

# “It Starts With One”: Reflections on BIO 2019

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This year’s Biotechnology Innovation Organization (BIO) meeting, held in Philadelphia from June 3 to June 6, had an impressive turnout of 17,307 attendees and 1,800 exhibitors. We review two sessions on the outlook for value-based payment for transformative therapies and what’s in store for future immunotherapies, and two poster presentations on the cost-effectiveness of multi-gene sequencing for patients with advanced non-small-cell lung cancer or advanced melanoma.

The 2019 annual meeting of the Biotechnology Innovation Organization (BIO) was portentously preceded by the Food and Drug Administration’s (FDA’s) approval one week earlier of the costliest drug ever invented—Zolgensma (onasemnogene abeparvovec-xioi), the new gene therapy for spinal muscular atrophy (SMA).

Several themes appeared throughout the meeting: how can payers and manufacturers agree on reimbursement for such important but expensive drugs; how can we know beforehand what long-term benefits patients will receive; and what does the future of oncology hold for patients, providers, and payers?

Insurers wouldn’t necessarily complain so much about a single-administration drug that cures a disease related to muscular atrophy, but with only four years of follow-up data, there is uncertainty about the long-term effects of the treatment. If it turns out that it doesn’t work, insurers would like to be able to ask for a refund. They would also like to spread the payment out over time (five years, perhaps).

## The Path Forward for Value-Based Payment for Transformative Therapies

- Marianne Hamilton Lopez, PhD, MPA, Research Director at the Duke–Margolis Center for Health Policy, in Washington, D.C; Steve Miller, MD, Chief Medical Officer at Express Scripts in St. Louis, Missouri; and Michael Sherman, MD, MBA, Chief Medical Officer and Senior Vice President, at Harvard Pilgrim Health Care in Boston, Massachusetts

Value-based payment (VBP) arrangements, which align payments with their observed value and outcome in a particular population, can be critical for improving patient outcomes and lowering overall healthcare costs. The method offers a unique approach to financing the curative or transformative therapies that are highly effective but that might impose considerable costs and uncertainties on the U.S. healthcare system.

“The most common way to handle outcomes-based contracting is by using rebates, but they don’t tend to be too big, because of Medicaid best-price concerns and challenges,” said Gregory Daniels, PhD, MPH, director of the Duke–Margolis Center for Health Policy in Washington, D.C., and moderator of one of the first sessions addressing reimbursement.

The chief obstacle is the Medicaid “best price” rule, which can be considered like the “most-favored nation” clause in a contract. In essence, manufacturers worry that if they agree to rebates for cases in which a costly new drug doesn’t perform as well as predicted, the Centers for Medicare & Medicaid Services (CMS) would demand the same price for all Medicaid patients (including those for whom the drug worked).

The rule also causes problems with installment payments: Medicaid does allow drug prices to be revised, but only over the course of three years. A four-year agreement, with a potential 20% down payment in the first year and 20% payment each year following, would be preferable for some. That agreement would follow patients if they were to change insurers, according to Dr. Michael Sherman. “There are also questions about outcome measures. We agreed we could talk about those without violating antitrust considerations. We’re not supposed to agree as a cohort, who we’ll cover it for,” he added.

## An Existential Dilemma for Plans?

Zolgensma, which is manufactured by Avexis, isn’t the only expensive new drug; its chief competitor Spinraza (nusinersen; Biogen) isn’t cheap, either—\$750,000 for the initial year and \$375,000 every year thereafter for the life of the patient, according to the Institute for Clinical and Economic Review (ICER). There is also Spark Therapeutics’ Luxturna (voretigene neparovic-rzyl), which treats a rare form of blindness, with an average wholesale price (AWP) of \$520,000 per treatment, and Kymriah (tisagenlecleucel) by Novartis Pharmaceuticals, for relapsed or refractory lymphoma, whose AWP is \$447,600.

The Massachusetts Institute of Technology’s New Drug Development Paradigms (NEWDIGS) program predicts the approval of a seemingly modest 40 to 60 new cell and gene therapies by 2030.

But Zolgensma could spell trouble for a smaller-sized insurance company if it were randomly hit with three potential claims in a given quarter. Spinal muscular atrophy is a comparatively rare disease that affects one in 10,000 children; however, “a small- to medium-sized health plan might make \$5 million in profit per quarter. If [treatment for] three babies cost \$4 million, that could wipe out the entire profit for that quarter,” said Mark Trusheim, MSc, strategic director at NEWDIGS.

One solution to address these financial challenges could be to set up “Orphan Reinsurer Benefit Managers,” of which Trusheim is an advocate.

Reports have been produced by ICER on Zolgensma and Spinraza, as well as Kymriah, Keytruda, and Luxturna. (The term ICER, which stands for incremental cost-effectiveness ratio, was popularized in a 1977 article in the *New England Journal of Medicine*; the unrelated organization was founded in 2006, according to Sachin Kamal-Bahl, PhD, a consultant and former Pfizer researcher).

Regarding Zolgensma and Kymriah, ICER’s value assessment was higher than the price point ICER had determined itself, which led the organization to say that the drugs were priced

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appropriately. But the cost–benefit discussion might be leaving out important aspects of value, Sachin added.

“What if you save a person for five years, and a gene therapy comes along; do we really want to [assign a] value [to] that? There’s the options value [and] ... the value of hope in oncology. If you tell somebody they have only a 15% chance of survival, they might still roll the dice,” he explained.

### Immuno-Oncology: Taking Immunotherapies to The Next Level

- Jennifer Buell, PhD, Chief Operating Officer at Agenus in Lexington, Massachusetts; Asthika Goonewardene, Senior Biotechnology Analyst at Bloomberg Intelligence; Bibhash Mukhopadhyay, PhD, Principal, New Enterprise Associates, in Chevy Chase, Maryland; Drew Pardoll, MD, Abeloff Professor of Oncology, Medicine, Pathology and Molecular Biology and Genetics at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland; Helen Sabzevari, MD, PhD, President of Precigen in Germantown, Maryland; and Emmett Schmidt, MD, PhD, Associate Vice President at Merck & Co. in North Wales, Pennsylvania

Recent breakthroughs in cancer immunotherapies have increased researchers’ understanding of the mechanisms and pathways that regulate how the immune system responds to cancer. But the leading agents, the checkpoint inhibitors (CPIs), which have had dramatic effects in certain cancers and patients, have shown only modest clinical benefit in other settings. Thus, there is a clear need for additional therapies, particularly ones that can be used in combination with CPIs to reverse innate or acquired resistance, for example.

The unavoidable controversy that surrounds the cost of treatment exerts a winnowing influence on cancer research, and it made the question of how quickly the effort to cure cancer is proceeding a hotly debated subtext at the BIO 2019 sessions.

“Everything else is being studied in combination with PD-1 inhibitors; Keytruda is getting close to being the silver bullet,” said Dr. Emmett Schmidt, during his presentation.

Other speakers at the session included investors who compared the effort to predict which therapies under development will ultimately have clinical efficacy to forecasting which way the wind blows, or “trying to read the spaghetti on the wall.”

Merck’s Keytruda (pembrolizumab) was the first tissue-agnostic therapy ever approved by the FDA, said Dr. Schmidt. (The second was Vitravki [larotrectinib], by Bayer and Loxo Oncology, which was approved late last year). He continued: “The hypothesis is that if you combine anything which shrinks the tumor with something else that shrinks the tumor, it will shrink the tumor even more. But if you hit the target, and the tumor isn’t smaller, you should stop. And nobody is [stopping].”

Dr. Schmidt is also the author of an article in the January 2019 issue of *Seminars in Immunopathology*, entitled “Developing Combination Strategies Using PD-1 Checkpoint Inhibitors to Treat Cancer.” He concluded that combining PD-1 inhibitors like Keytruda with standard-of-care chemotherapy and anti-angiogenesis inhibitors reveals some synergy, whereas combining PD-1 inhibitors with CTLA4 inhibitors does not.

Some providers are combining Keytruda, which is injected every week, with Kymriah, which uses genetically engineered

T cells and is classified as a chimeric antigen receptor (CAR) T-cell therapy.

According to Dr. Helen Sabzevari, most of therapy’s cost is a result of the manufacturing process. Precigen, of which Dr. Sabzevari is president, has three CAR T-like agents in phase 1 trials and is working on a way to lower costs by reducing manufacturing time and complexity.

Dr. Drew Pardoll spoke about an early, successful case he had worked on while treating patients with colon cancer. One patient had a complete response to treatment and seven years later was still in complete remission. “If you’re in the 4% of patients who respond, we may cure 50%,” said Dr. Pardoll. But if providers never do genetic testing for Lynch syndrome, for example, “that’s going to throw a lot of babies out with the bathwater,” he added.

### The Seamless Web of Genetic Medicine?

Several speakers at BIO noted that cures for hard-to-treat cancer cases may already exist and that oncologists should provide more comprehensive genetic screening, and highlighted the value of genetic screening in non–small-cell lung cancer (NSCLC) as an example. Other presenters also discussed research that demonstrates the value of screening for melanoma and colorectal cancer. And a poster at the recent American Society of Clinical Oncology (ASCO) meeting made the case for whole genome screening in pediatric cancer cases.

“We’ve seen a real advance over the last four or five years; more than 25% of all new drugs were personalized medicine, and that increased to 42% in 2018,” said Daryl Pritchard, PhD, vice president for science policy at the Personalized Medicine Coalition in Washington, D.C. But this presents new challenges that have not previously been seen, he added, pointing out that next-generation sequencing for children, for example, hasn’t yet been implemented very effectively, but that this was to be expected with any new technology. “We’re continuing to build evidence of value,” he explained.

### Opportunities—and Costs—in Lung Cancer And Melanoma

Dr. Pritchard, who spoke at a session entitled, “Clinical and Economic Value of Personalized Cancer Treatment,” was also a co-author on the poster “Cost-Effectiveness of Multi-Gene Panel Sequencing for Advanced Non–Small-Cell Lung Cancer,” presented at ASCO.

The researchers conducted a retrospective analysis of patients with stage 3 or stage 4 NSCLC, using information from 2011 through 2016 from the Flatiron Health database, which includes data from more than 250 oncology practices.

Patients were grouped in the multi-gene panel sequencing cohort if they had 30 or more genes sequenced, or grouped in the single-marker gene-testing cohort if they had fewer than 30 genes sequenced. The researchers then measured the number of patients in each cohort who had received a targeted treatment, the overall survival rate for patients on targeted or non-targeted therapy, and the total direct costs of care.

Of 5,688 patients with NSCLC, 875 received multi-gene testing (21.4% of whom received targeted therapy), and 4,813 received single-gene testing (18.7% of whom received targeted medicines). Patients who received targeted therapy

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experienced an overall survival rate of 2.31 years compared with a survival rate of 1.73 years for patients who received no targeted therapy (after adjusting for smoking history, age, and other factors).

The cost per patient for the multi-panel testing was \$1,948, compared with \$467 for each patient who had fewer than 30 genes tested. Nevertheless, the multi-gene testing was cost-effective, according to Lotte Steuten, PhD, vice president at the Office of Health Economics in London. “You can only make a difference in a small percentage of patients, but the survival benefit, looking toward the future, will only increase,” explained Dr. Steuten. “Even for those patients on the newer treatments, the increased survival is, on average, three weeks longer; but some patients experience a much longer gain,” she said.

Dr. Pritchard and Dr. Steuten were also co-authors on a poster presented at the May 2019 International Society of Pharmacoeconomics and Outcomes Research (ISPOR) meeting held in New Orleans. Their study, “Cost-Effectiveness of Multi-Gene Panel Sequencing for Patients with Advanced Melanoma,” also included Flatiron Health data. The researchers looked at data from 6,622 patients with stage 3b or metastatic melanoma during the same years, 2011 to 2016. The number of patients who had received multi-gene sequencing was 596, and patients who had undertaken single-marker testing numbered 6,026. Of patients in the multi-gene group, 19% received targeted therapies for B-Raf proto-oncogene, serine/threonine kinase (BRAF), NRAS proto-oncogene, GTPase (NRAS) or KIT proto-oncogene, receptor tyrosine kinase (KIT)-driven cancer, compared with 14% of those in the single-marker group.

The median survival rate for patients who received targeted therapy or immunotherapy was 1.4 years, which was almost twice as long as the rate for patients who received chemotherapy.

The researchers found that multi-gene testing had a 55% chance of being cost-effective at a willingness-to-pay threshold of \$150,000 per life year gained.

### CONCLUSION

The good news is that cancer seems less likely to escape the surgeon’s knife, absent acquired tumor resistance. If the patient’s cancer has metastasized, all of the cells will have the same genetic mutation; and this renders them susceptible to the same targeted therapy, according to Dr. Pritchard.

However, mutations in tumors that have been treated with a targeted medicine make things more complicated.

“Acquired cell resistance is a fundamental aspect of all cancer, and it will not go away. But in a small subset of patients, a combination of drugs can cure cancer by sheer mathematical probability,” said Dr. Schmidt. ■