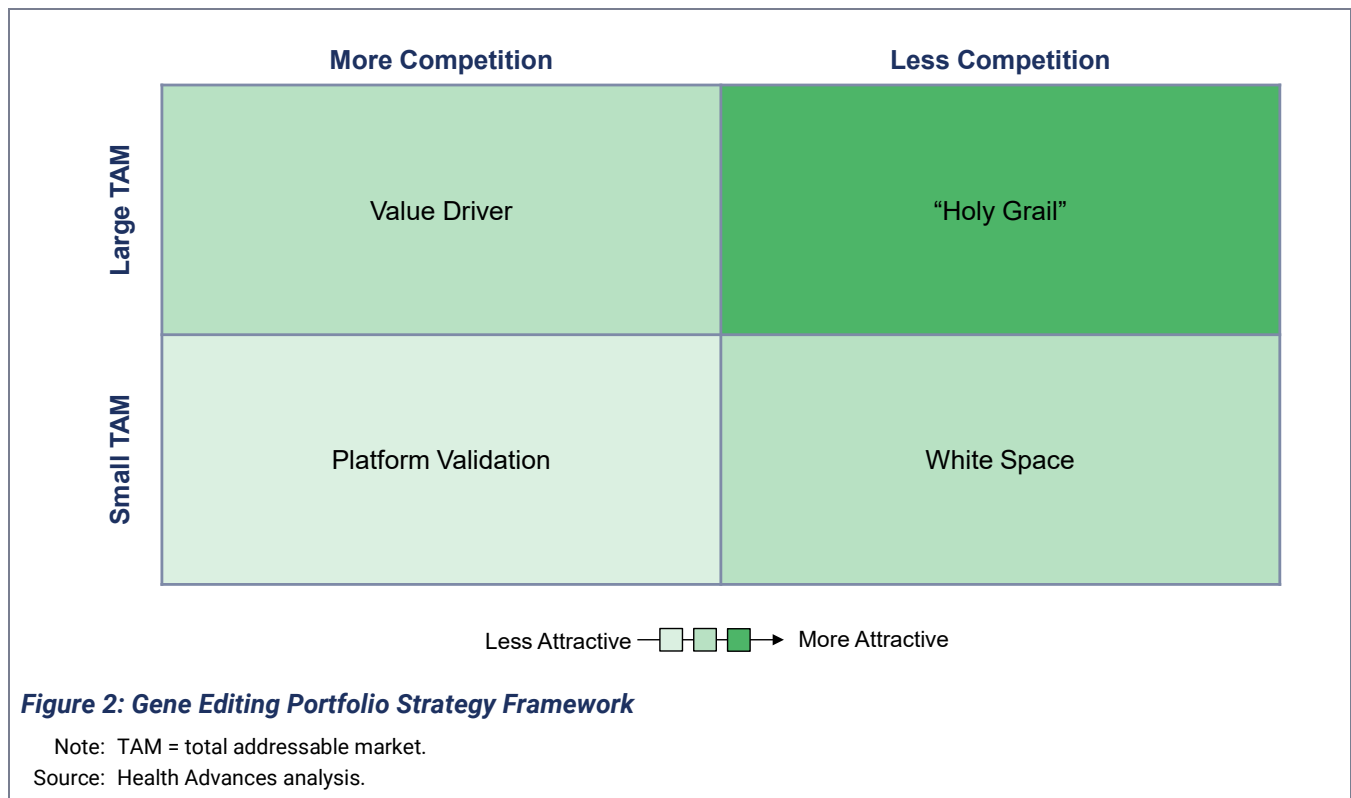
**Technical Advantages of Gene Editing Approach:** Sponsors should also weigh the rationale for using a CRISPR-based gene editing approach compared to other modalities, especially given the high costs and risks discussed above. For example, for a genetic disease caused by a single nucleotide mutation, a CRISPR base editing approach is arguably the superior modality, whereas a disease caused by multiple mutations or a large gene deletion may be better addressed by non-editing gene therapy approaches or enzyme replacement therapy. For a disease such as Huntington's, permanent gene editing may be required to prevent a fatal outcome. On the other hand, to inactivate proteins associated with high cholesterol, a less invasive approach via biologics or antisense oligonucleotides may be preferred over gene editing.

**Deliverability:** Finally, sponsors should consider the feasibility of delivering the gene editing tool to the desired tissue. CRISPR-based gene editing tools are large macromolecules that include protein and RNA components, and they cannot be delivered into cells without the use of a vector, such as a modified virus or lipid nanoparticle. In fact, the coding sequence for many CRISPR-based tools is so large that even standard viral vectors have insufficient capacity for the necessary payload. Given the current state of gene therapy delivery technology and limitations imposed by the size of CRISPR tools, near-term in vivo applications of CRISPR gene editing may be limited to organs more amenable to local delivery such as the eyes, ears, or the brain, and organs that serve as a vector sink, such as the liver, as well as ex vivo applications, which have lower barriers for delivery.

## How Should CRISPR Companies Approach Portfolio Strategy?

*Key takeaway: A balanced portfolio of CRISPR programs should align with the sponsor's capabilities, near-term clinical and commercial goals, and long-term strategy.*

In addition to unmet clinical needs and technical fit, commercial attractiveness is also a key consideration in designing a portfolio strategy. We propose a framework wherein commercial attractiveness is defined in terms of the addressable market size and level of competition. Opportunities with various market sizes and levels of competition could serve different strategic goals for CRISPR-based gene therapy companies, such as demonstrating proof of concept or maximizing commercial value.



In our framework, opportunities fall into four categories:

- **Platform Validation:** For many early-stage CRISPR-enabled gene therapy companies, demonstrating proof of concept of their novel platform is the critical first step toward enabling future success. Platform validation is a prerequisite to investing in more and potentially riskier programs, as well as and attracting investors and/or partners.

The ideal platform validation opportunity will clearly answer questions about a program's developmental risk, and it is therefore key to minimize other forms of risk. In practice, validation typically involves indications and/or therapeutic targets with the least challenging preclinical and clinical development path as well as relatively small addressable population are. As shown in Figure 2, these opportunities often have competitor gene therapy programs, making it a challenge to achieve first-mover benefits, but offer several advantages for quickly demonstrating proof of concept:

- **Validated Target:** It is established by precedent preclinical and clinical development that the role of the gene is essential, and that correction of the gene can restore protein level, resulting in the desired therapeutic benefit.



- *Clarity of Clinical Pathway*: Precedented gene therapy trials offer roadmaps for trial design considerations, such as selection of endpoints, sample size, the need for a control arm, time to endpoint, etc.
- *Low development burden*: Given prior research and market development activities by competitors in these indications, high disease awareness is expected, potentially simplifying patient recruitment. Comprehensive natural history may also be available, allowing for a smaller sample size and a lower development cost.
- **“Holy Grail”**: The ideal opportunity has a large addressable population, high clinical unmet need, and limited competition. However, given the rapid growth in the number of gene therapy programs in recent years, it will be more and more challenging to either identify such indication opportunities, or for the opportunity to maintain its “holy grail” status as more competitors flood into the space.
- **“White Space”**: Despite the relatively small addressable market, “white space” indications are attractive. These indications’ lack of competition allows for maximization of market share and commercial opportunity. For example, Editas Medicine and Beam Therapeutics are pursuing less competitive, “white space” indications such as inherited retinal dystrophies (e.g., LCA10) and inborn errors of metabolism (e.g., glycogen storage disorder 1a).
- **“Value Driver”**: Alternatively, “value driver” indications, such as sickle cell disease,  $\beta$ -thalassemia, Parkinson’s disease, may also be attractive due to the large patient population and thus large revenue potential, despite the larger number of competing programs.

**Additional Strategic Considerations:** Companies typically start off their portfolio with platform validation indications and then expand their portfolio to include “value driver”, “white space”, and (if possible) “holy grail” indications, alongside additional strategic considerations.

From a developmental burden perspective, indications with a clear regulatory pathway and a reasonable development time and cost burden are relatively more attractive to ensure fast time to market and minimize investment needed. We discussed development advantages of “platform validation” indications above, but the same criteria discussed there should be considered in other opportunities too. Quality of animal models, clarity of regulatory endpoints, availability of surrogate endpoints and natural history, to name a few, are key questions to determine development attractiveness.

In addition, CRISPR companies also need to consider how the indications will fit with the company’s long-term goals. For example, some CRISPR companies might set out to establish leadership and expertise in a single therapeutic area; such a strategy allows for synergies from focused investment in R&D and commercialization capabilities. In addition, the company can diversify by adopting multiple modalities within the same therapeutic area. On the other hand, some CRISPR companies might build their portfolios in a therapeutic area-agnostic fashion by driving all their best lead programs forward. Such diversified programs offer lower overall risks than betting the technology and future of the company on one therapeutic area or disease, expanding their total addressable market as well as attracting a large pool of potential pharma partners. However, pursuing a diverse portfolio may require a larger investment, as the company will need to develop expertise in each therapeutic area pursued.

## HOW DO CURRENT CRISPR COMPANIES FIT INTO OUR FRAMEWORK?

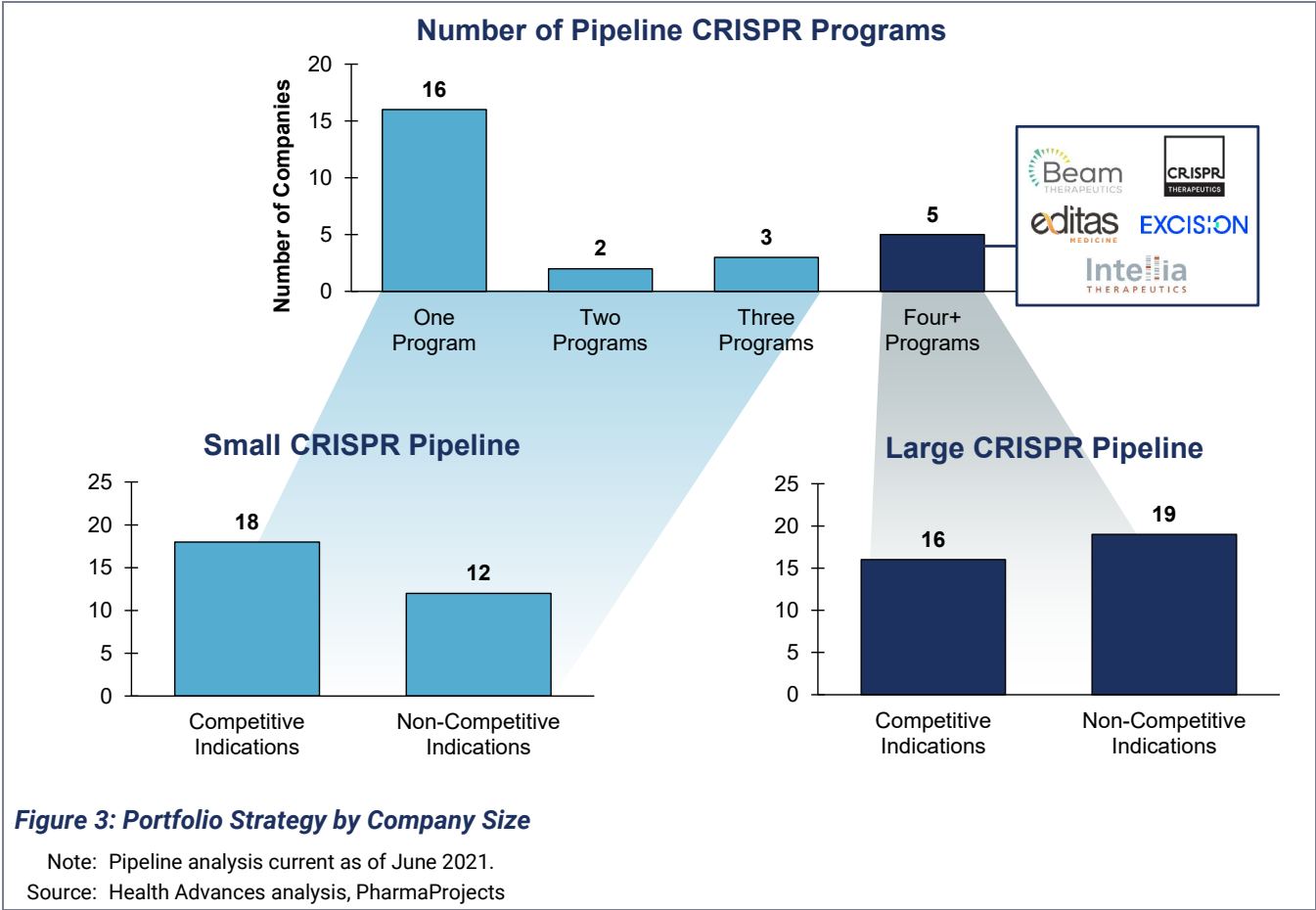
Based on our framework, we hypothesized that CRISPR gene therapy companies would pursue a mix of blockbuster indications with a large addressable market, as well as “goldilocks” indications with limited competition. To test this hypothesis, we analyzed the strategies of companies with CRISPR gene therapy



programs, and specifically the number of CRISPR programs they were pursuing and the level of competition within each indication (Figure 3). Overall, we observed a variety of approaches to building a portfolio by company.

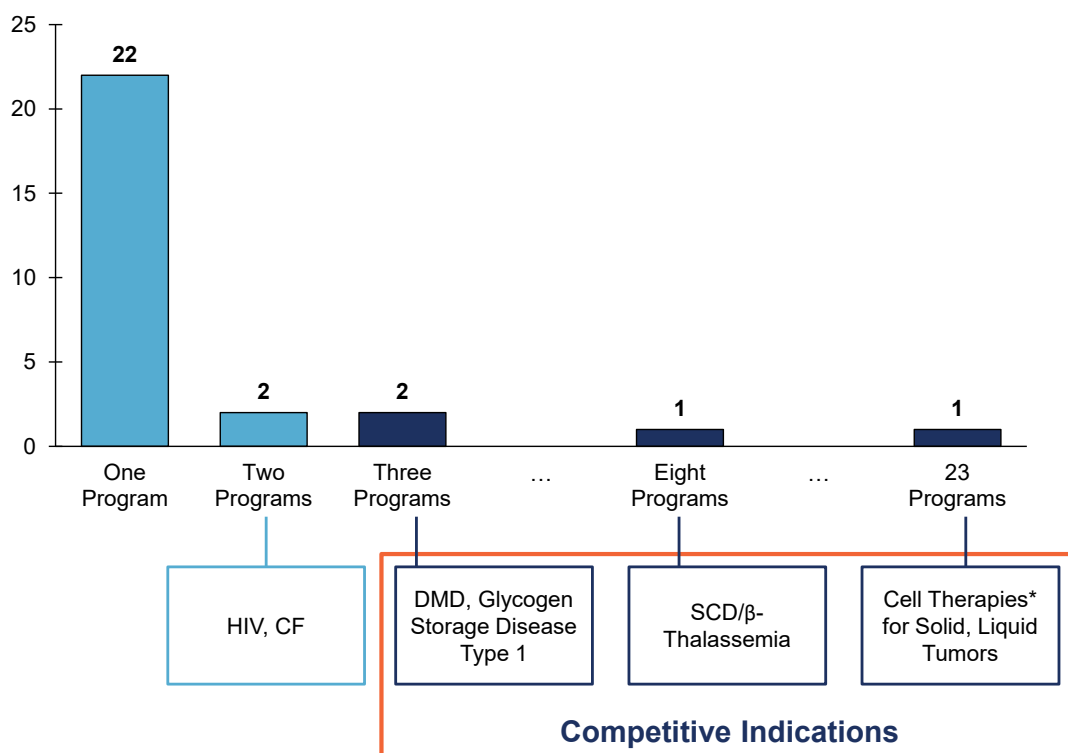
Most companies with CRISPR programs are pursuing gene editing in 3 or fewer indications. These sponsors with a small number of CRISPR gene therapy programs predominantly pursue competitive indications (defined as those with 3 or more CRISPR gene editing programs); this could be the result of recently launched companies pursuing platform validation, as well as companies with a diverse portfolio of multiple modalities, including CRISPR, that are pursuing “value driver” strategies.

In contrast, the handful of companies with a larger CRISPR pipeline have a more balanced strategy with both competitive and non-competitive indications, reflecting a longer-term commitment to CRISPR gene therapy. Generally, as companies have started with “platform validation” indications, they can move into “value driver” and “white space” indications as they are expanding their pipelines.



Additionally, indications for which CRISPR assets are in development are either highly competitive or highly non-competitive, reflecting a mix of “platform validation” and “value driver” versus “white space” indications (Figure 4). For example, a significant number of CRISPR programs are pursuing therapies for sickle cell disease,  $\beta$ -thalassemia, and various cancers, which have strong scientific validation, development precedent, and high unmet need. Outside of these highly competitive indications, however, nearly all the other programs are pursuing non-overlapping and less competitive “white space” indications in an attempt at differentiation.

### Number of Competing CRISPR Gene Editing Programs



**Figure 4: Competition Among CRISPR Gene Editing Programs**

\* Many companies are pursuing off-the-shelf cell-based therapies generated using CRISPR, as opposed to autologous cell editing.

Note: CF = cystic fibrosis, DMD = Duchenne’s muscular dystrophy, SCD = sickle-cell disease.

Source: Health Advances analysis, PharmaProjects.

## CONCLUSION

In summary, given the risks, timeline, and cost of development, as well as the unique and relatively limited lifecycle management opportunities of gene therapies, a deliberate approach to portfolio strategy is critical to the short- and long-term success of a CRISPR-enabled gene therapy company. To build a balanced and sustainable portfolio, companies should consider technical feasibility, commercial attractiveness, developmental burden, and strategic fit. Our framework addresses some but not all of the key considerations for CRISPR companies; a comprehensive approach to portfolio strategy must also take into account the sponsor’s technology, strategic focus, geographic focus, internal capabilities, long-term vision, and stage of development and growth.

The speed at which CRISPR technologies are developing underscores how critical it is to start strategizing about portfolios as early as possible. Competition will not only include companies with in vivo CRISPR gene therapy platforms, the focus of this article, but also ex vivo CRISPR programs, traditional in vivo gene therapy, RNA/mRNA therapies, and more, each with its own unique set of advantages as well as challenges. Health Advances’ expertise in cell and gene therapy means that we are uniquely positioned to help CRISPR companies analyze and optimize their portfolio strategy.

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