Business Trends in Precision Medicine

A report submitted in partial fulfillment of the course requirements for MBA 585

by

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I. Introduction

The discovery of genetic inheritance, the manipulation of genetic material, and the completion of the Human Genome Project are a few foundational research milestones that have led to a new field of medicine. The term “personalized medicine” was first used in the 1990s while the Human Genome Project was underway[1]. However, the general public and media outlets often misconstrued the term to refer to therapies designed for each individual patient[2]. Many subject matter experts felt that the term was too promising and did not accurately represent the emerging research[1]. The term “precision medicine” was coined in 2008 by a business strategist from Harvard Business School but did not gain significant traction in the field until a United States (US) National Research Council (NRC) committee published a report entitled *Toward Precision Medicine*[1]. Though some argued that the introduction of a new term would add to public confusion, the US Food and Drug Administration (FDA) continues to use “precision medicine” and “personalized medicine” interchangeably. However, “precision medicine” has taken hold with more PubMed and Google search engine queries, as depicted in Figure 1[2].

The NRC committee chose the new term, “precision medicine,” because they felt it more accurately described the mission of the field: to base treatments on patients’ “genetic, biomarker, phenotypic, or psychosocial characteristics”[3]. These characteristics would provide insights to enable novel, more efficacious therapies that could leverage this data, thus increasing the success rate or “precision” of a patient’s treatment regimen[3]. Though it will take decades of data collection to shift healthcare away from treating based on “signs and symptoms” to treating based on disease predispositions, the industry has already developed gene, cell, and biomarker-based therapies in the nearly two decades since the Human Genome Project’s completion. The actualization of these therapies has brought about challenges such as commercial and payment issues to ethical and social concerns. To narrow the breadth of precision medicine, this review will provide a market overview of gene therapy and an

assessment of the challenges of delivering these groundbreaking therapies to the public. The development of new gene therapies promises to usher in a new era of targeted, "precise" treatment options.

II. Market Overview

Early Movers

The term "gene therapy" made its first debut in media and news outlets following the approval of the first drug of this kind, Glybera, by the European Medicines Agency (EMA) in October 2012[4]. This therapy was developed at the University of British Columbia and acquired by a Dutch company known as Amsterdam Molecular Therapeutics, now UniQure, to treat lipoprotein lipase deficiency (LPLD)[5]. In brief, LPLD causes high blood lipid levels, persistent abdominal pain, and a high risk of acute pancreatitis[4,6]. As a rare condition, affecting approximately one in one million individuals worldwide, the development of an appropriate clinical trial process posed a unique challenge to the concerned regulatory authorities[6,7]. Ultimately, the clinical trials concluded with 31 patient participants and precipitated an accelerated regulatory process[4]. Despite the excitement and interest surrounding Glybera's approval, the drug was withdrawn from the European market in 2015[4,6]. In general, the failure of Glybera was largely attributed to its steep price of $1.2 million and the lack of suitable reimbursement mechanisms[4–6]. Critics of Glybera also pointed out that its efficacy, as determined by a reduction in pancreatic disease, was remarkably low given the cost[6]. Furthermore, LPLD patients had access to alternative treatments with similarly beneficial outcomes and without gene therapy's significant risks[6]. By the time Glybera was withdrawn from the market, only one patient had received the treatment commercially, a clear indication that Glybera had little to offer in the way of value to patient's treatment options[4,8].

Similarly, in May 2016, Strimvelis was also approved by the EMA as a treatment for adenosine deaminase deficiency–severe combined immunodeficiency (ADA-SCID)[9,10]. ADA-SCID is a heritable disease that severely impairs a patient's ability to fight infectious diseases,

often crassly referred to as “bubble boy disease”[9,11]. ADA-SCID is also an extremely rare disease with an incidence rate of one in one million newborns worldwide[9,11]. As with Glybera, Strimvelis is expensive with a cost of nearly $700,000[9]. In addition, logistical obstacles are a significant barrier to entry as the therapy relies on *ex vivo* modification of patient cells via an adeno-associated virus (AAV)[9,12]. Strimvelis was originally developed and marketed by GlaxoSmithKline (GSK), but just over a year later, GSK sold Strimvelis to Orchard Therapeutics for an undisclosed sum[9]. Strimvelis is still being marketed in Europe by the Italian pharmaceutical company Chiesi Farmaceutici[9]. It can only be administered at a single clinic located in Milan, Italy, a reality that dramatically limits patient access[9]. In addition to access challenges, the nature of autologous *ex vivo* gene modification also elicits a six-hour window among cell harvest, modification, and re-implantation[9,12,13]. This narrow window has further complicated quality control of treatments and standardization among patients[9,12,13]. Even with these limitations, the demand for Strimvelis has remained consistent due to the unmet need it addresses[9]. Prior treatments for ADA-SCID relied on the transplantation of donor stem cells from either a family member or anonymous donor[9]. In some situations there is no appropriate donor for the individual, in which Strimvelis is the only “curative” treatment[9]. Though Orchard Therapeutics has continued to market Strimvelis for the treatment of ADA-SCID, the company is working to develop a treatment with equal efficacy and improved quality and availability[9].

These two early gene therapies serve as important case studies to guide future success in the development of precision medicines. There are several key takeaways from the development, approval, and marketing of these therapies. Both Glybera and Strimvelis represent important milestones in the real-world application of molecular biotechnology. These sophisticated therapies provided a groundbreaking level of disease specificity. Not surprisingly, the novelty of these therapies, as well as their small patient populations, also resulted in new regulatory pathways and considerations[7]. For Glybera, however, the excitement surrounding the therapy was not enough to propel it into commercial success[4,6]. Ultimately, the combination of

its relatively low efficacy with its unprecedented price resulted in low demand[4,6]. In contrast, despite its high price, low availability, and low quality control, Strimvelis is still in use[9]. As demonstrated in the gene and cell therapy market, value is king, a point further discussed in this review[14]. These case studies demonstrate that there is simply no demand for advanced treatment options that provide incremental improvements and carry astronomically high price tags.

Major Players

Upon initial gene therapies overcoming early regulatory hurdles, the market began to shift. Starting around 2016, large pharmaceutical companies began to partner with smaller, less mature biotechnology companies to expand into the gene and cell therapy space[10,13,15,16]. For example, in August 2016, Pfizer acquired Bamboo Therapeutics, a small biotechnology company with a phase I gene therapy[15,17]. At the time, Bamboo was in the startup phase, recently spun out of the University of North Carolina at Chapel Hill[15,17]. Regardless, Pfizer acquired Bamboo for a sum of approximately $700 million to expand their portfolio into gene therapy[15,17].

Similarly, just one year later in August 2017, Gilead Sciences acquired Kite Pharma, a company best known for their chimeric antigen receptor therapy which utilizes a patient's own T-cells to target cancers[15,18]. This therapy, commonly referred to as CAR-T, was the primary driver in a deal worth approximately $12 billion[15,18]. At the time, Kite was in phase I/II clinical trials for its lead product Yescarta, treating an aggressive form of refractory B-cell lymphoma[15,18]. As with Pfizer's acquisition of Bamboo, Gilead acquired Kite early in the product development life cycle relative to traditional drugs and biologics[13,15,18]. In the years to follow, these early deals would mark a significant shift in the pharmaceutical industry, with cell and gene therapies witnessing an earlier adoption rate than monoclonal antibodies, as depicted in Figure 2[19,20]. Given the relatively early entry of two of the largest big pharma players into gene therapy, the genesis of a new sector of the pharmaceutical industry would not go unnoticed.

Perhaps the most categorical shift toward the adoption of gene and cell therapy occurred between 2018 and 2019. Amongst these deals was the acquisition of AveXis by Novartis for $8.7 billion and the acquisition of Spark Therapeutics by Roche for $4.8 billion[17,19]. Beyond these high-profile acquisitions, the remaining deals listed in Figure 3 are more accurately described as partnerships or alliances[21,22]. In a recent Nature Research feature, Pfizer, one of the earliest pharmaceutical companies, described its shift toward a corporate strategy that embraces a collaborative approach to the discovery and development of gene and cell therapies[16]. It is unclear if the emphasis on mutually-beneficial partnerships is purely altruistic in nature or if early-stage partnerships are simply a strategy to de-risk otherwise questionable deals. Regardless of the broader motivations, even the biggest players in the pharmaceutical industry are displaying a willingness to share the benefits of precision medicine.

Current Status

The transformation of healthcare from one-size-fits-all, trial-and-error medicine to precision medicine utilizing patient molecular data continues to accelerate as the FDA more regularly and rapidly approves diagnostic tools and treatments. As a result, the frontiers of precision medicine are expanding as the global precision medicine diagnostics and therapeutics market is expected to reach $85.5 billion by 2025 at a 9.9% CAGR[23]. The number of precision medicines has also steadily increased since 2008, as depicted in Figure 4[24].

In 2019, 11 new precision medicines were approved by the FDA. Today, precision medicines account for over 25% of all approvals throughout the past six years[23]. This demonstrates a sharp increase since 2005, when precision medicines accounted for 5% of all approvals[23]. In 2019, the agency also expanded indications for several existing precision therapies and approved a new gene therapy for the treatment of a rare disease[23]. These new technologies will help physicians develop safer and more efficacious treatment regimens[23].

In 2019, the FDA's Center for Drug Evaluation and Research approved 48 new molecular entities (NMEs), all but four being therapeutic products[23]. Of the 44 therapeutic

NMEs, 25% are precision medicines as classified by the Personalized Medicine Coalition (PMC)[23]. These approvals continue a trend from 2014 in which the PMC classified 21% of NMEs as precision medicines[23]. The trend accelerated in 2015, 2016, 2017, and 2018, as the PMC classified 28%, 27%, 34%, and 42% of NMEs as precision medicines, respectively, as depicted in Figure 5[23]. The newly approved therapeutic NMEs include treatments for multiple sclerosis, urothelial carcinoma, breast cancer, narcolepsy, multidrug-resistant tuberculosis, non-small cell lung cancer, cystic fibrosis, acute hepatic porphyria, sickle cell disease, Duchenne muscular dystrophy, and spinal muscular atrophy[23]. Gene therapies, which have made tremendous strides during the past few years, are now emerging as a more practical approach to treating disease.

The gene therapy market was $393.35 million in 2018 and is estimated to reach $6.2 billion by 2026 with a CAGR of 34.8%[25]. This growth can be attributed to increases in research funding, government initiatives, and cancer prevalence rates[25]. However, significant costs and immune response challenges are expected to hamper the growth of the market. This was also noted in an interview with Mathew Sweede, Director of Business Development at Locus Biosciences[26]. He believes cost is gene therapy's largest challenge, as payers experience substantial hurdles in the reimbursement of such novel therapies[26]. Despite the costs, Mr. Sweede also noted that the efficacy and reliability of these products are still in question[26]. Therefore, payers are hesitant to reimburse in such an uncertain ecosystem[26]. Lastly, he also highlighted the challenge of many companies using the same technologies to target the same indications with small patient populations[26].

In 2018, most gene therapy market revenue was accounted for by North America[25]. This trend is expected to continue due to increases in cancer prevalence rates, disposable income levels, and research budgets[25]. The Asia-Pacific region, however, is expected to witness the highest CAGR during the forecast period due to increases in cancer prevalence rates, healthcare infrastructure initiatives, and healthcare expenditures[25].

As the US strives to continue its dominance of the gene therapy market, it has three FDA-approved gene therapy products on the market: Zolgensma, Luxturna, and Imlygic. Zolgensma was developed by AveXis, a subsidiary of Novartis, to treat pediatric patients less than two-years-old with spinal muscular atrophy[27]. It was approved on May 24, 2019 and costs $2.1 million, with insurers paying $425,000 per year for five years[28]. Luxturna was developed by Spark Therapeutics and approved on December 18, 2017 as the first gene therapy for a disease caused by specific gene mutations[29]. In specific, Luxturna treats pediatrics and adults with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. The treatment costs $850,000 total or $425,000 per eye[30]. Imlygic was developed by Amgen to treat unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery[31]. It was approved on October 27, 2015 and costs $65,000[32].

The gene therapy market has evolved since the first product, Glybera, was approved in 2012. Glybera ultimately failed, and it was not until 2016 that the market began to shift. Large pharmaceutical companies began to partner with smaller companies, creating a sizable market with a healthy projected growth rate into the next decade. Although there are several gene therapy products on the market, commercialization of these products continues to face challenges such as manufacturing limitations and regulatory hurdles.

III. Commercialization Considerations

Manufacturing Challenges

Large-scale production of gene and cell therapies poses a number of challenges within the current manufacturing network[21,22]. During the latter half of the twentieth century, the pharmaceutical industry began to shift away from small molecule drug production, which largely relied on large-volume organic chemistry reactions[19,21]. With the advent of monoclonal antibody therapies and other biologics, drug manufacturing grew to also include cellular biology techniques[19,21]. Moving away from chemical distillations and precipitations, manufacturing plants began to introduce cell expression systems and bioreactors[19,21]. The genesis of these next-

generation gene and cell therapies has created another paradigm shift[21,22]. The sophistication and novelty of these new therapies have meant that new considerations and optimizations must be taken into account for large-scale production to be possible[21,22].

Brammer Bio is a viral vector contract development and manufacturing organization (CDMO). Thermo Fisher Scientific acquired Brammer Bio for $1.7 billion in 2019 to expand its own CDMO capabilities[33]. Patrick Robertson, Ph.D., is Head of Technical Sales at Brammer Bio and provided extensive insights into gene therapy manufacturing[21].

According to Dr. Robertson, much of the difficulty associated with the production of gene therapies stems from the use of suboptimal equipment and materials originally designed for production of biologics[21]. Senior scientist from the NC State University Biomanufacturing Training and Education Center, Laurie Overton, expanded on this challenge, noting that the large-scale production of a viral vector can be an insurmountable hurdle for some companies[34]. Dr. Robertson mentioned that a $1 million monoclonal antibody run could produce enough product to treat thousands of patients, while a single $1 million gene therapy run would likely only produce enough product to treat a single patient[21]. In addition to the inefficiency of these platforms, many necessary molecular biology techniques have been developed for bench-scale rather than commercial-scale production[9,21,22,34]. Dr. Roberston specifically mentioned that transient transfection, one of the most popular techniques employed in gene therapy development, has not been scaled beyond 200 liters[9,21,22]. Scale-up is also a challenge for autologous *ex vivo* therapies like Strimvelis which rely on small cell populations and bench-scale molecular techniques[9,21,22]. Even materials required for production, such as buffers, media, and single-use equipment, are challenging to source given the increased demand from organizations like Brammer Bio[9,21,22]. CRISPR expert Dr. Rodolphe Barrangou explained that gene editing technologies, such as CRISPR, may provide a more scalable and affordable solution for future gene therapies[35]. However, these new technologies bring additional challenges, such as off-target editing, that must be overcome.

With the expanded interest in gene and cell therapy platforms, large pharmaceutical companies have begun to invest in proper development platforms[21]. According to Dr. Robertson, many companies are adopting a two-pronged approach by both building more capacity and improving production efficiency[21]. For example, companies like Pfizer, Aventis, bluebird bio, Cellectis, and AveXis are adapting to this trend by expanding their gene therapy footprints[10,19,21]. Despite the current inefficiencies and challenges of gene therapy manufacturing, the pharmaceutical industry is likely to continue investing in these technologies.

Regulatory Considerations

As all novel therapies, including precision and gene therapies, must undergo regulatory approval, it is crucial to understand the regulatory history and landscape. As most gene therapy and precision medicine market share is held by companies from the United States, this section will focus on gene therapy regulation by the FDA.

In response to the surge of recombinant DNA technologies in the late twentieth century, the US National Institutes of Health (NIH) sponsored the creation of the Recombinant DNA Advisory Committee (RAC) in 1974[16]. This committee's goal was to educate and advise NIH leadership on upcoming gene editing research. However, as gene therapy in humans became more feasible over time, the RAC began assisting the FDA in the review of gene therapy protocols[16]. Although the RAC is not a regulatory body, the origin of the RAC serves as a landmark event in the internal regulation of the scientific community.

After decades of pre-clinical gene therapy research, largely guided by the NIH's RAC, the FDA reviewed the first gene therapy clinical trial in 1990 in Bethesda, Maryland at the NIH Clinical Center[16]. This trial sought to investigate the efficacy of a gene therapy for ADA-SCID with two young girl participants[16]. At the conclusion of the study, investigators stated "the results of the study are very gratifying and will help to forward the field of gene therapy"[36]. In 1991, as this nearly five-year clinical trial was underway, the FDA published its first regulatory guidance document: *Points to Consider in Human Somatic Cell Therapy and Gene Therapy*[37]. This

guidance provided the first regulatory considerations for gene therapy quality and manufacturing[37]. At this time, both the NIH's RAC and FDA held responsibilities in approving human gene therapy clinical protocols[37]. However, in 1997, the FDA became the sole agency with the authority to review and approve protocols[16]. This event further established boundaries between scientific research guidelines and federal regulatory guidelines.

Although there was much gene therapy regulation reform in the 1990s, the decade also elicited significant concerns regarding the safety of human gene therapies. In 1999, eighteen-year-old Jesse Gelsinger participated in a phase I safety trial for an ornithine transcarbamylase deficiency gene therapy[16]. The trial's goal was to develop a treatment for infants with the deficiency, though Gelsinger qualified as he had a milder form of the deficiency[16]. Unfortunately, Gelsinger passed away due to a severe immune response and became the first patient to die in a gene therapy clinical trial[16]. Although devastating, this event marks a major turning point in the re-evaluation of both the safety and efficacy of human gene therapies[16]. The next year, the FDA implemented strategies to better protect its clinical trial participants[16]. After decades of research and development, the first gene therapies were approved by the FDA in 2017[16]. These approvals provided the initial regulatory framework for future gene therapy technologies.

Since 2017, many gene therapy regulatory applications have leveraged existing accelerated approval tactics, such as orphan designation and several expedited development programs[38]. The expedited development programs include fast track, priority review, accelerated approval, breakthrough therapy, and regenerative medicine advanced therapy programs[38]. These programs have their individual nuances, although they all were established as incentives to develop innovative therapies addressing significant unmet needs[38]. Companies engage with the FDA before and throughout these pathways to identify and mitigate potential risks as early as possible[7]. Not only do these programs support pharmaceutical companies in being first to market, but they also support the therapies in reaching patients sooner in their disease progression.

In addition to approving novel gene therapies, the FDA releases specific regulatory guidance documents to support product launches[39]. The FDA has published gene therapy guidances since 1998, although most content has been published since 2013[39]. Most were first published by therapeutic class, such as retinal disorders and rare diseases[7]. However, as the industry continued to research, develop, and scale-up gene therapies, the guidances evolved to outline topics ranging from manufacturing challenges to patient interaction[7].

Together, pharmaceutical companies and regulatory agencies have made significant strides toward the development and approval of gene therapies. However, there is much room for improvement and optimization to ensure that each patient receives a safe, efficacious, and high-quality gene therapy.

Commercialization Practices

Gene therapy development has surged over the past five years, but the life sciences commercial sector is still facing challenges[23]. Due to the high costs of gene therapies, payer organizations and healthcare organizations are struggling to develop payment and reimbursement structures[23]. This was echoed by Dr. Edward Abrahams, President of the PMC, when he said that "all of the stakeholders, no matter who they are, need to come together to create a shared value whereby patients will receive better products and society will benefit[23]." The PMC also issued a report in 2018 entitled *Personalized Medicine at FDA: A Progress & Outlook Report* which outlines the need for policymakers to develop legislation that favors precision medicine and gene therapy[23]. Many precision and gene therapy reimbursement structures require that patients first try traditional therapies and later try precision therapies, a process known as "step therapy" by insurers or "fail first" by critics[23]. The report also emphasizes the urgency of precision medicines. For example, in the time a patient must first use a less expensive, one-size-fits-all therapy, the disease may have progressed so far that the personalized therapy can no longer treat the disease[24].

Payment structures are also significant hurdles in the commercialization of precision and gene therapies. The average health plan, pharmacy benefit manager, or pharmaceutical manufacturer traditionally focuses on short-term goals and endpoints[23]. However, as the industry moves toward a value-based model, long-term goals and endpoints become more important[23]. Alternative payment models, such as pay-for-performance, are likely to become common for precision and gene therapies[23]. At a Senate Finance Committee hearing in February 2019, pharmaceutical companies testified their willingness to enter outcome-based agreements with payers[40]. Ultimately, reimbursement must be proportionate with value to realize the full benefits of precision medicine[23]. Andrew Harmon, finance and bioscience management MBA candidate and previous Pfizer gene therapy employee, mentioned that there is currently no insurance model that fits all gene and cell therapy costs[41]. To elaborate, Harmon described a scenario in which an insurance company offers long-term payments for gene therapies[41]. In the event a patient switches insurance providers, it is unclear which provider would be responsible for payments[41]. Major insurance questions remain unanswered though gene therapies continue to be approved.

Value assessment frameworks (VAFs) have emerged as tools for supporting data-driven decisions in healthcare[23]. VAFs quantify the costs and benefits of precision therapies, influencing payer coverage and reimbursement decisions[23]. These frameworks have the potential to encourage the use of precision and gene therapies, though they are also criticized for failing to account for the heterogeneity of treatment outcomes[23]. For example, the Institute for Clinical and Economic Review's value framework describes conceptual methods to guide the development of precision medicine[14]. Dr. Abrahams and others criticized this framework, as "it does not incorporate how different patients are impacted by the therapy but rather is based on population averages"[23]. Further, patient advocacy groups also negatively responded to the framework. The Multiple Myeloma Research Foundation publicly criticized the framework as "the promise of precision medicine is that each patient is unique and will consequently respond

to treatment differently based on their particular genetic profile"[42]. Therefore, all stakeholders must engage to bring precision and gene therapies to market.

IV. Concluding Remarks

The promise of a more targeted medical future in which billions of dollars from ineffective therapies could be saved has many optimistic and eager to stake their claim in the precision medicine market. However, early movers, such as Amsterdam Molecular Therapeutics and GSK, ended up serving as guinea pigs in this space. The US opted to incentivize and reassure pharmaceutical companies with the launch of the Precision Medicine Initiative by the Obama administration in 2015[43]. This proved to be the confidence boost that big pharma needed to begin acquiring smaller biotechnology companies with promising precision and gene therapies. Although there are three gene therapy approvals in the US so far, there are still many unanswered questions to address.

Despite several approvals, future consequences of gene therapies are still uncertain. What are the long-term safety effects for these therapies[7,44]? What if the "fixed" genes are down-regulated over time? Might a previous AAV infection impact the delivery success[7]? How can physicians safely pre-screen for negative immune responses[7]? Trials for these therapies also require standardization of data collection, storage, and governance activities to protect patient data[43]. How do investigators appropriately compensate these patients in trials and ensure informed consent[43]? It remains to be seen how the FDA will handle nearly one thousand gene therapy applications per year by 2021[7]. Further, development of a gene therapy is extremely expensive due to manufacturing challenges. With such high economic risks, how will companies overcome these costs following application denials or trial failures[43,41]? Payment plans are still in development as current plans are not conducive to this new field of medicine[43]. Precision medicine is in its infancy and requires a high demand of genetic and biochemical data from pharmaceutical companies, healthcare providers, and payer organizations. Programs such as the NIH's "All of Us" campaign work to gather genomic data on millions of Americans,

requiring robust bioinformatics and machine learning tools. Lastly, as these therapies remain on the market, the FDA will need to control for manufacturing changes and process improvements as science advances[7].

It remains to be seen how the public will accept these new therapies, especially in a time in which the pharmaceutical industry has an extremely bad reputation. There is a fear of scientists “playing God” and enabling eugenics and socioeconomic discrimination[26,41]. The path to precision medicine is underway yet demands further efforts to pave the way for an entirely new way of thinking about health. Public education will continue to be a critical part of this process. Terms such as “precision health” and “genomics wellness” have been proposed to capture this new way of learning how traits may impact human health and well-being[44]. The industry has just begun to explore the possibilities of precision medicine.

V. Figures

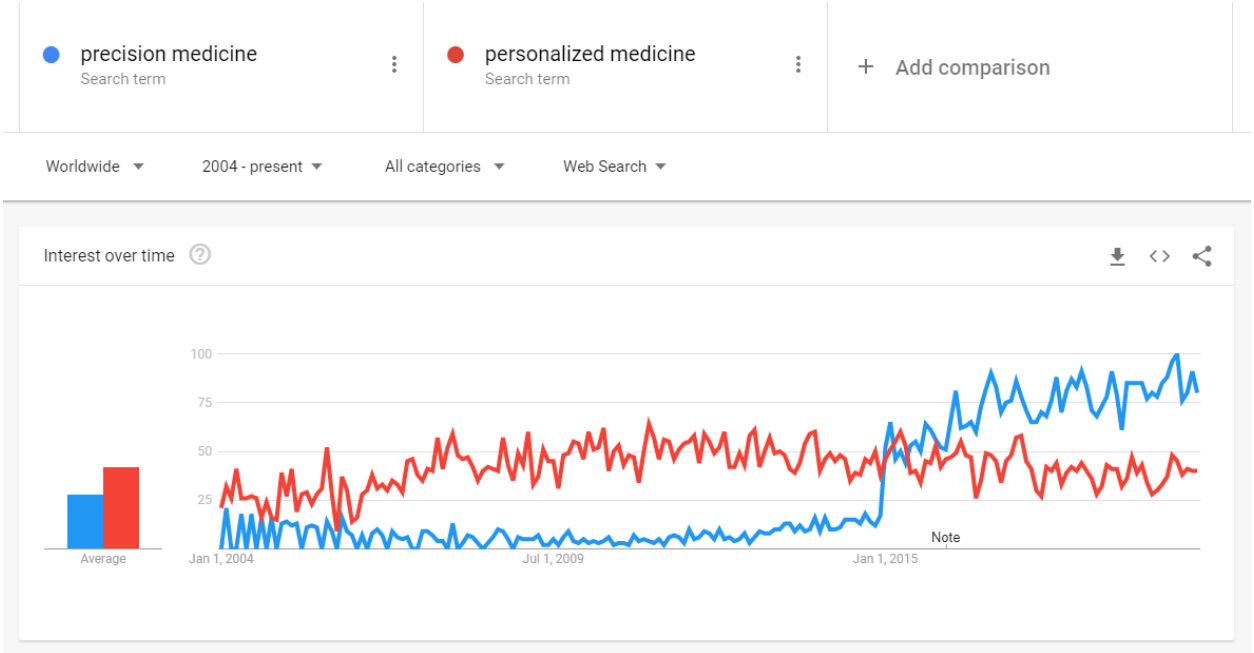

Figure 1. Schematic from Google Trends which reports the average searches of terms "precision medicine" versus "personalized medicine" from 2004 to present-day. "Precision medicine" is shown in blue, and "personalized medicine" is shown in red. Google Trends was launched in 2004, which explains the data collection timeline. A clear shift, with "precision medicine" overtaking "personalized medicine," is shown in early 2015.

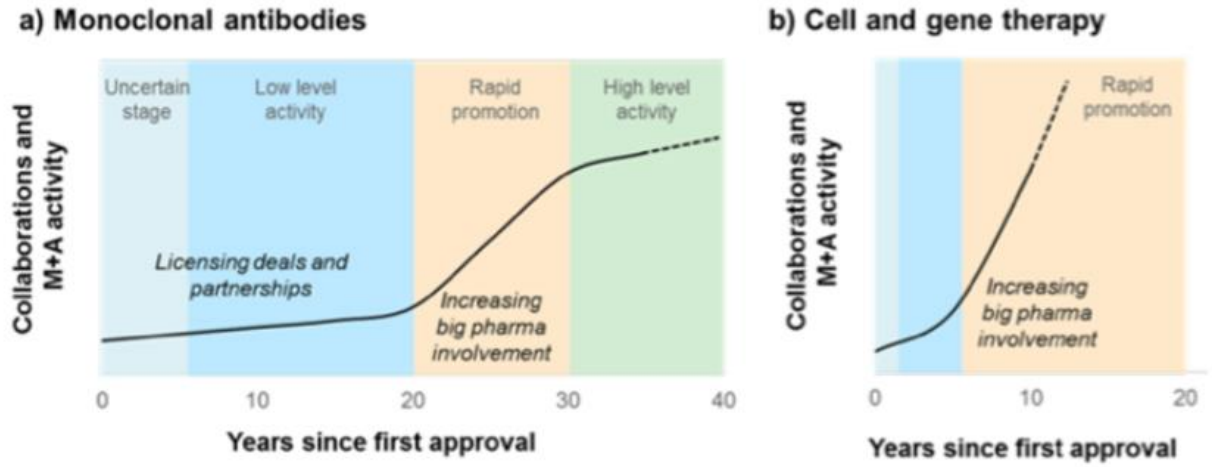

Figure 2. Graph depicting the pharmaceutical industry's rapid adoption of cell and gene therapies in present-day compared to monoclonal antibodies in the 1980s and 1990s.

Select cell and gene therapy deals since 2018

Buyer (ticker)	Target (ticker)	Target therapeutic areas	Announcement Date	Deal value ($B)
Gene therapy deals				
Novartis AG (NOVN)	AveXis Inc.	Neuromuscular	04/09/18	8.65
PTC Therapeutics Inc. (PTCT)	Agilis Biotherapeutics LLC	Central nervous system	07/19/18	0.95
Astellas Pharma Inc. (4503)	Quethera Ltd.	Ophthalmology	08/10/18	0.11
Roche Holdings AG (ROG)	Spark Therapeutics Inc. (ONCE)	Ophthalmology, hematology, metabolic, central nervous system	02/25/19	4.76
Biogen Inc. (BIIB)	Nightstar Therapeutics PLC (NITE)	Ophthalmology	03/04/19	0.88

Figure 3. Selected gene and cell therapy partnerships occurring in 2018 and 2019.

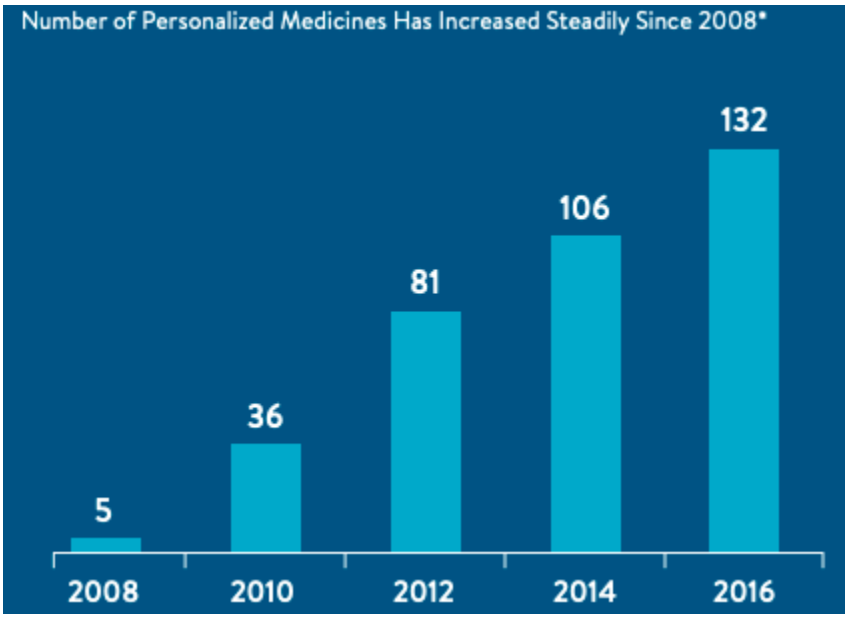

Figure 4. Personalized Medicine Coalition graph depicting the increase in personalized therapies since 2008.

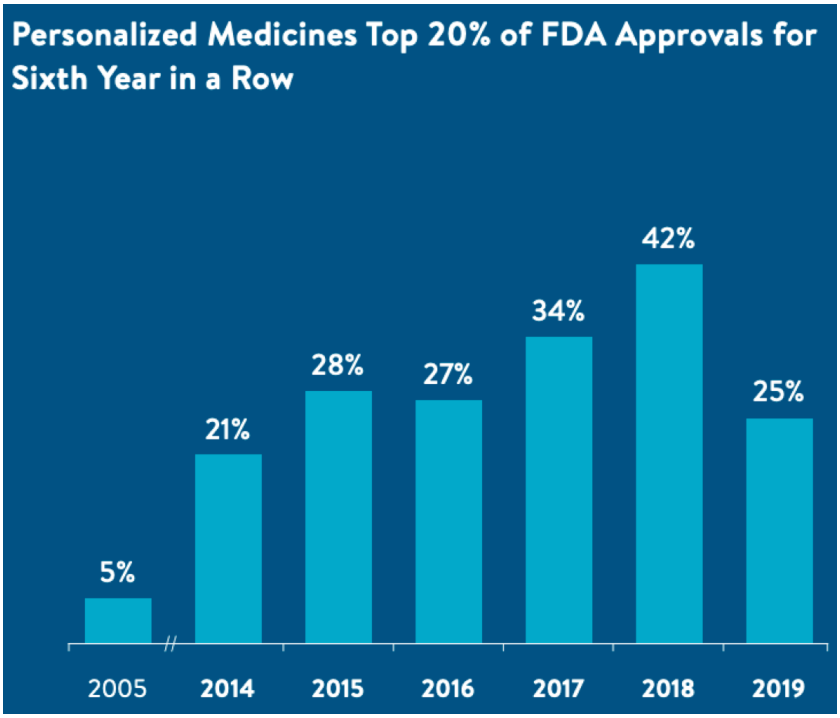

Figure 5: Personalized Medicine Coalition graph depicting the increase in new molecular entities classified as personalized medicines.

VI. Professional Interviews

Name	Title	Organization
Rodolphe Barrangou, Ph.D.	Professor, Principal Investigator, CRISPR Subject Matter Expert	NC State University
Andrew Harmon, MMB	Finance and Bioscience Management MBA candidate	NC State University, Pfizer (previously)
Laurie Overton, M.S.	Senior Scientist	NC State University Biomanufacturing Training and Education Center
Patrick Robertson, Ph.D.	Head of Technical Sales	Brammer Bio by Thermo Fisher Scientific
Matthew Sweede, M.S.	Director of Business Development	Locus Biosciences

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