



Personalized Medicine: It's the right time for the right strategy

Clinical researchers and life sciences companies are moving quickly to develop and commercialize personalized medical treatments, but the market remains fraught with challenges. A careful strategy that is mindful of the financial, regulatory, and scientific considerations is required to achieve commercial success.

This is a breakthrough moment in medical history – as medical science can finally begin to deliver highly personalized treatments for cancers, metabolic disorders, and genetic conditions that have until now been untreatable or addressable only through considerably less precise tools. This paradigm shift is the product of decades of interdisciplinary research in genetic testing, immunology, oncology, and health data analytics.

Recent developments, such as the landmark approvals by the US FDA of CAR-T cancer therapies Kymriah and Yescarta and hereditary blindness gene therapy Luxterna, suggest that these revolutionary technologies – and the pipeline of associated therapeutics in development - will soon become widely integrated into general medical practice. This stands in contrast to earlier cell and gene therapy launches that had limited success due to high prices and small target populations, such as uniQure N.V.'s Glybera (withdrawn from the EU in 2017) and TiGenix's Chondrocelect (withdrawn in 2016). At a time when the number of personalized medical treatments has grown more than twenty-fold, when a record number of genetic-testing products – over 65,000 – are for sale, and when multi-billion dollar acquisitions of cell and gene therapy developers and health care analytics companies are frequently in the news, these examples illustrate the need for strategies to understand the limiting factors of target populations, address pricing pressures, mobilize government support, expedite regulatory approval, and solve distribution challenges, in order to mitigate the financial constraints that can determine a commercial success or failure:

- **For the moment, development costs and narrowly defined population targets are acting as limiting factors.** Certain structural barriers will represent a near-term drag on innovation in this area: the relatively high expense of development – and the inherent need to tailor, rather than mass produce a product for individual use - leads to costly therapies with narrowly defined patient populations. Developers should seek to minimize the cost of manufacturing such treatments, including raw materials (e.g., live viral vectors), protocol design and quality control processes such as release testing, and the associated requirements of Good Manufacturing Practices (GMP), considering emerging closed manufacturing systems to manage quality control and/or limit clean room expenses.

- **Pricing of novel treatments is a work in progress, and “sticker shock” is a significant barrier to reimbursement and adoption.** High development and manufacturing costs, as well as limited target patient populations have driven pharmaceutical companies to set high price points for personalized therapies (e.g., Luxturna, \$850k; Strimvelis, \$665k; and Glybera, \$1M).

Reimbursement by public and private payors has been mixed by market and therapy, as payors evaluate the cost and benefit of personalized therapies relative to their benefit to patients, considering alternative options. In the EU, reimbursement policies are the responsibility of individual member states and even regions within member states. Local stakeholders may have different perspectives on the value of therapies (e.g. Chondrocelect and Glybera in France and Germany). Germany’s InEK (Institute for Hospital Remuneration) gave high ratings to Chondrocelect and awarded hospital-level reimbursement to Glybera, while France’s HAS (*Haute Autorité de Santé*) assigned poor ratings to Glybera and rejected Chondrocelect. (3) The US presents multiple challenges for therapy developers and investors: private and public insurers may require different pricing models (e.g., outcomes-based reimbursement for Kymriah) and their ability to administer the reimbursement for the therapy or the administration may lag the commercial launch significantly (e.g., Medicare’s delay in reimbursement of Yescarta due to lack of billing code).

Treatments that cure disorders rather than ameliorate symptoms, address lethal conditions, or provide significant improvement over existing regimens have greater opportunity for reimbursement. Developers and investors should establish a clear vision of the clinical endpoints, the size of the target market, the potential manufacturing issues, and opportunities to offer innovative value-based pricing when exploring the personalized medical treatment landscape.

- **Government involvement in catalyzing development varies widely by market.** Due to the significant investment costs and threats of competition, developers of personalized medicines seek to expedite approval and minimize expenses along the way to commercialization. National markets are not equal with regard to progress in personalized medicine. The governments of both the US and Japan, for example, have shown enthusiasm for cell and gene therapy treatments, and have made legislative and regulatory moves designed to promote and expedite commercialization of cell and gene therapies. In the US, the 21st Century Cures Act and support for a Regenerative Medicines and Advanced Therapies (RMAT) pathway are evidence of an interest at the Federal level in supporting and expediting the development of novel therapies. In 2015, Japan authorized the SAGIKAKE strategy to support Japanese pharmaceutical innovation, expediting review of treatments in development. This followed its 2014 enactment of an expedited pathway for “regenerative medical products” that allows for faster marketing authorization and conditional 7-year approval for medications targeting unmet needs. The EU has also adjusted its regulatory requirements around ATMP (advanced therapy medicinal products) to facilitate manufacturing. In addition, nations within the EU have developed a variety of local incentives related to research and development, to bolster national scientific industries and promote scientific development. To accelerate the realization of revenue, developers should plan their clinical research considering the regulatory pathways in their prioritized geographic markets; protocols such as multi-site trials may address the requirements of multiple regulatory bodies simultaneously.
- **Distribution and provision of novel personalized therapies may be constrained by clinical expertise.** The most recent advances in personalized cancer treatment have, not coincidentally, been made in the treatment of the most vulnerable and critically ill patients; for this reason, their distribution has been somewhat limited in institutional scope. Currently, only medical centers with access to the sickest patients, which possess the clinical and operational expertise to administer complicated, potentially lethal treatments and address their side effects, can act as outlets for the transformational therapies reaching the market. However, given the serious morbidity and

mortality of the conditions being treated, patients have been willing to travel to gain access. As progress continues, side effects are made more manageable, and less-morbid conditions are addressed by these novel means, there will likely be a surge in the number of providers who can deliver treatments, and in the size of the eligible population, and geographic access considerations will likely ultimately vanish.

- **Alternative pathways may undercut the market for personalized therapies.** Today's autologous cell therapies may not be the final word in the advancement of cell and gene-based treatments. Cell and gene therapies that can be engineered using cells that are immunologically compatible with many subjects would inherently lower the *per capita* cost of manufacture and permit a profit margin at a lower price point (for example, an improved allogeneic stem cell therapy for thalassemia (6)). Therefore, where they can be developed, scientific advances that are based on this biological approach may represent an existential threat that could in the medium to long term displace the entire category of autologous treatments.

These considerations are already shaping the direction of current research. Marwood's recent review of FDA-registered clinical trials related to autologous cell and gene therapy identified several hundred studies, of which approximately 40% focused on oncology. Hematologic cancers are prime targets, capitalizing on the successful mechanisms of CAR-T treatment for acute lymphoblastic leukemia and large B-cell lymphomas, but research in the treatment in solid tumors is also robust. At the same time, progress has been made in severe combined immunodeficiency, and significant efforts to treat monogenetic diseases such as cystic fibrosis are underway. High-reimbursement therapies that provide years of benefit in critical illnesses are complemented by research aimed at large markets such as orthopedics and wound healing, which as of now may continue to struggle to demonstrate cost-effectiveness.

Despite some growing pains and a few notable disappointments, there is strong demand for personalized medicine. With a clear vision of where, when, and how to develop such treatments, scientists, clinicians, and the investing community will be certain to drive change and boldly shape a transformative future. The future of personalized medicine is bright, and the rewards for well-informed investors and developers – both financial and social, could be great.

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- (1) [“The Personalized Medicine Report, 2017”](#). *The Personalized Medicine Coalition*
 - (2) See, e.g., Ogden, Joy. [“QALYs and their role in the NICE decisionmaking process.”](#) *Prescriber*, April 2017, pp. 41-43
 - (3) Jones-Phillips, Dominic. [“Cell and gene therapy: Are payers willing to pay for a cure?”](#) *Valid Insight* blog. May 5, 2017
 - (4) See, e.g., Miller S. "Gene therapy holds great promise, but big price." *Express Scripts*, September 21, 2017. Accessed February 6, 2018
 - (5) Mullin, Emily. [“A year after approval, gene-therapy cure gets its first customer.”](#) *MIT Technology Review*. May 3, 2017
 - (6) See, e.g., Srivastava, A and Ramachandran VS, [“Cure for thalassemia major – from allogeneic hematopoietic stem cell transplantation to gene therapy.”](#) *Haematologica* 2017 Feb; 102(2): 214-23.

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Contact Information

For more information on any of the content in this publication, we encourage you to please contact us.

Adam Flisser, M.D. FACOG

Senior Vice President

Office: 212-532-3651

aflisser@marwoodgroup.com

About the Authors

Jennifer Yaggy MBA is Director of Strategy and Adam J. Flisser MD FACOG is Senior Vice President of Strategy in New York; Stephen Williams PhD MBA is Director of Life Sciences and Kim Vukhac MBA is Senior Vice President of Life Sciences in Washington, DC; Kayleigh Hartigan MSc is Managing Director, Tim Read PGDip is Assistant Director, and Caroline Antoine MES is Senior Associate in London.

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