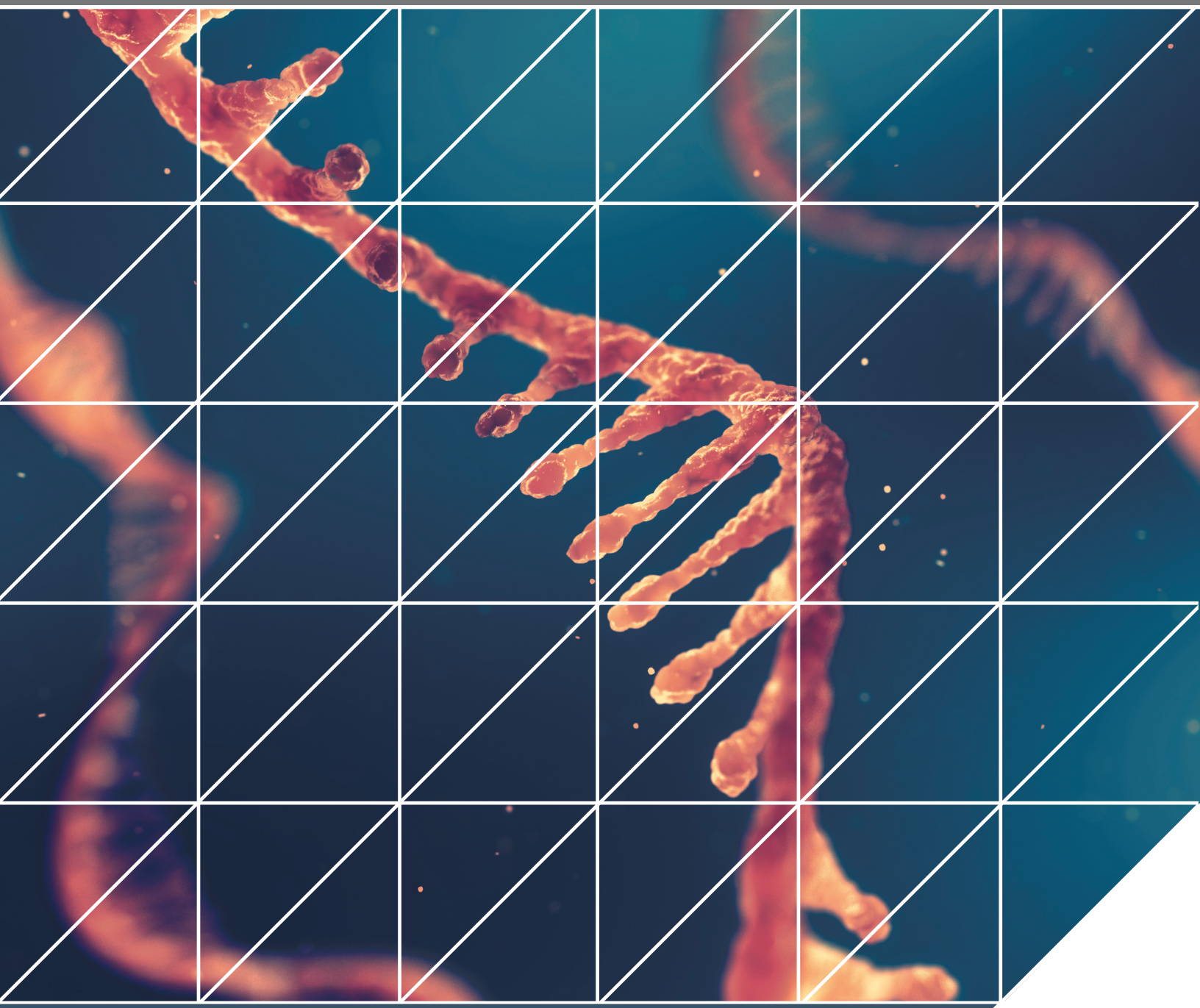

State of the Union for Advanced Medicines

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State of the Union for Advanced Medicines

The cell and gene therapy (CGTx) sector has flourished over the last 2 to 5 years due to continued investor confidence. However, the recent downturn in public markets has undermined that confidence.

This white paper is based on a panel discussion, sponsored by Precision ADVANCE, featuring insights from diverse industry perspectives on the current state of the CGTx sector; the investment landscape; scientific and technical advances; progress in drug development, manufacturing, regulatory, pricing, and reimbursement; and expected key trends in 2023 and beyond. Hosted by Endpoints News and moderated by Anshul Mangal, President of Project Farma and Precision ADVANCE, the roundtable included the following panelists:

- **Dave Greenwald**, Vice President, Business Development, Deerfield Management
- **Rajul Jain**, Managing Director, Vida Ventures
- **Joseph LaBarge**, Chief Executive Officer, Apertura Gene Therapy
- **Adrian Woolfson**, Executive Chairman, President and Co-Founder, Replay Bio
- **Phil Cyr**, Executive Vice President, Precision Value & Health

Current state of the CGTx sector in 2022

Greenwald led off the discussion by offering a bullish outlook on CGTx. Although a high unmet need remains for very serious diseases, recent approvals in the sector suggest CGTx products will "be around for a while and will have an ongoing place in medicine." He acknowledged that the pricing of Zolgensma® (onasemnogene abeparvovec-xioi) at just over $2 million generated questions about the sustainability of high-priced gene therapies, but described the situation as a "net positive," in that the availability of a one-time treatment represents an overall savings to the healthcare system, despite its high price.

Jain characterized CGTx approvals in 2022 as very helpful for investor confidence. He recalled that several "failed trial" reports in early 2022 precipitated the flight of "generalist" or non-healthcare-focused monies from the sector, impacting valuations. The recent approvals therefore "help with overall positive sentiment for the space, even if the sector as a whole is in a little bit of a tough time."

Continuing in that vein, LaBarge commented that the current economic downcycle will necessitate "a bit of cleanup" across the CGTx segment. "We'll come out stronger on the other end" with slightly fewer companies and assets, he predicted; those that remain will have a higher probability of reaching market.

> "Recent approvals in the sector suggest **CGTx products** will be around for a while."
>
> – Dave Greenwald
> Vice President,
> Deerfield Management

According to Woolfson, this is no time for complacency, even for companies with "nice runways." He offered the almost paradoxical advice of leaning into the economic downturn: "When things look really bad, maybe that's the time to raise money," he said. Nevertheless, Woolfson described himself as "pretty optimistic despite the apparent environment that we're in right now."

Meeting investors' criteria and expectations

Whereas the rising cost of capital might be a deterrence, "There is money out there for good ideas and for good teams and good technology," Greenwald opined. Echoing that position, Jain noted that investors are looking for "real innovation" even as they find it more challenging to differentiate one CGTx developer from another. Awareness of the growing size and scope of the sector, and of each company's place in it, can help companies explain and differentiate themselves to investors.

Overcoming regulatory roadblocks

Despite the pain caused by clinical holds, delays, and other regulatory hurdles, these developments are fostering "almost collegial" conversations between manufacturers and the FDA, according to Cyr. He said the aim of such "evolutionary" interactions is to assemble an evidence-based blueprint of what makes a successful cell and gene therapy, noting that some of the recent hurdles "have definitely led to innovation, and this is a journey we're all on."

Manufacturing challenges

As the gene therapy sector continues its shift from internal to external manufacturing, "all the dust needs to settle," LaBarge commented. He noted that prospective manufacturers face considerable regulatory risk, adding that gene therapy manufacturing is still "more art than science." Mitigating that risk means being mindful of the FDA's major focus: What's in the product? What's not in the product? How do you know what's in the product? LaBarge added that scalability to commercial production will become a more prominent issue as sponsors pursue bigger indications with larger patient populations.

> Gene therapy manufacturing is still
> **"more art than science"**
> – Joseph LaBarge, Chief Executive Officer, Apertura Gene Therapy

Pricing and reimbursement

Mention of bigger indications led Mangal to ask the panelists how targeting of more prevalent conditions will change the reimbursement model and evidentiary criteria to support pricing of CGTx products. Woolfson responded by specifying cost of goods (COG) as the expected rate-limiting step for human healthcare. In the short term, he said, the market may see more success-based pricing: "You pay if it works." However, that approach is not sustainable, given the number of new drugs anticipated over the next decade. Cost-effective medications, therefore, are "the only way forward." As for efforts to reduce COG, Woolfson characterized universal cells as an almost infinitely scalable approach, in that one hypoimmunogenic cell "off-the-shelf for everybody" can enable switching constructs in or out. He added that many drugs currently administered systemically will be made in the body by cells controlled via synbio circuitry. That possibility makes the monoclonal antibody category "just ripe" for disruption, which will "hugely" reduce COG. Additionally, synthesizing proteins within cells via inducible synbio switching may also help limit the costs of combination therapies.

Cyr observed that payers and governments are shifting away from cost-per-quality pricing models and are contemplating affordability and budgetary impact. That model has been adopted in Germany, where authorities will "approve the drug, approve a price, and then they'll come back [with] real-world data and renegotiate with you." At the same time, in the fragmented US system, therapy benefit managers are carving out gene therapies to sell to the next generation of pharmacy benefit managers (PBMs).

Pharmacoeconomic price justification often depends on the indication, and high-priced therapies must be viewed in the context of how much it would cost not to treat or to use a current standard of care. Greenwald remarked upon the inevitability of value-based care, or paying for treatment over time, noting that this approach underscores the need to demonstrate lasting benefit. Performance-based models will likely evolve but will need large amounts of capital to underwrite. Nevertheless, Greenwald expressed cautious optimism about pricing for CGTx products: "If you're treating serious diseases with high unmet need… there will be a market for it and a price for it."

Mangal interjected that much of the commentary surrounding CSL Behring's $3.5 million price tag for Hemgenix® (etranacogene dezaparvovec-drlb), its recently approved, 1-dose gene therapy for hemophilia B, does not mention the $17.5 million per-patient savings to the Medicare system. "That is the more eye-opening and eye-popping statistic," he said, adding that such a level of investment "makes a ton of sense" in terms of outcomes. Moreover, installment payments over time can reduce patients' up-front burden. He expressed confidence that "our system, because of the high unmet need, will figure out the solution."

> "Our system, because of high unmet need, **will figure out a solution."**
>
> – Anshul Mangal, President, Project Farma and Precision ADVANCE

Thus far, payers have been willing to pay for high-priced drugs "because they see the benefit themselves," Mangal continued. As more such drugs come to market, different types of models will emerge, benefiting patients. Moreover, looming competition from multiple gene therapies within the same disease area will drive down prices and, ultimately, COG. That is "the only way out of the Gordian knot," according to Cyr.

Pricing discussions are an increasingly important part of the due-diligence process for venture capital firms. As part of that process, Jain said he seldom seeks direct input on pricing from payers but speaks directly with pharma R&D and business development heads, as well as with bankers because they know where investors "want to put their money."

LaBarge reminded the panelists that the pricing debate centers on the expected clinical benefit. A company developing a CGTx product should aim to get "in a ballpark of where you think the art of possible is… from a clinical perspective." He said novel payment structures will be key because the system cannot tolerate a number of gene therapies with extremely high price tags. Meanwhile, he noted that Medicaid is the "gorilla in the room," as the price of gene therapies will impact each state's Medicaid program budget.

Scenario-based pricing models will likely gain traction, according to Greenwald. "If you hit it out of the park and you're saving kids' lives, you're going to get upside pricing," he commented. "If it's okay, it extends or maybe halts the disease, maybe it's a baseline pricing. And if it doesn't really work, then it might be a zero, but maybe it's not as good pricing." Greenwald said Deerfield's

approach is to calculate a weighted average based on different pricing scenarios and input from team members and key opinion leaders. He added that recent approvals boost those experts' confidence in pricing for future approvals, although numerous unknowns remain, and pricing will likely be indication specific. Clinical data are still the ultimate proof. If a sponsor faces obstacles such as a "pretty good," low-cost standard of care, he says they need to question whether they have chosen the right modality.

Reasons for excitement in 2023

Looking to the year ahead, Jain said he is most excited about positive CGTx data readouts and their potential impact on enthusiasm for the space, as well as the prospect of positive societal impact. At the fund level, he expressed excitement about "finding the stuff that we don't know about." Jain added that he expects to see "a lot of interesting companies and hopefully make some interesting investments in teams that we want to [accompany] on the journey."

The continued evolution from "gene therapy 1.0 to 2.0" will drive demand across the sector, noted LaBarge. He said excitement will mount as bioengineered capsids, cell- or tissue-specific payloads, and other technologies move "to the next phase."

Woolfson is optimistic that Krystal Bio will receive approval for the first herpes simplex virus (HSV)-based gene therapy. He also anticipates positive developments from allogeneic cell therapy programs, particularly in solid tumors, and mentioned induced pluripotent stem cells (IPS), cord blood-derived, and pooled donor approaches as "probably my favorites there." Additionally, Woolfson lauded multiplexing for its potential to enable polygenic approaches, and zinc finger proteins as still "the best editors." His other reasons for excitement include reprogramming and transcriptional repressor approaches, recombinases and integrases, and big DNA.

Cyr said his focus is on new technologies and their potential to reduce COG. Additionally, larger payloads may accelerate the CGTx sector's transition from rare to more prevalent diseases. He characterized the field as no longer conducting "a science experiment; it's actually now therapies and drugs."

With numerous technologies expected to emerge from academia, incorporating these advances into clinical practice will be the "key value inflection," at least in the early stages, according to Greenwald. He said he expects obstacles but "the overall arc in this field is tremendous." Progress therefore will not be a "straight line, but it's going to be exciting."

Conclusion

As the CGTx field has progressed, new challenges have emerged amid persistently high unmet need. Fortunately, experts are now addressing those challenges with what Greenwald called "real technology solutions." New innovations and investments will thus benefit patients and society, making this an exciting time to be in the CGTx space.

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ADVANCE, a collection of interconnected services and complementary teams, uniquely focuses on the complexities of clinical, regulatory, manufacturing, and commercial needs to successfully bring cell or gene therapies to market.

Connect with one of our experts. Contact us at **precisionadvance@precisionmedicinegrp.com**.
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