



## ADOPTING PRECISION MEDICINE WITH SMART PLATFORM

### Abstract

Advances in medical research augmented by emerging innovative technologies such as Gene Sequencing and Artificial Intelligence made new frontiers in treating rare forms of diseases possible. Precision medicine is one of the primary beneficiaries of such advancements. Though the outcomes of precision medicine have been highly promising, it is still in the very early stages and targets only rare genetic diseases. This paper discusses the approach to enable commercially viable treatments to large populations through adoption of the supply chain for precision medicine based on our experiences and expertise working with major pharmaceutical companies.

## Introduction

Precision medicine, also referred as 'personalized medicine' or 'individualized medicine', is an innovative approach for disease prevention and treatment that considers differences in people's genes, environments, and lifestyles. The goal of precision medicine is to target the right treatments to the right patients at the right time.<sup>1</sup>

Great progress has been made in medical research and gene sequencing in the last two decades that resulted in Cell and Gene based therapies for some rare conditions for which no effective treatments or drugs are available. Since 2017, when the U.S. Food and Drug Administration (FDA) approved the first in-vivo gene therapy for inherited retinal dystrophy and treatments based CAR-T cell therapy to treat specific types of refractory hematologic malignancies, there are over 1200 investigational drug applications for ongoing clinical trials for Cell and Gene based therapies that are focused on variety of cell types and indications<sup>5</sup>. The FDA anticipates approval of 10–20 gene therapies a year beginning in 2025. Over \$19B financing was raised in the

year 2020 alone for cell and gene-based drug development<sup>5</sup>. The estimated addressable global market for Cell and Gene Therapies will be well over \$35B by 2026<sup>9</sup>.

Cell Therapy and Gene based Cell Therapy are two forms of Precision Medicine. Cell therapy is the transfer of live cells into a patient to treat

a disease, which may originate from the same patient (autologous cells) or a healthy donor (allogeneic cells). Gene therapy uses genetic material with the goal of changing the course of a disease and this is investigated for the treatment of multiple diseases. Gene addition and Gene editing are two types of Gene Therapies as shown in Figure 1.

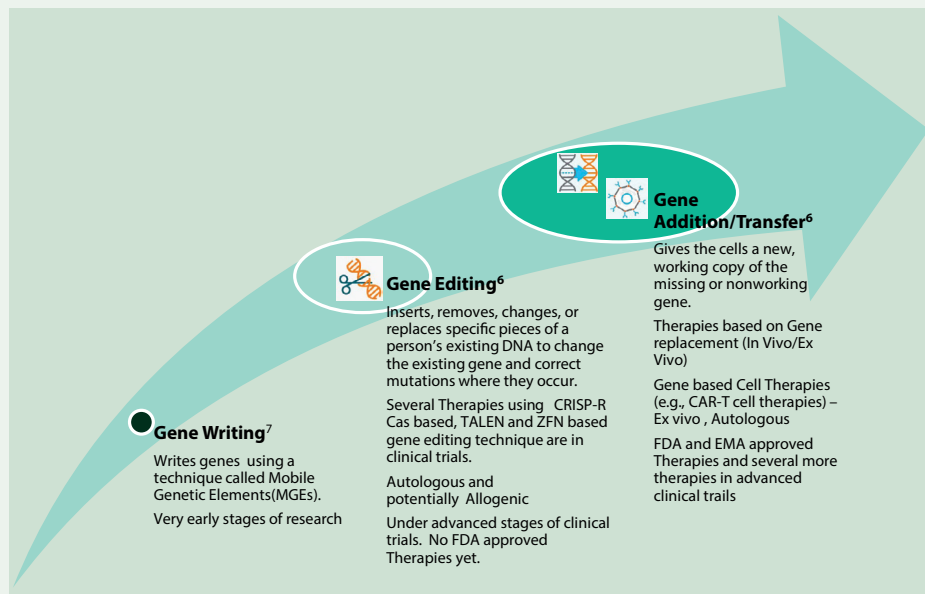


Figure 1: Types of Cell & Gene Therapies

## Consulting Approach to Precision Medicine Implementation

### Business Transformation with IMPACT™

Historically, the pharmaceutical industry has dealt with a small molecule based, large volume, make to stock drug supply chain. Precision medicine is centered around the patient with specific conditions and the product journey starts with a patient (apheresis) and ends with a patient (infusion). IMPACT™ methodology, developed by Infosys, has the necessary features to take into consideration the uniqueness of precision medicine solutions like evolving scientific and technological advancements, complex manufacturing and supply chains, chain of identity (COI), higher treatment costs, patient privacy and time sensitivity; and define the roadmap for precision medicine country sites launches.

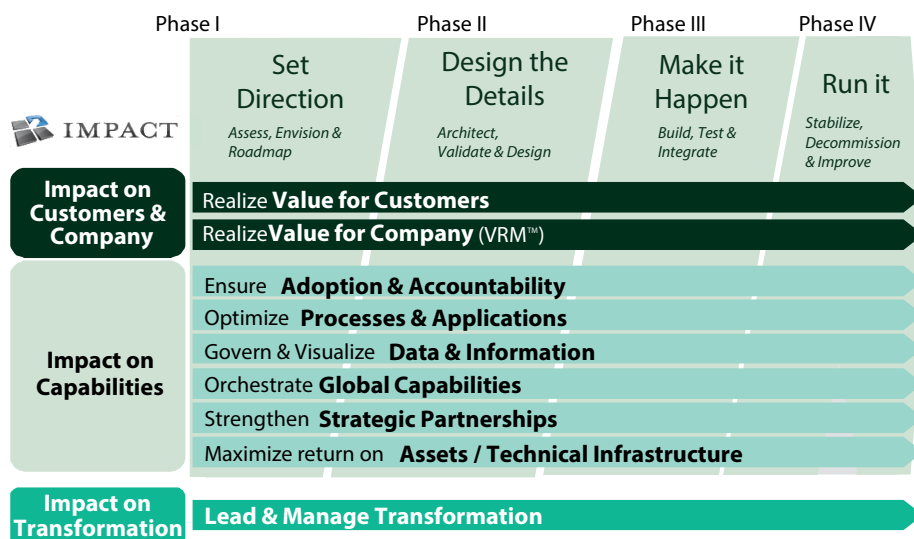


Figure 2: IMPACT™ Methodology for developing precision medicine solution

## Business Process

As shown in Figure 3, Cell & Gene therapy starts with a treatment request from Health Care Professionals (HCPs) and is followed by scheduling and capacity planning for apheresis and infusion centers, collection of Apheresis and shipment processing, manufacturing and quality control, cryopreservation, shipment to infusion centers, patient infusion, patient monitoring and billing. Quality Control (QC) along the entire supply Chain and ensuring the tracking of Chain of Identify and Chain of Custody are crucial to meeting regulatory compliance.

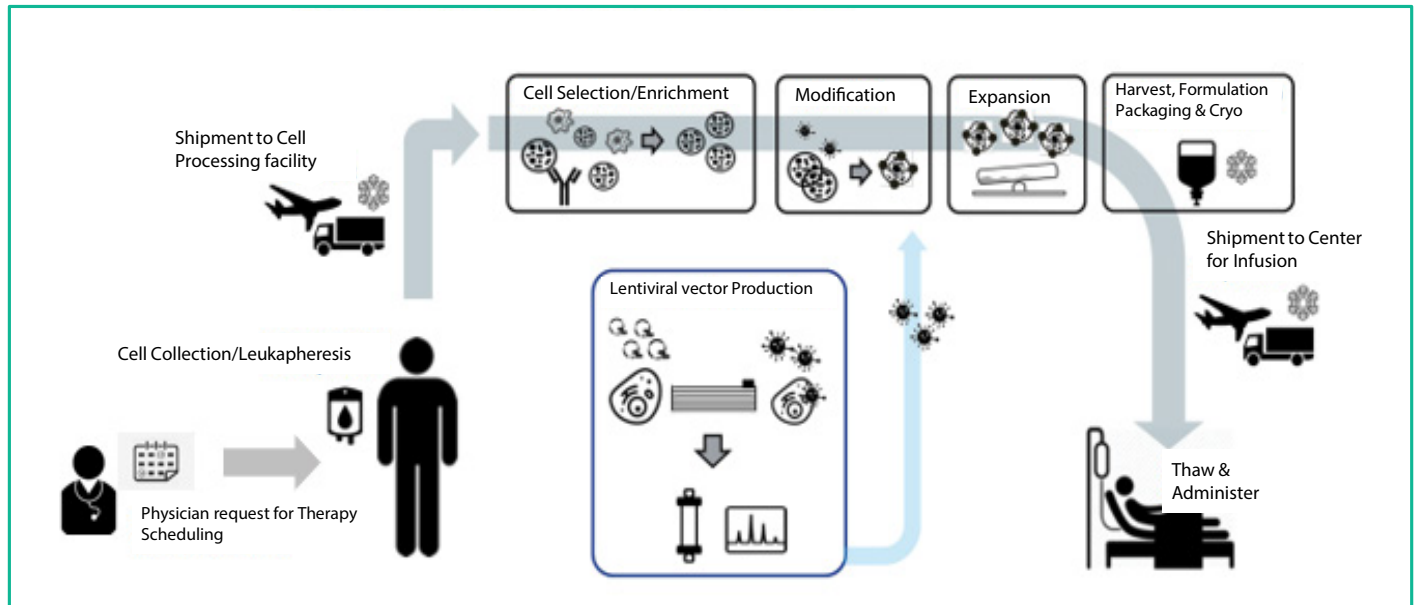


Figure 3: Cell processing in Cell & Gene Therapy using CAR-T cells<sup>4</sup>

The autologous T cell manufacturing process starts with patient selection followed by apheresis collection at a certified facility. Collected cells are shipped to a Cell Processing center, where the T cells are activated, selected for 'cluster of differentiation 3' (CD3), and subsequently transduced with a viral vector harboring a chimeric antigen receptor or a T-cell receptor. The expanded cells are washed and cryopreserved for QC release tests. Products are then shipped to an infusion center and infused to the patient.

## Autologous Infusions

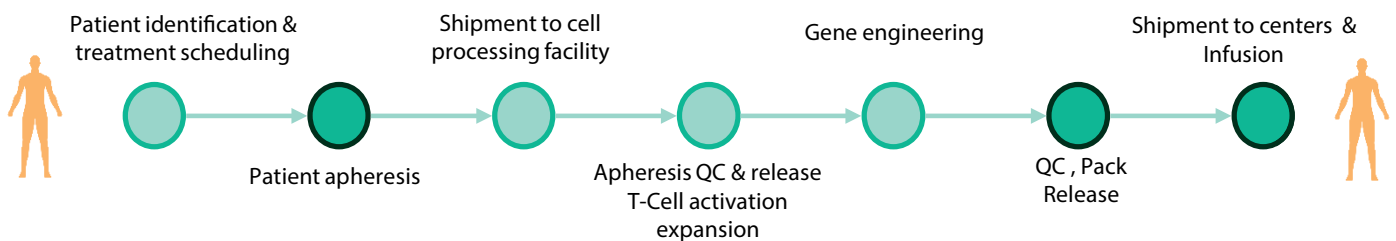


Figure 4: Processes flow in Cell & Gene Therapy (Autologous)<sup>2</sup>

In autologous therapies, the entire process of isolating specific cells from the individual's blood, then genetically engineer them to multiply before reinfusing them back into the patient is time-consuming and costly. Additionally, in cases of severely ill patients or pediatric patients, it may not be possible to obtain the required count of T cells to

manufacture the therapy, which has led some drug developers to explore allogeneic cell therapies derived instead from healthy donor cells and could be available to patients "off-the-shelf" as shown in figure 5. Therapy manufacturers source the cells from donors by matching the patient's genotype and match Human

Leukocyte Antigen (HLA). This reduces the overall time from prescription to infusion compared to autologous therapies. Researchers are working on ways to overcome the risk of Graft versus Host (GVH) disease associated with allogeneic therapies by HLA matching of the donor and recipients.

### Allogenic Infusions (healthy donor PBT)

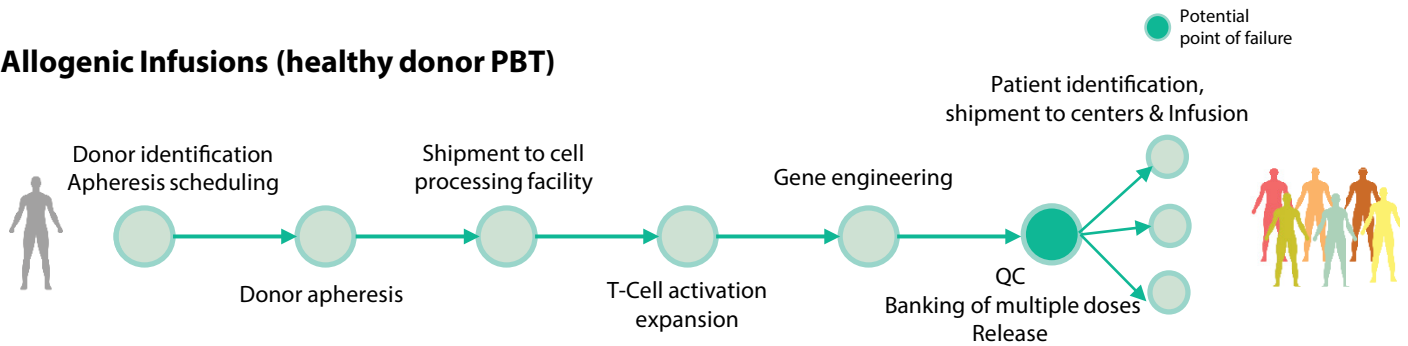


Figure 5: Process flow in Cell & Gene Therapy (Allogenic with cells from healthy donor)<sup>2</sup>

Figure 6 shows another variation of allogenic treatment with alternate cell sources

### Allogenic Infusions (iPSC-T)

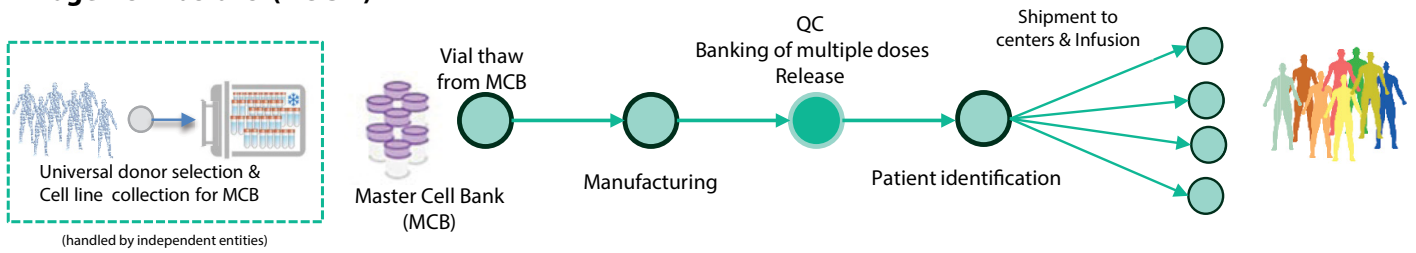
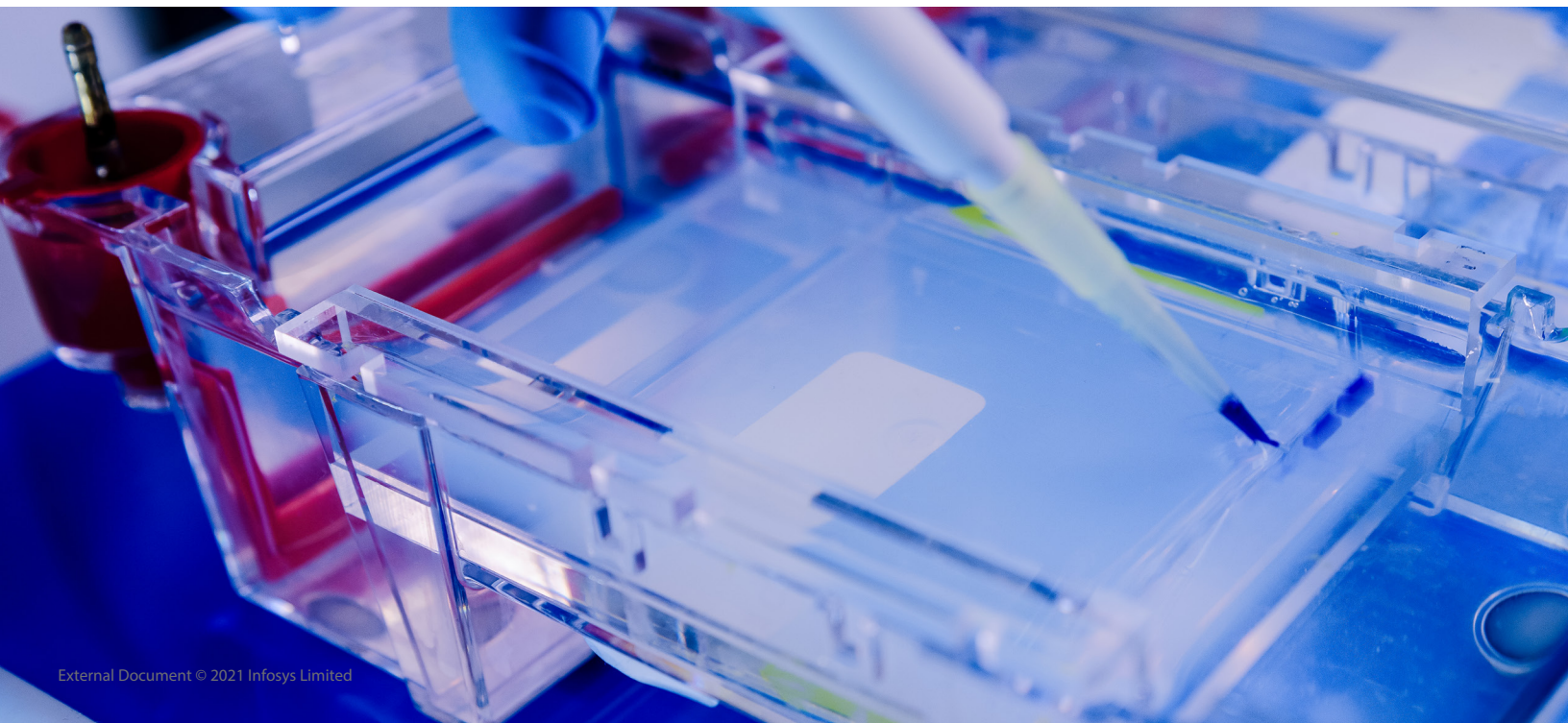


Figure 6: Process flow in Cell & Gene Therapy (Allogenic with iPSC-T)<sup>2</sup>





## Supply Chain mapping of Cell & Gene Therapy processes

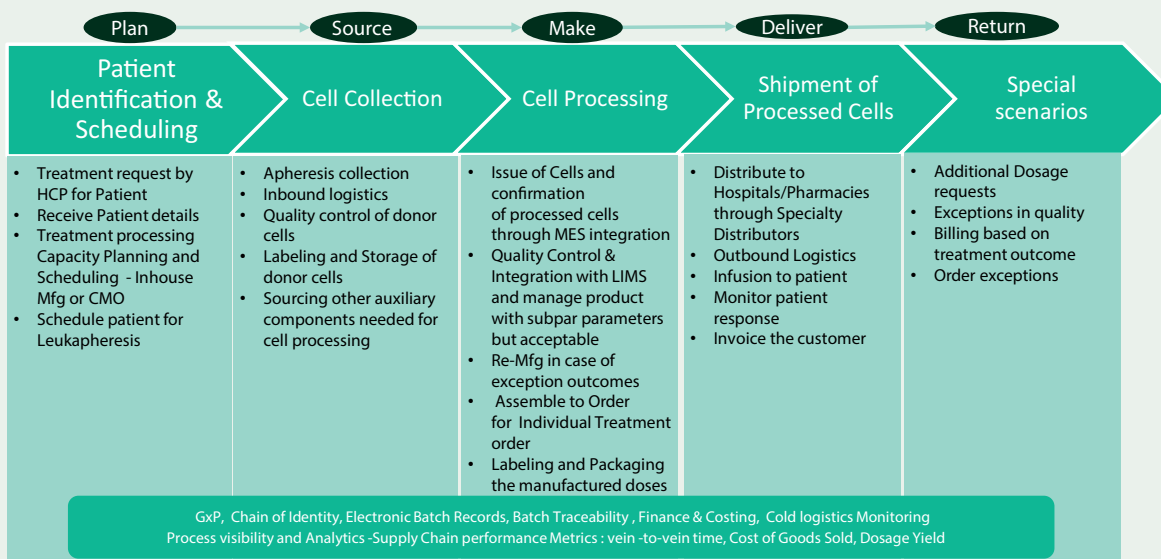


Figure 7: Supply Chain mapping of Cell & Gene Therapy using Supply Chain Operations Reference (SCOR) matrix

### Plan

The planning activity involves forecasting the demand for therapies to ensure sufficient skilled resources, manufacturing capacities such as cell activation and expansion modules, critical components such as vectors and cryopreservation capacities to meet demand. Visibility into the available resources and capacity time slots allow the prescribing physicians to prioritize scheduling patients for therapy based on the severity of their condition. The available capacities are presented to prescribing physician in an intuitive calendar like view to choose a time slot with estimated apheresis date and treatment delivery dates. COI is established when the prescriber requests the treatment

### Source

Apheresis is a critical and unique step as patients' cells are the prime ingredient in therapy manufacturing. After a patient's identity is verified, apheresis is performed at the certified lab. Required identification labels for Chain of Identify and necessary documents are attached to the collection. Various parameters of donor cells are documented and collected cells are stored in a freezer. Cryopreservation logistic providers pick up the cells packaged in cryopreservation containers from the lab and delivered to the manufacturing plant. This includes completion of any relevant

customs and regulatory procedures. The logistic providers then continuously monitor temperature and product location.

The manufacturing facility also procures/ makes other ingredients such as viral vectors and secures resources for manufacturing. Once the cells are received at the manufacturing facility, quality inspections are performed and recorded. The cells are stored in the freezer until manufacturing can begin.

### Make

The manufacturing phase is unique and complex with quality and Chain of identity built into every step of the process. COI is validated to ensure the cells being issued to Therapy manufacturing are the cells received from the same patient (in case of autologous).

Cells collected from patient are enriched in a highly controlled manufacturing environment following current Good Manufacturing Practices (cGMP) standards and the right type of vector is introduced to the cells and cells are then allowed to expand to the required cell count. The batches of harvested cells go through several quality checks. Approval and release are recorded electronically as Electronic Batch Records (EBRs) and the yielded dosage is packed in temperature-controlled containers, which are shipped to the infusion centers.

In case harvested cells do not meet the required criteria for cell count, HCPs are informed and depending on HCP's decision, remanufacturing of therapy may be required. Remanufacturing using available bags of patient cells goes through the same stringent quality check and release processes before being shipped to the infusion center.

### Deliver

After harvested cells are released by quality control, the product is shipped to the infusion center and the infusion center is informed through advanced shipping notifications. Quality certificate, regulatory and customs documents are part of shipment. The logistic provider then delivers the product to the hospital where infusion takes place.

The certified hospital completes the necessary treatment prerequisites before enrolling the patient for infusion. COI is ensured before the therapy is infused to the patient. Manufacturer's require physicians to record the infusion date, preliminary outcome, and other necessary parameters. Post infusion recording, the manufacturer bills the hospital, insurance company or specialty distributor as per the contract. Periodic health checkups and data recording by physicians for billing based on treatment outcome is becoming very common due to high cost.

## Smart Platform Architecture

Figure 8 depicts a smart platform to enable the Collection, Transportation, Manufacturing, Shipping and Quality Control of the Cell Processing Supply chain in a very integrated environment. This platform provides an end to end visibility interface to HCP as well as other partners/vendors and affords organization's business agility needed in the fast-evolving precision medicine eco-system.

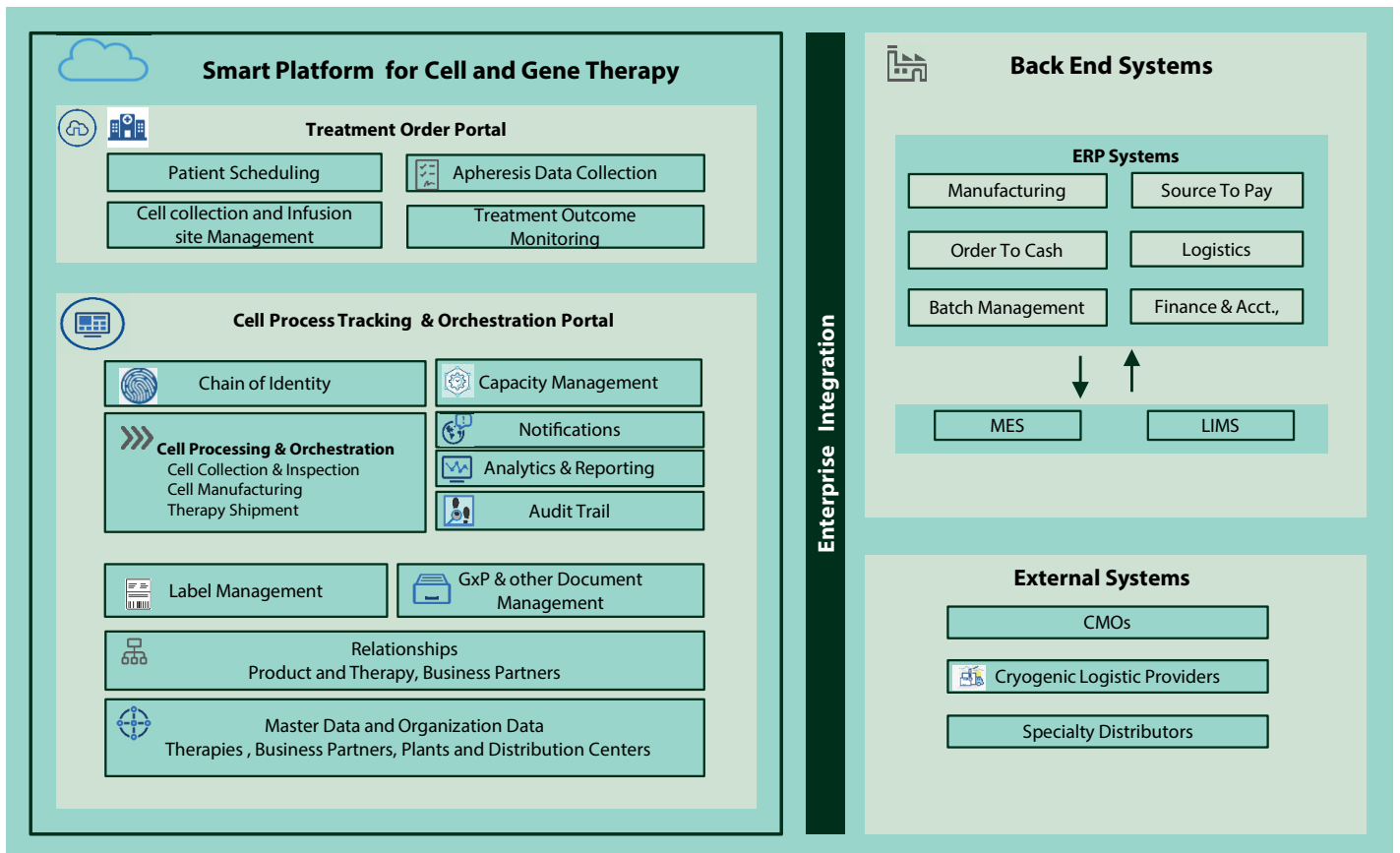


Figure 8: Representative Architecture for a smart platform for Precision Medicine



## Unique Master Data considerations:

A flexible and scalable master data structure and a well-defined master data strategy are important for quicker enablement of new therapies and extending or launching the therapies to new country sites.



Fig 9: Master Data aspects of Precision Medicine

In addition to standard master data, the unique master data below are required to support precision medicine.

**Therapy/Product Association:** establishes relationships between indication, region, manufacturing plant, and specific parameters of the patient which in turn determines the downstream processes

**Site and Therapy Associations:** establishes relationship between hospitals, labs and infusion centers that are certified to treat patients' specific indications

**Therapy and Label Association:** establishes relationship between Therapy, Site, and Label Template. Label templates may differ by countries for the same Therapy due to local regulatory agencies. Labels facilitate validating the COI throughout the product journey.

## Organizational Change Management

To drive successful adoption of precision medicine solutions, it is imperative to align the changes to key components of the organization, understand the impacts of those changes, drive buy-in at all levels and engage leadership. The proven Change Management Framework in Figure 10 illustrates five key phases to achieve the expected outcomes.

Stakeholders, such as, healthcare providers, hospitals / laboratories, customer care, specialty distributors and manufacturing facility must be actively engaged throughout the product journey and create buy-in and ownership for new systems and processes to facilitate smooth adoption. Treatments based on Precision Medicine are highly time sensitive and, in many cases, the last hope for patients. They involve a high degree of human intervention at multiple points throughout the product journey. As processes evolve with advances in medical science and



Figure 10: Organization Change Management Framework

technology, certain processes may need to be eliminated or new processes introduced. Regulatory requirements require transitioning to newer approaches based on various scenarios, such as, treatment, patient country, contract, or technology. External and internal users must be trained sufficiently and have clarity on their roles and responsibilities within the common overarching goal of saving lives

## The importance of Customer Experience

Pharma companies that manufacture Cell & Gene therapies must have close interaction with the hospitals/physicians (HCPs) that prescribe treatments to their patients and contract manufacturers (CMOs). Design Thinking workshops (Figure 11) involving key business stakeholders from all functional areas are a proven approach for designing an intuitive and user-friendly customer experience platform for cell processing supply chain tracking and orchestration.

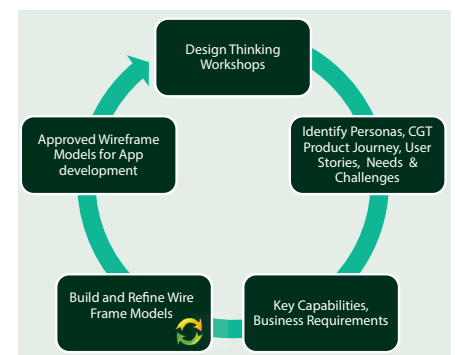


Figure 11: Design Thinking to enable Precision Medicine Smart Platform

## Challenges and Opportunities

As the technology of precision medicine-based therapies evolve, it will influence the end to end process. Some key challenges to focus on are:

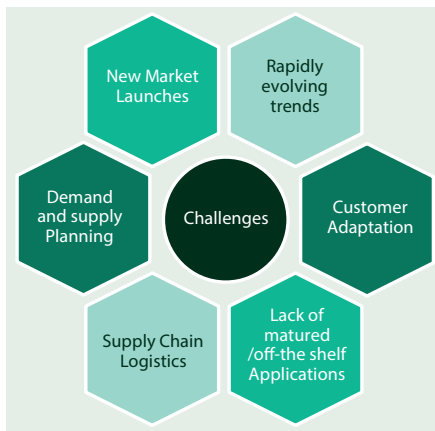


Figure 12: Process Challenges in Personalized Medicine

- New Market launches – Business process for Precision Medicine must consider localization requirements such as infrastructure, compliance to regulatory authorities like FDA, European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA - UK), Therapeutic Goods Administration (TGA - Australia), Ministry of Health, Labor and Welfare (MHLW - Japan), customs regulations etc., to enable smooth launching of products in various countries. The systems and applications must be capable of supporting compliance to local governance and regulatory requirements quickly and easily. An example of compliance requirements is patient privacy where some countries require the patient data to be stored within the country.
- Lack of off-the shelf applications - Precision medicine is a relatively new and evolving field and lacks industry defined best practices. Organizations

need to consider enhancing the capabilities of their existing portfolio of systems and applications by building scalable & modular solutions. In addition, the major software vendors are either building products or adding additional capabilities to the existing suite of products. Nevertheless, this should be an essential part of an organization's IT roadmap.

- Forecasting/Demand Planning - Pharma companies need to work with hospitals and research institutes to forecast the demand for therapies for various indications. Similarly, close collaboration with Apheresis centers, Infusions centers and CMOs is extremely critical to forecast the supply/ resource capacities to balance supply and demand. This would require adding necessary capabilities in the systems/applications supporting Forecasting and Demand and Supply Planning.
- Customer Adoption – An intuitive and easy to use customer experience is crucial for both external and internal users to have real time information on treatment processing. Organizations need to consider this as one of the critical capabilities of their application portfolio.
- Technological advances/ emerging trends – Currently manufacturing is mostly in lab setting with open systems. As demand increases and technologies improve, manufacturing will move from laboratory scale to commercial scale and adopt to closed systems. Business processes should be flexible enough to adopt to any future therapies for the same indication or other indications. As the research in Science and Biomedical technology

advances, better ways to manufacture and administer cell and gene therapies may be possible, which in some cases may obsolete process steps or change the processes radically. Organizations should plan for such changes/disruptions so their business processes and supporting systems and applications will be suitably flexible.

- In-house manufacturing – The ability to manufacture high-quality GMP-grade, scalable, and cost-efficient gene therapy product remains a challenge and some companies have been relying on CMOs. However, with the recent explosion of precision medicine programs, a shortage of contract manufacturing capabilities and human capital, is driving many companies to bring manufacturing in-house. Though this is a significant upfront investment, it allows companies to have more control over product quality, production schedules, capacity, and costs, while protecting the proprietary knowledge that contributes to the unique capabilities of each company's platform.
- Supply Chain Logistics - The increasing push for biologics and gene therapy drugs will further drive demand for temperature-controlled/cold chain logistic companies, potentially elevating costs of precision medicine. Disruptions due to natural disasters, pandemics and human induced conditions must be factored into logistics planning. Some of the options that organizations are exploring are, hub and spoke models in which manufacturing facilities are located near the apheresis and Infusion centers or extending the manufacturing facilities to the major hospitals where patients are treated.



## Industry Trends for future

- Innovation in Medical Sciences:**

Recent successes in genetic medicine have paved the path for a broader second wave of therapies and laid the foundation for next-generation technologies. Gene editing technologies are enabling an entirely new modality for treatments based

on precise modification of human genome sequences. As successes of early gene therapies are being expanded to other conditions and patient populations, next generation technologies like gene editing, potential use of human induced Pluripotent Stem Cells (iPSCs) as alternate cell

sources are dramatically expanding the impact of these therapies on treating human disease (Figure 13)<sup>3</sup>. Hence, it is essential that pharmaceutical companies continuously revise and align their manufacturing and supply chain strategies to adopt to the rapid advances in this space.

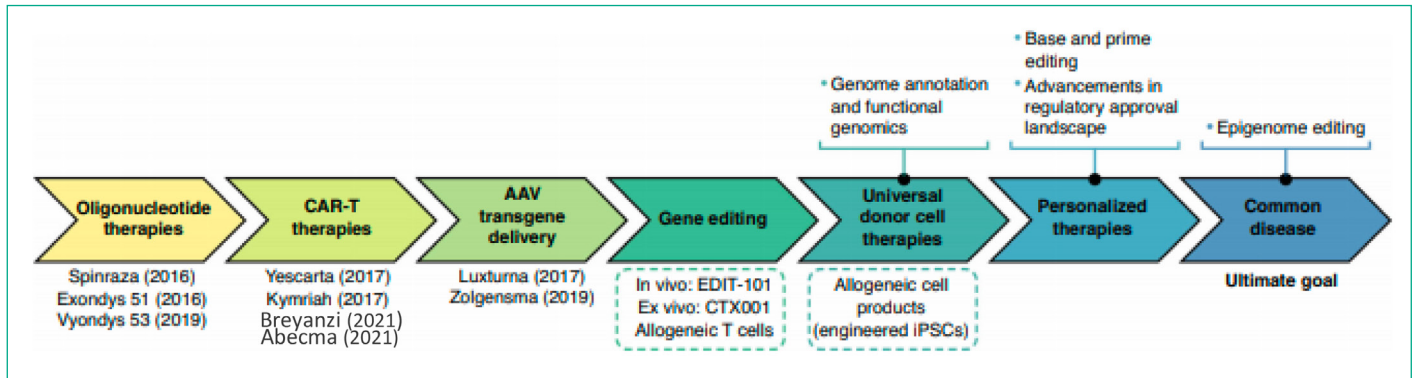


Figure 13: Milestones and potential future developments in precision medicine<sup>3</sup>

- Strategy:**

Optimizing prescription to infusion cycle time due to the high cost and time involved in autologous cell and gene therapies, there is an increased focus on the possibility of manufacturing the therapies sourced from healthy donors with histocompatibility match. This approach is still in very early pre-clinical stages but if the efficacy and safety are comparable to autologous cell therapies, allogeneic therapies will be adopted by more Pharma companies owing to the overall cycle time reduction and cost advantages. Companies need to build their business processes and the systems and applications to be flexible to adopt this approach in addition to autologous processes.

Supply Chain Value Engineering - While reducing the cycle time has many constraints that need to be addressed by the technological advancements in cell processing/manufacturing and bio-technology, any improvements outside that space, say logistics, quality control and any other processes that involve human intervention must be continuously analyzed further to continuously optimize the overall cycle time for the patients benefit.

- Business Process innovations:**

Insurance coverage & outcome based payments – As precision medicine-based therapies mature and cost of treatments over the long-term decrease, they will be widely accepted by insurance companies, government entities and other payers. Business

processes will need to be refined to handle various types of payments/reimbursements by insurance and/or government entities. The payer entities are increasingly advocating for payments based on the treatment outcomes.

- Technological Innovations:**

Leverage Robotic Process Automation (RPA) to proactively identify and resolve issues throughout the product journey. This will improve productivity and efficiency while ensuring quality. Adopt Blockchain technology for tracking and validation of batches and chain of identity. Dashboards can be leveraged based on advanced analytics and data visualization to provide KPIs and process visibility.

## Conclusion

As a rapidly evolving field of medicine, personal medicine provides great hope to patients with rare genetic diseases but pharmaceutical companies developing the therapies must rethink their processes, systems, and applications. This whitepaper presents a consulting approach to enabling precision medicine by highlighting key process differentiators, the underlying challenges and several important insights from our experiences implementing a digital platform framework that supports realizing supply chain efficiencies in cell and gene therapies. To realize the full potential of precision medicine solutions, all stakeholders involved in the healthcare ecosystem must collaborate and adopt it.





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