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OPENING MOVES:

An Early View on Nine Aspects of the Emerging Gene Editing Market

- Gene editing technologies will disrupt markets beyond therapeutics.
- Intense competitive battles will arise all along the gene editing value chain.
- There will be multiple categories of gene modification.
- Accessibility to cells for gene editing will drive initial prioritization of targets.
- Even within a disease, there will be prioritization.
- Innovation in business models will need to keep pace with clinical advances.
- New approaches to pricing will be necessary.
- Big pharma will be an early and important player.
- The technology that is provided by one set of bugs may be used as a protection against others.

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Introduction

In the months between February 2014 and August 2016, gene editing was featured on the covers of *Time*, *The Economist*, *National Geographic*, and the *MIT Technology Review*. As awareness of the technologies has grown, expectations have risen. Investors are seeing validation for their early bets and the general public has begun to anticipate a series of near term and profound breakthroughs.

At the same time, far sighted thinkers are pairing enthusiasm for scientific possibilities with calls for public policy caution. They have identified several areas with troubling potential if the technology is taken in the wrong direction.

Leaders across the life sciences industry are beginning to realize that they must quickly get up to speed on the potential disruptions gene editing will bring to the industry. Having a ready means of silencing, activating, correcting, or even replacing individual genes will undoubtedly scramble the "Opportunity" and "Threat" sections of numerous strategic positioning maps. However, leaders need to be careful that they do not underestimate the challenges that must be overcome in moving these extraordinary technologies from the laboratory to the clinic.

In the next few pages, we identify nine aspects of the emerging gene editing market that should be considered by life sciences strategy teams tasked with anticipating the impact that rapid development of gene editing techniques will have on their companies' businesses.

1. Gene Editing Technologies Will Disrupt Markets Beyond Therapeutics

When considering the potential for gene editing technologies, it is natural to focus on potential cures for genetic diseases. The benefits offered by a technology that could "select and replace" or silence offending genes is hard to ignore. However, as will be discussed later in this paper, there are many hurdles that will need to be overcome before gene editing becomes an option for the vast majority of patients. In the meantime, the ability to alter gene functions will find application in a wide variety of areas that are not subject to the complexities and risk-intolerance of human therapeutics.

Already, researchers are feeling day-to-day impact of the new technologies. Older gene editing approaches such as zinc finger nucleases (ZFN) have been applied to research activities for many years. Using these techniques to achieve highly targeted breaks in double stranded DNA has allowed researchers to elucidate gene function through selective gene disruption. By dramatically lowering the requirements and cost of gene disablement, new technologies such as CRISPR are allowing evaluation of whole chains of protein interactions. The knowledge gained is proving vital to traditional downstream pharmaceutical development activities.

Cost effective gene editing will also bring new capabilities to the agriculture, energy, and environmental services industries. Recognizing that industry knowledge will be critical to exploiting these opportunities, the early stage gene editing companies have established sector specific structures and strategies. Some have adopted a corporate design that puts in place divisional organizations and licensing approaches that segment responsibilities according to industrial sectors. CRISPR Therapeutics and Caribou Biosciences established early agriculture partnerships with industry leaders Bayer and Dupont respectively. Sector segmentation was also evident as Precision Bioscience, a company applying homing endonucleases to genome editing, initially focused primarily on agriculture, negotiating collaborations with Dupont, Bayer, and BASF.

2. Intense Competitive Battles Will Arise All Along The Gene Editing Value Chain

The ability to manipulate genes at the individual nucleic acid level is an extraordinary development, but the competitive environment will not be isolated to those companies at the end of the value chain. In fact, competitive battles can be expected wherever there is an opportunity to enable or enhance the technology's performance.

Delivering gene editing systems to targeted cells is one of the primary technical challenges facing developers. For *in vivo* applications in particular, the delivery packages must be able to target specific cell types among complex tissue and organ systems and must be large enough to carry the gene editing machinery. Further, the system must be able to target enough cells for gene editing events to cause phenotypic change. Fierce competition can be expected to emerge across technologies that bring these capabilities to different applications. Electroporation, for example, might bring a balance of features that make it the best choice for *ex vivo* gene editing applications while adeno-associated viral vectors (AAV) may be applied to strategies requiring delivery of RNA guide/protein nuclease systems to the liver. More importantly, developers and investors must be aware that no matter which delivery approach they adopt, alternatives are likely to emerge. These are very early days for the exploration of other methods, but given the value of successful innovation in this area, promising alternatives will not lack for development investment.

Delivery systems represent only one area of anticipated competitive battles. Suppliers of reagents such as RNA guides will similarly face demand to target and differentiate their products to the needs of individual areas of gene editing. In addition, we can expect to see wholly new product categories emerge including devices to aid system delivery and, eventually, clinics that specialize in providing gene editing services.

3. There Will Be Multiple Categories of Genetic Modification

Communication is eased through adoption of the short hand term, gene editing. In reality, technologies such as CRISPR, TALEN, ZFN, or other editing systems present the ability to disable, repair, insert, repress, or activate genes. Certain monogenic diseases such as Huntington's chorea are associated with genes that produce an undesirable protein. In others, such as hemophilia, the protein that is formed cannot execute its function. These represent two very different tasks for gene editors. In the first, the only requirement is for the system to find and disable the offending gene. While this may seem an easier task, a therapeutic effect will only be achieved if protein levels are adequately reduced. If the gene editing system does not alter enough cells, the disease state will continue.

On the other hand, a treatment that depends on gene repair needs to achieve both a DNA break function and reconstitution with the desired sequence. Preclinical trials have validated the potential to achieve this goal, but often with a low share of cells being altered. Researchers will search for means of increasing the share of cells successfully altered, but, in the meantime, programs are likely to be prioritized that have the potential to achieve clinical efficacy despite low cell conversion levels. Often, hemophilia is cited as a condition that meets this criterion.

Sangamo is taking a promising approach to the area of gene insertion. Among the company's leading programs are treatments for Hurler syndrome and Hunter syndrome. Both of these conditions emerge when mutations hinder the body's ability to produce a required enzyme. Sangamo's approach uses the company's zinc finger nuclease technology to place a working gene at the albumin locus where high levels of expression are then driven by the albumin promotor. For patients, the goal is to have liver cells manufacture the required proteins rather than rely on genetically engineered replacement proteins.

4. Accessibility To Cells For Gene Editing Will Drive Initial Prioritization of Targets

Because delivery is likely to pose a challenging problem, conditions that present easier access to the relevant cells will be prioritized. *In vivo*, conditions are being prioritized for eye and liver tissue because promising methods exist to deliver gene editing systems. It is easier still to target blood cells *ex vivo*.

According to the Online Mendelian Inheritance in Man database (OMIM), there are approximately 600 genetic disorders and subtypes with a hematologic component . Of those, approximately 100 are monogenic and affect a cell of hematopoietic lineage. In select cases, and for certain patients, some of these conditions are

currently treated through a stem cell transplant, where the patient's hematopoietic stem cells are replaced with those from a matched donor who does not share the deleterious mutation. However, the risks of stem cell transplants are too high unless the condition is mortal, a very closely matched donor can be identified, or the consequences of living with the disease are considered severe enough to warrant the risks of a less perfectly matched donor.

The advent of gene editing presents the potential to remove a patient's own stem cells, conduct an *ex vivo* modification process, select cells where the editing process has been effective, expand those cells, and return them to the patient. Since the returned cells are the patient's, the graft vs. host risk of the transplant should be very low. Moreover, technologies are being developed by companies like Bellicum Pharmaceuticals that will allow selective removal of transplanted cells if graft vs. host disease does occur.

There are approximately 2,500 patients born annually in the US with the monogenic blood diseases mentioned earlier who would benefit if this procedure were safe and available enough to warrant widespread adoption. That day may be a long way off, but the benefits to patients and the economic value to the healthcare system suggest this opportunity alone could justify substantial investment in the pursuit of gene editing innovations.

5. Even Within a Disease, There Will Be Prioritization

Even at this early stage, investors and forecasters are beginning to build models of the eventual size of the market for gene editing technologies. Pursuing such analysis demands a deeper understanding than simply the disease level incidence rates.

Gene editing procedures are likely to be expensive and to hold meaningful risks. As noted above, early applications of the technology may complement an autologous stem cell transplant. Others are likely to require use of viral vectors or other delivery systems such as nanoparticles. Pairing the risks of these delivery systems with small but remaining potential for off-target disruptions, patients are only going to turn to gene editing procedures if the consequences of the disease are dire.

Today, the severity of the disease and suitability of a matching donor drive decisions of whether or not to pursue a stem cell transplant in children born with genetic blood disorders. In SCID (severe combined immunodeficiency) or Wiskott Aldrich syndrome, there is no chance of long term survival without a transplant, so compromises are made in pursuing transplants with less well matched donors. In severe anemias or hemoglobinopathies (sickle cell disease and beta thalassemia), where the risks of transplants outweigh the consequences of the disease, use of the procedure is much less frequent.

Effective approaches to gene editing could substantially increase the share of transplant candidates. However, trade-offs will still need to be considered. There are four genetically defined sub-types of sickle cell disease. The safety and efficacy threshold for gene editing therapy will be different for each type. Similarly, there are multiple sub-groups of beta thalassemia. Projections of the number of candidate patients will need to consider the benefit risk trade-offs of each group.

6. Innovation In Business Models Will Need To Keep Pace With Clinical Advances

With treatments that will require new approaches to product delivery, innovative procedures and services, as well as advances in the core gene editing systems, the companies that succeed in this arena will need to develop innovative business models. Unfortunately, there are many examples such as Zevalin, a radioimmunotherapy used in the treatment of NHL, where demands for business model innovations undermined the ability of pharmaceutical companies to succeed even when they held therapeutics that had proved to be superior to existing treatments. The companies that take the first steps into commercialization of gene editing systems will need to prepare well in advance for all of the parties involved in influencing adoption. They will need to understand the motivations of each group, and they will need to assure that every party is aligned—in many cases, the gene editing innovators are going to need to take on activities that are far removed from the research innovations that make the new treatment possible. Decisions of whether to take on each of these roles will drive choices of whether to partner, whether to source, or whether to develop capabilities. In any case, these companies are unlikely to look similar to today's pharmaceutical companies—even the ones that rely on specialty product commercialization.

7. New Approaches To Pricing Will Be Necessary

Analysts seem to have a "plug" value for gene therapies. Regardless of the condition being treated, the administration characteristics of the treatment, or the suitability of alternative therapies, a price of $1M per patient is often assumed. This was the price assigned to Glybera, the first approved gene therapy in Europe; it was anticipated for Strimvelis, GSK's recently approved gene therapy for SCID; and the assumption can be found for the later stage gene therapies in the pipeline.

The early evidence suggests more thoughtful approaches to pricing must be considered. Four years after being approved, there was a single reported use of Glybera.[1] Recent reports suggest GSK will be charging $665K per patient for Strimvelis. The company has taken a further step, however, by providing guarantees where fees will be returned if the treatment is not successful.[2]

Only modest lessons can be taken from these experiences. It is questionable whether the clinical trial results for Glybera provide support for the substantial price, so perhaps healthcare systems would be more receptive if patients with the condition simply had no other options or if the clinical results were more definitive.

Health economic models of the benefits to the patient may easily exceed the $1M placeholder value. On the other hand, payers and health systems may view the benefits through a lens of cost reductions relative to alternative treatments. As odd as it seems, those parties may begin a discussion of the value of a gene editing-based cure by suggesting a price equivalent to the cost of hospital stays the patient might otherwise have experienced.

The disparity in these perspectives suggests there will be a need for new reimbursement models. The money-back approach from GSK may become a touchstone for future products addressing genetic conditions, but such an option becomes cumbersome with larger patient numbers and the potential for more ambiguous definitions of therapeutic success.

An alternative suggested approach to pricing would extend payments over time. Such a system for aligning the reimbursement to the period when the patient is benefiting from the therapy are not out of the question, but they would require new operations within payer organizations. Leaders in single payer health systems are likely to be more receptive to those changes than decision makers in the US where patients frequently change insurers. There will, however, be little patience among public payer systems for prolonged large per-patient payments if treated populations extend beyond the ultra-orphan populations that have been the early targets of gene therapies.

While substantial uncertainty will remain for some time, innovators pursuing gene editing technologies cannot approach pricing casually. Even at this early stage, they must evaluate the benefits provided by their therapies and they must understand which parties will receive those benefits. They then must be open to reevaluation of their plans as the earliest pioneers blaze the path across this entirely new terrain.

[1]Regalado, A., The World's Most Expensive Medicine Is a Bust, MIT Technology Review, May 4, 2016

[2]Staton, T. GSK Inks Money-Back Guarantee on $665K Strimvelis, Blazing a Trail for Gene-therapy Pricing, FiercePharma, August 9, 2016

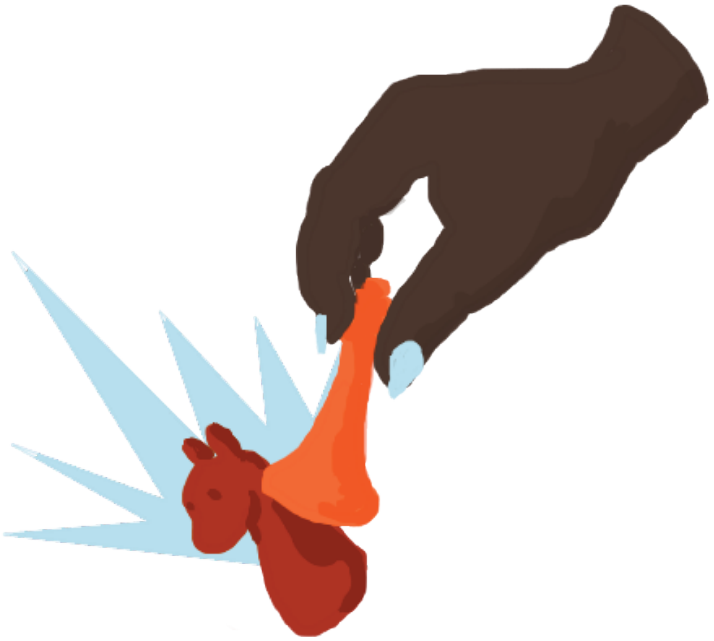
8. Big Pharma Will Be An Early and Important Player

So far, gene editing has been a province of daring biotech companies and risk tolerant venture investors, but large pharma companies are not sitting on the sidelines. Corporate venture groups have been important participants in the early funding of gene editing companies. In fact, there are several instances where more than one strategic was included in early funding. Both SR One (the GSK venture fund) and Celgene took early positions in CRISPR Therapeutics. Funds from Baxter and Amgen invested in the Series A round of Precision Biosciences.

Large pharma has also stepped in as the promise of particular applications have become more evident—and clinical development costs have become realities. In CAR-T (chimeric antigen receptor T-cell therapy) applications, Novartis is working with Intellia, Pfizer is collaborating with Cellectis, and Shire (through its acquisition of Baxalta) is paired with Precision Bioscience. Shire also has an on-going collaboration deal with Sangamo for the development of a treatment for Huntington's disease.

In the past, intrepid biotechnology companies might have resisted such early overtures from large pharma suitors. With gene editing, however, early partnering is justified because of the broad application fields remaining for the biotech partner. Large pharma capabilities will be particularly relevant when navigating the complicated later stage trials and uncharted pricing challenges expected in this arena.

Going forward, large pharma can be expected to be an important player in establishing the commercial landscape for gene editing applications. However, once the primary structures are in place, the scientific innovators are likely to forward integrate and pursue independent commercialization with application areas that have been carefully preserved.



9. Lastly, and In Conclusion, the Technology That Is Provided By One Set of Bugs May Be Used As a Protection Against Others

Many reviews of gene editing technologies start by explaining that CRISPR and associated proteins emerged as something of a rudimentary immune system by which bacteria resist repeated viral infection.

The opportunity to break nucleic acid sequences at highly specific sites suggests the potential to target invading pathogens without affecting the host. Reflecting this potential, some of the first applications of gene editing technology might be better termed gene disruptors, and the target will be the nucleic acid sequences of viruses and bacteria. In these cases, alternative delivery approaches may be relevant, including the use of bacteriophages. One might conclude that there is some irony in the observation that the gene breaking proteins that evolved as a protection against viral infection of certain bacteria could be engineered to offer higher species protection against other bacterial invaders.

Closing

The expectations for gene editing technologies are already high and, with an increasing level of public awareness, they are growing. Already, questions seem to focus more on which applications will develop first rather than whether the technology will be successful. The implications for patients will be profound. The associated commercial opportunities will draw tremendous levels of investment.

Consider some of the numbers that have been discussed in this paper. If a treatment for just one condition, sickle cell disease, is brought forward, and the risk benefit trade-off makes it relevant to only half of the 1,600 patients born each year with the condition in the US, and if a comparatively modest treatment price of $500,000 is applied, the annual value for one condition in one geography approaches a half a billion dollars. Extending these observations to treatment of existing prevalent patients, incorporating additional disease areas, and adding justification for higher pricing will reveal opportunities in the tens of billions. Such numbers will drive continued enthusiasm for gene editing and justify the investments that will be necessary to maintain the current rapid pace of development.

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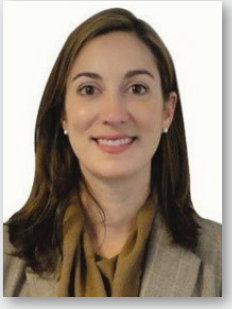
Recent by-lined articles have appeared in Pharmaceutical Executive, InVivo, Nature Biotech, RPM Report, and Scrip. In addition, Ben's case studies on the pharmaceutical industry have been used in graduate business programs.

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.