

Regenerative Medicine Is Here: New Payment Models Key To Patient Access



Potentially curative regenerative medicine therapies are no longer theoretical, but instead have become reality. As more and more gene, cell and tissue-based therapies reach the market, the need for payment solutions is becoming more pressing. The Alliance for Regenerative Medicine has consulted with payers and other stakeholders to consider the barriers to alternative payment models and look at possible solutions.

BY FRANCESCA COOK, TED SLOCOMB AND MICHAEL WERNER

More and more regenerative medicines are reaching the market, but the payment solutions are not yet in place.

Patient access to these transformative therapies will be hindered if the health care system is not prepared for the implications of such medical innovation.

Payers are consistently concerned about the limited data available and long-term effects of regenerative medicines, as well as the affordability and budget impact of one-time treatments.

So what? Ensuring sustainable access requires both market-based solutions and action by governments, insurers and manufacturers. Demonstration projects are needed.

Many regenerative medicines seek to provide a transformative and long-lasting effect with a single treatment, potentially enabling a shift from a focus on chronic therapy to possible cures. Patient access to these transformative therapies will be hindered, however, if the health care system is not prepared for the implications of such medical innovation.

The current system is organized around paying for chronic interventions based on episodes of care rather than based on value and patient outcomes. The political and payer uproar associated with the launch of **Gilead Sciences Inc.**'s *Sovaldi* (sofosbuvir) for hepatitis C in 2013 illustrates how the transformative clinical impact of a product is not always sufficient to ensure patient access post-launch, and that short-term payer budget considerations play a significant role in public and private payer decision-making. (Also see *"Cost Pushback Limiting Hepatitis C Drug Utilization"* - *Pink Sheet*, June 20, 2016.)

To ensure access to regenerative medicines, key stakeholders – including developers, public and private payers, health care providers, patient advocacy groups and policy makers – must work together to optimize and modernize the health care system to ensure the benefit from these new, transformative products can be realized. The Alliance for Regenerative Medicine (ARM), a global, multi-stakeholder organization dedicated to the advancement of gene and cell therapies, is concerned about reimbursement issues and has reached out to payers and other stakeholders. Here we review legal barriers to gene and cell therapy adoption and present several US-focused, market-based and policy solutions to overcome reimbursement challenges.

Curative Gene And Cell Therapies Require Unique Thinking

Regenerative medicines can address the underlying cause of disease, providing a persistent impact after one administration. Such curative therapies are therefore uniquely valuable, whether that value is measured in saved lives, improvements in health-related quality of life, savings to the health care system due to averted costs associated with chronic disease management, or the broader impact to society as individuals and caregivers can more fully contribute to economies. Exhibit 1 summarizes the ways in which potentially curative regenerative medicines are different from conventional therapies and chronic disease management.

High expectations for durable, and transformative therapies are tempered, however, by concerns that the treatment cost could overwhelm the health care system as new therapies become available. If paid for as drugs are today, the cost of regenerative medicines intended to be administered once or only a few times would be incurred up front and could present a financing challenge for some insurers. Associated savings, however, will accrue over a longer period of time.

This is the third part of an annual review of issues facing the regenerative medicine field by the Alliance for Regenerative Medicine. The first article considered the prospects for curative therapies and potential barriers to adoption, and the second looked at the need for new payment models.

Curative Regenerative Medicines: Preparing Health Care Systems For The Coming Wave, November 15, 2016

New Payment And Financing Models For Curative Regenerative Medicines, July 24, 2017

For rare diseases, common targets of gene and cell therapies, there are fewer patients and often higher annual treatment costs. Currently, chronic therapies for rare diseases, such as enzyme replacement therapies, often cost \$300,000 to \$800,000 per year – many millions of dollars over the lifetime of a patient – but the costs are spread out over time, thereby reducing any one-time budget expense. Regenerative medicines offer the potential to move from

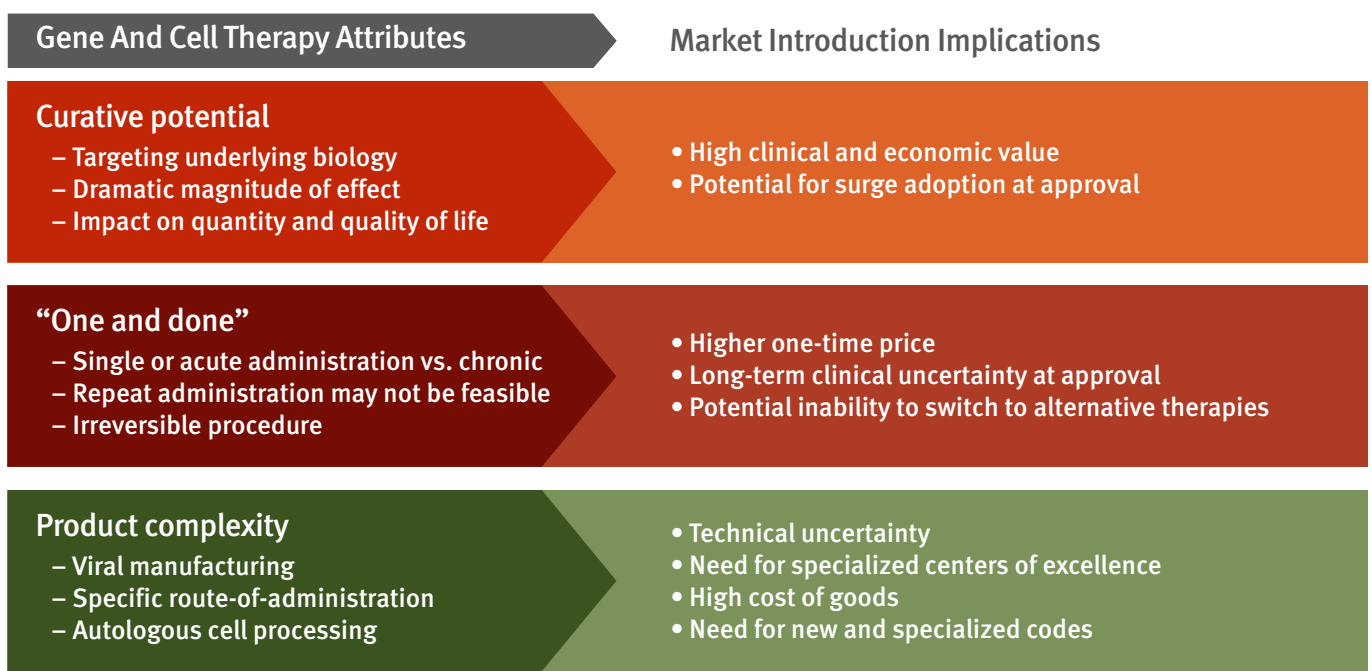
chronic treatments to potentially one-time treatments, both transforming the lives of patients and in some cases significantly reducing lifetime treatment costs.

Potential Challenges

Recent experience from the first gene and cell therapies approved in Europe suggests that turning the promising science of regenerative medicine into sustainably successful business models will not be easy:

- **uniQure NV's Glybera** (alipogene tiparvovec), a gene therapy approved by the European Medicines Agency (EMA) in 2012, was the first and only therapy for an orphan lipid disorder lipoprotein lipase deficiency and was priced at €1 million. Only four patients were treated in Germany before uniQure withdrew the product from the market in 2017, citing significant investments and low patient demand. (Also see "White Flag Raised: UniQure Gives Up On Glybera, But Not Gene Therapies" - *Scrip*, April 21, 2017.)
- **GlaxoSmithKline PLC's Strimvelis**, the first *ex vivo* gene therapy, received EMA approval in 2016 to treat ADA-SCID

Exhibit 1. Summary Of Unique Attributes Of Many Gene And Cell Therapies And Their Implications



SOURCE: Alliance for Regenerative Medicine

WHERE DOES THE FIELD OF REGENERATIVE MEDICINE STAND?

As of mid-year 2018, there were more than 950 regenerative medicine therapies in clinical trials, of which more than 90 are in Phase III. In addition, according to the MIT NEWDIGS consortium FoCUS Project (Financing and Reimbursement of Cures in the US), around 39 gene therapies will be approved by the end of 2022. Product candidates in development address diseases involving almost every major organ system, from ultra-orphan neurodegenerative diseases like adrenoleukodystrophy, to highly prevalent public health concerns such as several forms of cancer, congestive heart failure and diabetes, ailments that affect tens of millions of patients worldwide.

The US FDA has recognized the need to accelerate regenerative therapies. In November 2017, FDA commissioner Scott Gottlieb noted the “transformative promise” of these technologies and said this potential is the reason the FDA is “so committed to encouraging and supporting innovation in this field.” Gottlieb has continued to look for ways to facilitate development of regenerative medicines. (Also see “Gottlieb On Gene Therapies: ‘Very Seductive’ To Think About Accelerated Approval Pathway” - Pink Sheet, May 7, 2018.)

The FDA has awarded Breakthrough Therapy Designation to more than 20 regenerative medicine product candidates, to date. And more than 20 product candidates have received Regenerative

Medicine Advanced Therapy (RMAT) designation, a regenerative medicine-specific accelerated approval program created under the 21st Century Cures Act that acknowledges and incorporates the unique attributes of gene and cell therapies and enables enhanced interaction opportunities with the agency.

Two autologous chimeric antigen receptor T-cell (CAR-T) products, Novartis AG’s Kymriah for critically ill children with refractory or relapsing acute lymphoblastic leukemia and Yescarta (axicabtagene ciloleucel), Kite Pharma Inc.’s therapy for adults with relapsed or refractory large B-cell lymphoma, were approved by the FDA in August and October of 2017, respectively. In May 2018, the FDA approved Kymriah for a second indication, the treatment of adult patients with relapsed or refractory large B-cell lymphoma. These technologies are prime examples of the promise of regenerative technologies, achieving dramatic and durable cures. In addition, in December 2017, the FDA approved the first adeno-associated virus (AAV) *in vivo* gene therapy – Spark Therapeutics Inc.’s Luxturna (voretigene neparvovec-rzyl) for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy.

Other gene and cell therapies for conditions as diverse as spinal muscular atrophy, hemophilia A and inherited retinal disease have also recently delivered promising clinical data and are poised for regulatory approvals in the next few years. [IV005372](#)

and was priced at £600,000. As of June 2018, five patients have been treated, following a total of 13 referrals received to date, with more patients scheduled for 2018. This is in line with GSK’s projections, according to the incidence of ADA-SCID across Europe (about 15 patients diagnosed per year). GSK divested its rare disease gene therapy assets, including Strimvelis, selling the portfolio to Orchard Therapeutics in April 2018. (Also see “Orchard To Use Divested GSK Rare Disease Gene Therapies To Grow Globally” - Scrip, April 12, 2018.)

Private and public payers, for their part, appear to be cautiously optimistic about the coming wave of gene and cell therapies, based on favorable public comments and direct engagement with ARM and its member companies. They intuitively understand that these therapies represent unique value propositions as compared with more traditional biopharmaceuticals. However, payers also consistently articulate concerns that broadly fall into two categories:

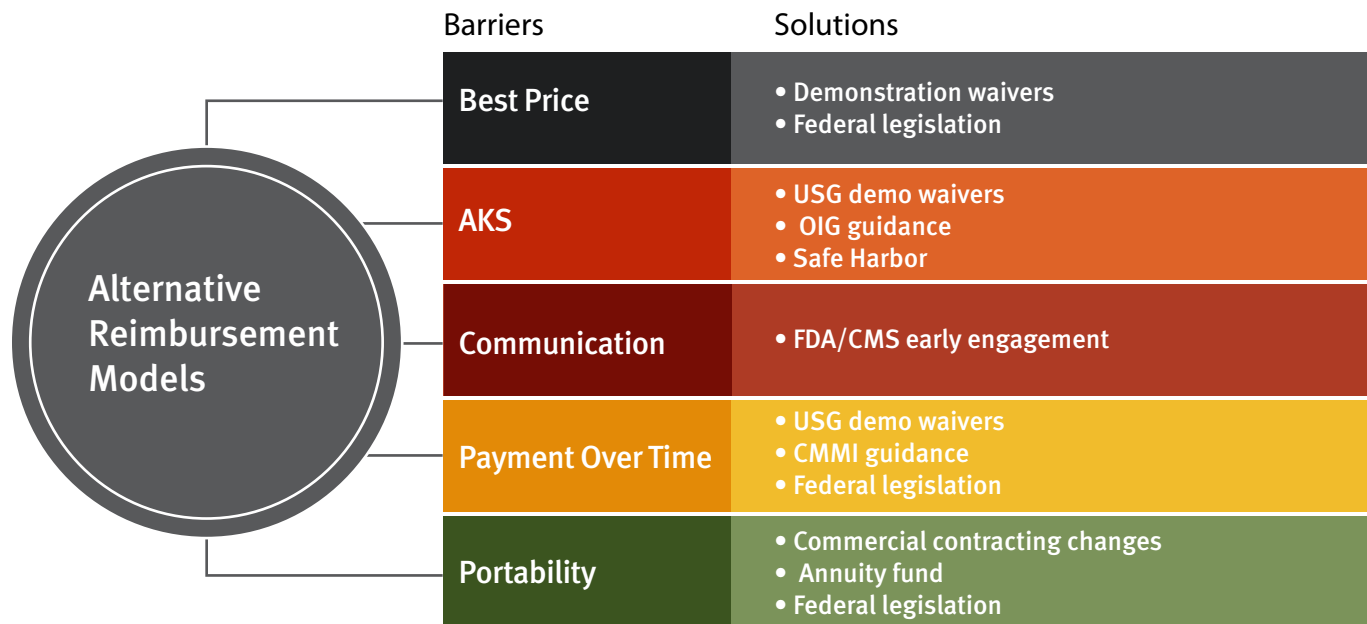
- **Uncertainty:** regenerative medicines are still relatively new, and there remains considerable uncertainty around their long-term efficacy and safety. In addition, many gene and cell therapies are targeting first approvals in orphan indications via small clinical trials or single-arm studies, and therefore lack traditional, statistical data on the magnitude and duration of the treatment effect at the time of launch. While regulators often agree that small single-arm studies are acceptable for ultra rare indications, the limited data this provides sometimes translates into undesirable unpredictability for payers regarding how many patients will need such therapies, what proportion of patients will respond, how long the effect will last and how much long-term value will ultimately be realized.
- **Affordability:** many initial cell and gene therapies will target rare diseases, and, given the number of therapies under

development, insurers are concerned they may face a portfolio of new one-time therapies for patients that could collectively strain health plan budgets – already a source of concern. Additionally, for regenerative medicines that target larger, more prevalent diseases, payers may need to plan for a surge in use to durably treat (and potentially cure) an existing prevalent population – with learnings from the Sovaldi instance.

New Payment Models Being Tested

Against this backdrop, both innovators and payers increasingly are accepting that new models for reimbursement and financing may be needed to support adoption of the wide range of gene and cell therapies. Indeed, several multi-stakeholder efforts are exploring such arrangements. These consortia include the Biotechnology Innovation Organization (BIO), the New Drug Development Paradigms (NEWDIGS) initiative at MIT, the

Exhibit 2.
Alternative Payment Model Barriers And Solutions



SOURCE: Alliance for Regenerative Medicine

Institute for Clinical and Economic Review (ICER), the American Society of Gene and Cell Therapy (ASGCT), and the Margolis Center for Health Policy at Duke University.

The Centers for Medicare and Medicaid Services (CMS) has also highlighted the need to revisit payment models for innovative, high-cost, high-value therapies, including regenerative medicines. **Novartis AG** launched *Kymriah* (tisagenlecleucel) in August 2017 with an outcomes-based contract agreement already in place with CMS, which said at the time it was committed to “identify[ing] and alleviat[ing] regulatory barriers [to new payment models] in Medicare and Medicaid.” The agency has continued to look for new ways to handle CAR-T reimbursement.

There is a growing consensus among stakeholders that reimbursement models that enable payers to make their payments over time and/or enable payment tied to the therapy performance may be appropriate for regenerative medicines, as they facilitate patient access to new therapies quickly while enabling payers to manage their overall budget impact and limit risk if the therapy does not perform as expected. The most common reimbursement models discussed in this context are annuity and pay-for-performance models:

- **Annuity models:** under an annuity or installment payment model, first raised as a potential option by Jim Wilson *et al.* in a 2014 *Nature Biotech* article, payments would be spread over a pre-determined time period. This model recognizes the long-term therapeutic durability of single-administration cell and gene therapies, matches the payment to the multiyear benefit and minimizes large up-front or annual costs for payers.

- **Pay-for-performance models:** in a performance - or outcomes-based payment system, the reimbursement for a treatment would be adjusted based on whether a pre-specified health outcome is achieved. There are many variations of this value-based model. It could be implemented through discounts on future payments, indication-based pricing, rebates or even outcomes-based money-back guarantees. This model shares risk between the innovator and the payer.

While annuity payments are a relatively new concept, outcomes-based contracting models have been fairly common in the single-payer systems of Europe and are on the rise in the US. Several US biopharmaceutical companies currently do offer money-back guarantees if performance-

based metrics are not met for certain chronic therapies, including **Merck & Co. Inc.** for *Januvia* (sitagliptin) and *Janumet* (metformin and sitagliptin) for diabetes, Novartis for its heart failure drug *Entresto* (sacubitril/valsartan), and **Regeneron Pharmaceuticals Inc./Sanofi** and **Amgen Inc.** for their PCSK9 inhibitors for dyslipidemia and secondary prevention of major adverse cardiovascular events.

Finding Acceptance For New Payment Models

Several implementation barriers must be overcome for either annuity models or pay-for-performance models to become a widespread reality. These barriers can be logistical, legal or regulatory. Importantly, many of these implementation barriers are not unique to regenerative medicines and are already being actively discussed in the context of pay-for-performance arrangements for existing products. For example:

Medicaid Best Price: manufacturers must report pricing data for drug therapies to the federal government to ensure that the US government, certain health care providers and state governments always receive the “best price” possible for these products under the Medicaid program. The Medicaid best price rule may inhibit manufacturers

from tying price to outcomes.

Alternate payment methods, such as annuities or pay-for-performance agreements that include paybacks or rebates, could artificially lower the price by which the government will calculate pricing or rebates. This situation raises the question of how to report the price of a treatment whose true price will not be known until after performance is determined.

Potential Solutions:

1. CMS has the authority to address this issue through several mechanisms, including informal discussions with manufacturers, formal guidance, or demonstration waivers, which can be approved to test changes in payment methods for Medicare and Medicaid. Individual innovators or industry groups on behalf of manufacturers can seek guidance from CMS on how to develop performance-based arrangements without triggering unwarranted rebates and/or how to secure such demonstration waivers. This solution would hinge, in part, on CMS being able to provide this guidance in a timely manner and ensure confidentiality of the information stakeholders provide to the agency as part of the guidance process.

2. Legislation may be necessary and appropriate to codify the types of payment arrangements that can be exempt from best price requirements.

Anti-Kickback Statute (AKS): the AKS prohibits the payment or receipt of any remuneration for the referral of items or services reimbursable by federal health care programs. Violators are subject to civil and criminal penalties, as well as the exclusion from participation in federal and state health care programs. Outcomes-based payments introduce new financial arrangements between innovators, payers and providers and have the potential to fall afoul of the AKS if they are perceived to impermissibly create incentives for the adoption of one product over another or for increased use of services or products billed to Medicare or Medicaid. The risks associated with potential violations of the AKS can be a barrier to broad adoption of alternative payment models.

Potential Solutions:

1. The Office of the Inspector General (OIG) enforces compliance with the AKS

“
Both innovators and payers increasingly are accepting that new models for reimbursement and financing may be needed to support adoption of the wide range of gene and cell therapies.
”

and will be instrumental in overcoming AKS-related payment barriers by providing clarification on whether alternative payment models are covered under existing “safe harbors,” or by establishing new safe harbors specifically designed to enable alternative payment mechanisms. (Also see “US FDA Extends Payor Communications Safe Harbor To Off-Label Uses” - Pink Sheet, June 12, 2018.)

2. CMS may be able to use its authority to conduct demonstration projects and coordinate with the OIG to protect such arrangements under the AKS in order to test new payment models.

If health care system stakeholders address barriers of the kind described above to the implementation of pay-for-performance models for more traditional therapies, the benefits of these changes may also then accrue to innovative regenerative medicines.

However, gene and cell therapy innovators will still face other implementation barriers to new payment models that are more unique to the durable impact of regenerative and other transformative medicines. The idea of annuities or pay-for-performance arrangements under which payers reimburse innovators for the value of a regenerative medicine that accrues over years or even decades after the original administration introduces two fundamental issues:

Payments Over Time: government payers (Medicare and Medicaid) generally require payment at the time of treatment. Under generally accepted accounting rules for financial reporting, an annuity payment model could require insurers to recognize the entire cost of the treatment at the time the therapy was administered, even though full payment has not yet been made. This could cause issues in adopting such a payment model, especially for government insurers.

Potential Solutions:

1. Pursue guidance from CMS to ensure that proposed amortized and annuity payment models could allow for the recognition of costs over time until the total amount is gradually paid down.

2. Pursue demonstration waivers with CMS, as described earlier.

3. Pursue exploration of innovative models via the Center for Medicare and

Medicaid Innovation (CMMI), which was created to develop and test new payment and service delivery models.

4. Federal legislation to eliminate state-to-state variability that may create challenges for the implementation of alternative payment models.

Portability: a major challenge in enacting an annuity payment model involving payment over many years is the issue of portability of obligations related to such payments as patients move from one plan to another. Especially in the US, patient movement across health plans is common and there is no specific statutory or regulatory provision that requires one payer to continue making payments associated with the contract between another payer and a product manufacturer. Therefore, if an insurer enters into an annuity or performance-based arrangement intended to span several years, the insurer could be forced to continue payments for an individual who is no longer a member, while another insurer reaps the long-term clinical and cost benefit of the curative therapy.

Potential Solutions:

1. Insurers and manufacturers work together and with state insurance regulators to identify and implement policies that can support alternative payment mechanisms. For example, insurance contracting changes could be made to allow annuity contracts to follow patients if they switch plans, enabling the transfer of any financial commitment.

2. Create arrangements (e.g. via developer-sponsored patient data registries) that allow original insurers to continue to gain access to relevant patient outcomes data for their former members so that they can continue to make payments or discontinue as appropriate, based on product performance against the original contract.

3. Create an annuity fund, funded by insurers, to cover out years should patients switch plans. This option transfers the burden of monitoring patients and tracking health care outcomes to a third party who would manage and administer the fund.

One or more of these contracting changes could be piloted at the state level, while federal legislation is pursued to enable consistency across the country.

Addressing Payer Financing And Patient Access Are Key To Adoption

In addition to new reimbursement models to pay for gene and cell therapies, employing financing mechanisms, such as reinsurance, stop loss or risk pools, adapted for high-value treatments, also are necessary to give insurers time to determine and accommodate any budgetary impact of these new therapies, which may introduce higher costs in the near term but generate patient value and cost offsets over the medium to long term. Likewise, new tools may be needed to facilitate patient access to regenerative medicine products. Patients are increasingly facing higher out-of-pocket costs due to increased deductibles, co-insurance and premiums for their care, which could impact affordability for patients. Additionally, some gene and cell therapies target rare genetic diseases that are treated at specialty centers across the country. Travel and lodging associated with accessing these specialty centers are often not covered by insurance, limiting access to those who can pay.

ARM and its affiliates are working both independently and in collaboration with others to support initiatives to address payer financing and patient access issues. These activities include engagement directly with government and commercial payers and regulatory

bodies on value-based payment options and the establishment of a foundation focused on education and patient access.

Finding a path forward requires both market-based solutions and action by the federal and state governments, insurers and manufacturers. No one entity can achieve these changes on its own, nor will every solution be ideally suited to each new therapy or circumstance.

As with all medical technologies, regenerative medicines will have to demonstrate significant and durable clinical benefit and economic value supported by strong data to ensure successful adoption and potential price premiums. The goal of the payment models described here is to build an early platform that allows innovators, payers, providers and patients to successfully engage around new gene and cell therapies during the initial period of potential uncertainty and patient demand.

Multi-disciplinary efforts involving all groups need to continue to critically assess such models, and to initiate demonstration pilots, where appropriate. ARM and its member organizations will continue to do such work in collaboration with others to help pave the way for regenerative medicines to deliver on their transformative promise to patients, to the health care system and to society. ▶

IV005371

Francesca Cook, PhD, REGENXBIO, fcook@regenxbio.com; Ted Slocomb, Audentes Therapeutics, tslocomb@audentestx.com; Michael Werner, Alliance for Regenerative Medicine, Holland & Knight LLP, michael.werner@hklaw.com; Ted Haack, LatticePoint Consulting, ted.haack@haack-assoc.com; Donald Han, Pfizer, donald.han@pfizer.com; Faraz Ali, REGENXBIO, Fali@REGENXBIO.com

LET'S GET SOCIAL

In Vivo
Pharma intelligence | informa

@INVIVOnow