Cell & Gene Therapy Deep Dive

Email: Info@deepsailcapital.com
Website: www.deepsailcapital.com

Topics Covered: Cell & Gene Therapy, RNA Therapy, Ex-Vivo Treatment, In-Vivo Treatment, CDMOs, CRISPR CaaS9, Gene Editing, Cellular Production

Relevant Companies: Thermo Fisher (TMO), Danahar (DNR), Lonza(LOON:SWX), Catalent (CTLT), Biolife Solutions (BLFS), Clearpoint Neuro (CLPT), Maxcyte (MXCT), Repligen (RGEN), Cryoport (CYRY), Andlauer Healthcare (AND:TSX), Kite Pharma (Gilead Acquisition: GILD), Bluebird Bio (BLUE), Juno Therapeutic (Bristol Myers Acquisition: BMY), Vertex Pharmaceuticals (VRTX), Crispr Therapeutics(CRSP)

List of top CGT development companies

Nuggets

"C&GT programs have grown 20% per year. There are 3,000 programs in the pipeline but less than 5% in Phase III."

"Gene therapy patients must be followed for 15 years, and the FDA may require follow-up for many other types of cell therapies, a process that will improve the safety of products but requires significant tracking and administrative resources"

"With approximately 70,000 sickle cell disease patients nationwide, a gene therapy priced at $1 million to reflect the avoided cost of future health services would cost $70 billion"

"Yescarta has a list price of $373,000, and Kymriah costs between $373,000 or $475,000, depending on the type of cancer. In 2017, the FDA approved Luxturna to treat a rare form of inherited blindness that affects 1,000 to 2,000 people in the U.S. This treatment costs $425,000 per eye"

"Traditional tool providers have often been slow to adapt their operations and product portfolios to serve the necessary components C+GT developers require for product development, manufacture, and distribution. Instead, new, specialized tools suppliers have emerged to fill the gap between what C+GT developers require and what legacy pharmaceutical manufacturers and suppliers can't"

"There is currently no standardized platform approach for commercial-scale viral-vector DSP (as is seen with monoclonal antibodies),m. Consequently, a high degree of process optimization is still required for each product"

"Traditional supply chain models will not effectively meet the needs of these companies that are producing personalized therapies that must quickly and efficiently be delivered to their customers and patients. Supply chains that support the manufacturing and delivery of cell and gene therapies are long, complex, and highly controlled."

Levelsetting

Cell and Gene Therapy (CGT or C&GT): Cell & Gene therapy is a broad set of therapies that fall into three major buckets: Gene Therapy, Cell Therapy, or RNA Therapy. CGT therapies can work by several mechanisms including replacing a disease-causing gene with a healthy copy of the gene, inactivating a disease-causing gene that is not functioning properly or introducing a new or modified gene into the body to help treat a disease.

Gene Therapy: A technique that modifies a person's DNA to treat or cure disease.

Cell Therapy: A technique in which whole cells are inserted or infused into the body. Might include therapies in which cells are removed from a patient's body, genetically modified and then reinserted into that patient's body.

RNA Therapies: RNA and mRNA Therapies are designed to correct a mistake, or mutation, in the RNA of someone with a genetic disease without changing the DNA itself.

Ex Vivo: Refers to CGT treatment in which cells are removed from a patient's body, then modified, and then reinserted into the patient's body.

In Vivo: Refers to CGT treatment in which new genes are inserted directly into a patient's body via a vector (usually a virus).

Autologous: "From One's Self" Refers to CGT treatment that uses cells within one's own body for treatment.

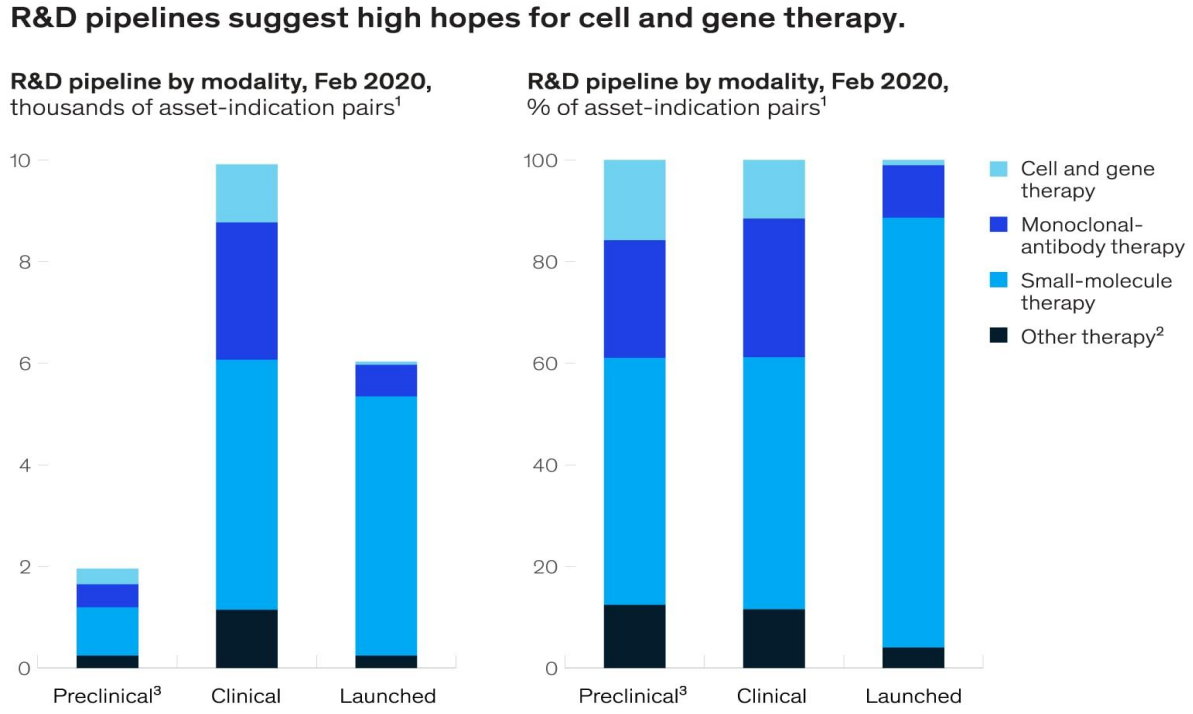
Allogenic: "From Another Person" Refers to CGT treatment that uses cells from another person.

CDMOs: Contract Development and Manufacturing Companies do both the development and manufacturing of drugs. Within CGT, most pharmaceutical companies prefer to partner with CDMOs and other technology providers early in the development process because of the wide range of production specifications that might be required and the master data file process.

CMOs: Contract Manufacturing Companies that take pre-formulated drugs and manufacture them on behalf of pharmaceutical clients.

Master Data File: As part of drug and medical device applications to regulatory agencies, a company may need to reference data from another product used in the manufacture of its own, such as packaging, ingredients, or accessories. The owner of this data may choose to submit a Master File to disclose proprietary or confidential information concerning their product to a regulatory agency without providing it to parties that need to reference it.

CGT R&D Pipeline large and early: With only a few CGT approvals to date (~20 FDA approvals) the CGT pipeline is significantly larger than approved CGT Therapies.



Source: [Mckinsey Biopharma Portfolio Strategy]

Current Approved Cell and Gene Therapies: The pace of CGT therapies has been slowed by COVID, but expect that to pick up in 2023 & 2024. We are getting close to the first Gen 2 CGT using CRISPR CaaS9 gene editing by Vertex and CRISPR's beta thalassemia therapy.

Approved gene therapies as of Q2 2022 (1/2)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Gendicine	recombinant p53 gene	2004	Head and neck cancer	China	Shenzhen SiBiono GeneTech
Oncorine	E1B/E3 deficient adenovirus	2005	Head and neck cancer; nasopharyngeal cancer	China	Shanghai Sunway Biotech
Rexin-G	mutant cyclin-G1 gene	2006	Solid tumors	Philippines	Epeius Biotechnologies
Neovasculgen	vascular endothelial growth factor gene	2011	Peripheral vascular disease; limb ischemia	Russian Federation, Ukraine	Human Stem Cells Institute
Imlygic	talimogene laherparepvec	2015	Melanoma	US, EU, UK, Australia	Amgen
Strimvelis	autologous CD34+ enriched cells	2016	Adenosine deaminase deficiency	EU, UK	Orchard Therapeutics
Kymriah	tisagenlecleucel-t	2017	Acute lymphocytic leukemia; diffuse large B-cell lymphoma; follicular lymphoma	US, EU, UK Japan, Australia, Canada, South Korea	Novartis
Luxturna	voretigene neparvovec	2017	Leber's congenital amaurosis; retinitis pigmentosa	US, EU, UK, Australia, Canada, South Korea	Spark Therapeutics (Roche)
Yescarta	axicabtagene ciloleucel	2017	Diffuse large B-cell lymphoma; non-Hodgkin's lymphoma; follicular lymphoma	US, EU, UK, Japan, Canada, China	Kite Pharma (Gilead)
Collategene	beperminogene perplasmid	2019	Critical limb ischemia	Japan	AnGes
Zolgensma	onasemnogene abeparvovec	2019	Spinal muscular atrophy	US, EU, UK, Japan, Australia, Canada, Brazil, Israel, Taiwan, South Korea	Novartis
Zynteglo	betibeglogene autotemcel	2019	Transfusion-dependent beta thalassemia	EU, UK	Bluebird Bio
Tecartus	brexucabtagene autoleucel	2020	Mantel cell lymphoma; acute lymphocytic leukemia	US, EU, UK	Kite Pharma (Gilead)
Libmeldy	atidarsagene autotemcel	2020	Metachromatic Leukodystrophy	EU, UK	Orchard Therapeutics
Breyanzi	lisocabtagene maraleucel	2021	Diffuse large B-cell lymphoma; follicular lymphoma	US, Japan, EU, UK, Canada	Celgene (Bristol Myers Squibb)

Source: Pharmaprojects | Informa, July 2022

8 / Q2 2022

Text highlighted in yellow represent new approvals during Q2 2022

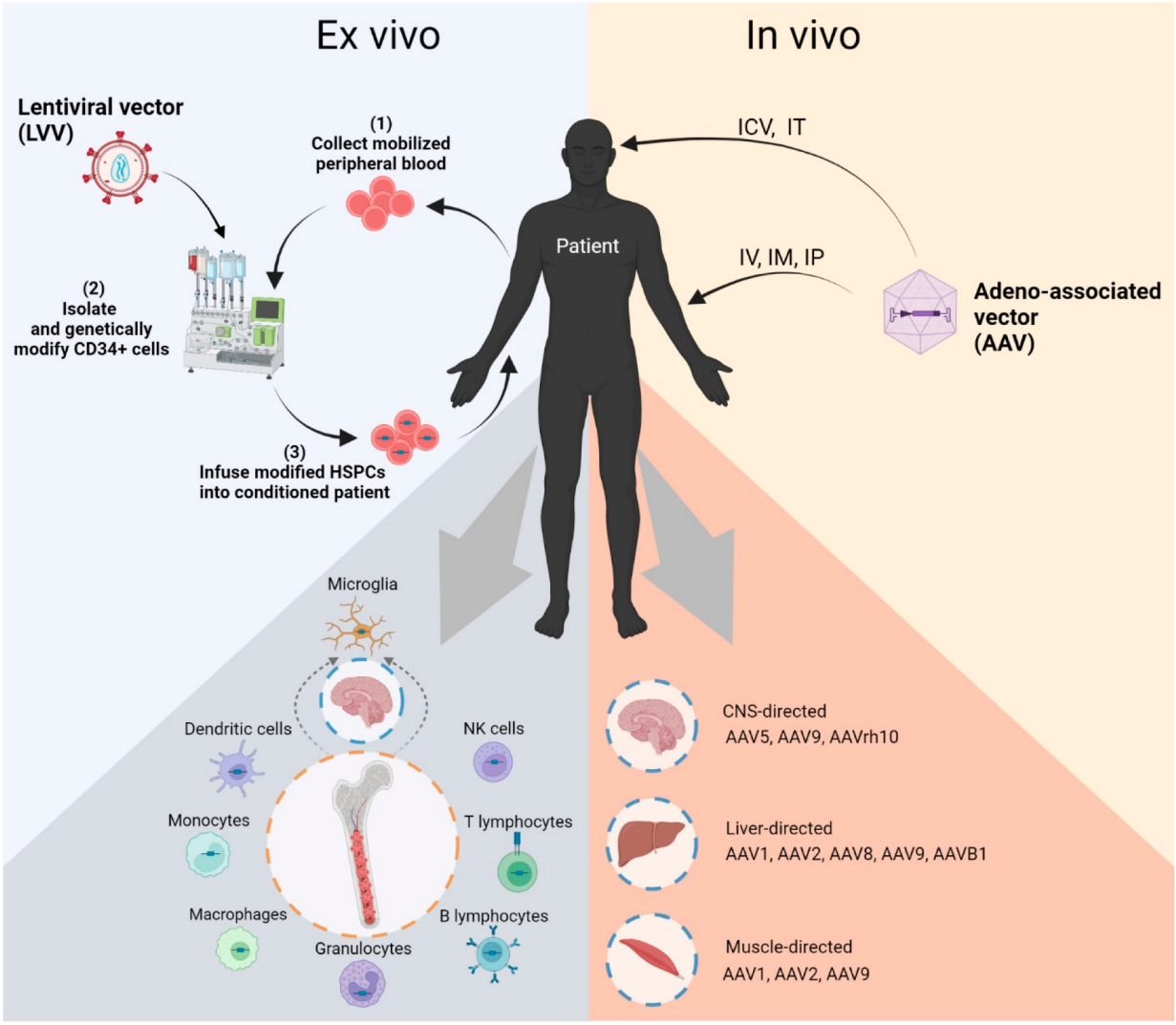
American Society of Gene + Cell Therapy

Approved gene therapies as of Q2 2022 (2/2)

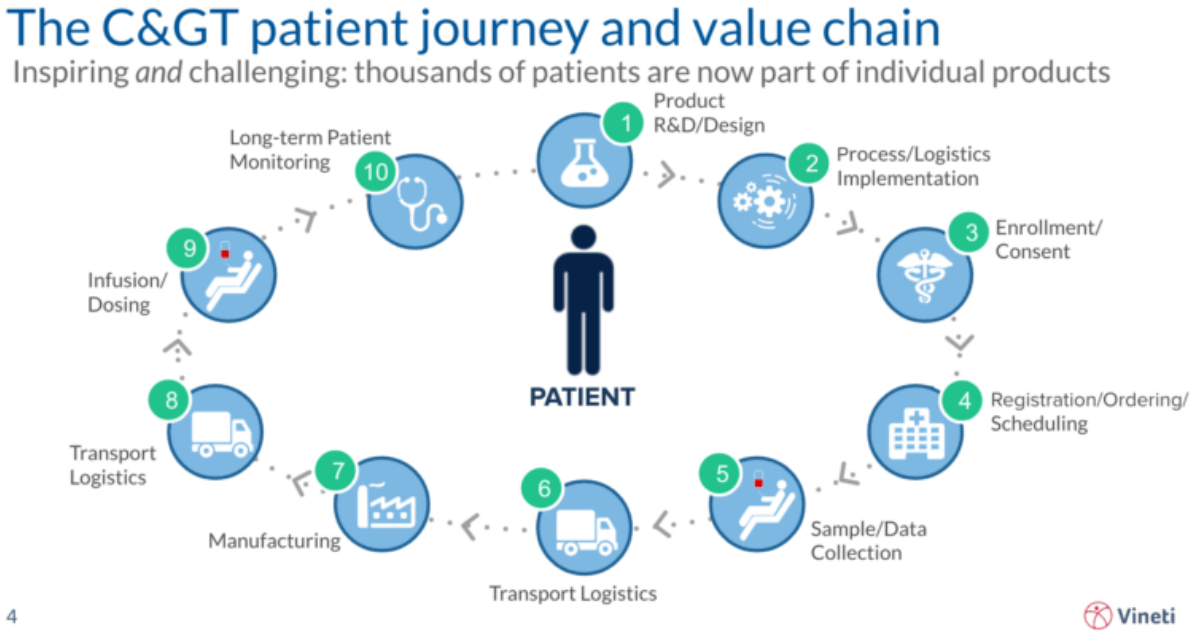
Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Abecma	idecabtagene vicleucel	2021	Multiple myeloma	US, Canada, EU, UK, Japan	bluebird bio
Delytact	teserpaturev	2021	Malignant Glioma	Japan	Daiichi Sankyo
Relma-cel	relmacabtagene autoleucel	2021	Diffuse large B-cell lymphoma	China	JW Therapeutics
Carvykti	ciltacabtagene autoleucel	2022	Multiple myeloma	US, EU, UK	Legend Biotech

Source: https://asgct.org/global/documents/asgct-pharma-intelligence-quarterly-report-draft-q.aspx

EX Vivo vs In Vivo Vectors: Different pathways and vectors are required for different parts of the body, cell types, and treatment types.



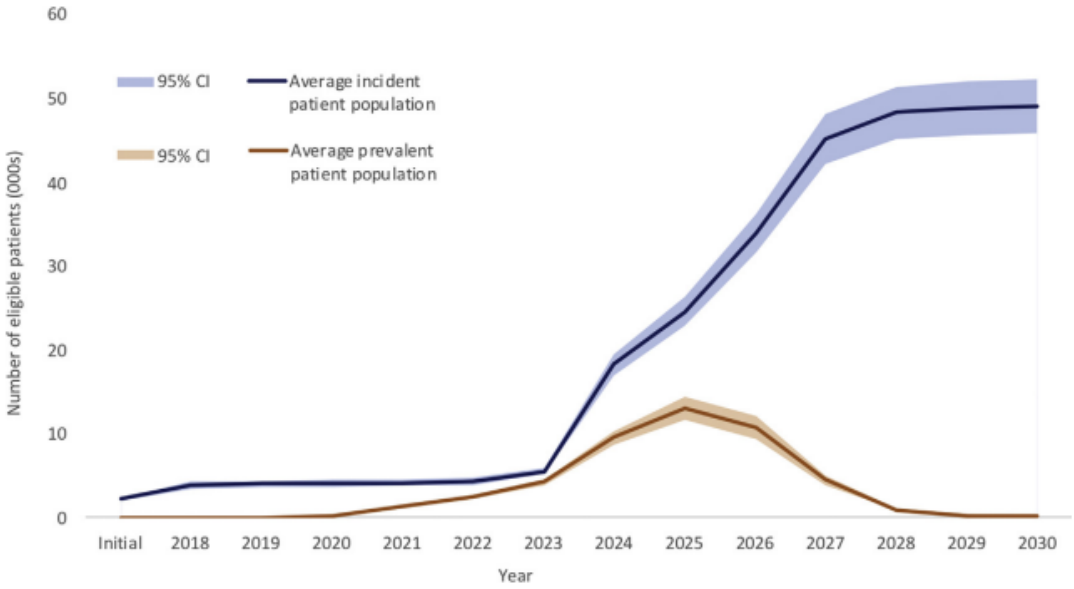
CGT Patient & Process: The patient and production process for CGT is a long process which requires significant planning, manufacturing, development and administration resources.



Source: https://vineti.com/resources/blog/isct-2019-data-elements-in-the-cell-therapy-value-chain/

The CGT S Curve: 2023-2024 is when the S Curve will significantly jump in terms of patients treated with CGT.

Figure 3. Predicted annual treated patient numbers, 2018-2030.



CI indicates confidence interval.

Source: https://www.valueinhealthjournal.com/article/S1098-3015(19)30188-3/pdf

CGT Revenue Growth: Currently approved CGT Therapies are expected to double revenues over the next 5 Years.

Cell Therapy	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
KYMRIAH	-	$6	$76	$278	$474	$587	$576	$626	$644	$679	$693
YESCARTA	-	$7	$264	$456	$563	$695	$1,000	$1,248	$1,452	$1,600	$1,744
TECARTUS	-	-	-	-	$44	$176	$288	$373	$451	$521	$593
BREYANZI	-	-	-	-	-	$87	$317	$574	$863	$1,114	$1,375
ABECMA	-	-	-	-	-	$164	$328	$579	$850	$1,110	$1,407
CARVYKTI	-	-	-	-	-	-	$35	$124	$247	$365	$472
Gene Therapy											
GLYBERA**	-	-	-	-	-	-	-	-	-	-	-
STRIMVELIS*	-	$3	$4	$3	$3	$1	-	-	-	-	-
LUXTURNA	-	-	$27	$89	$82	$86	$121	$137	$137	$135	$131
ZOLGENSMA	-	-	-	$361	$920	$1,351	$1,518	$1,581	$1,705	$1,848	$1,908
ZYNTEGLO	-	-	-	-	-	$3	$10	$43	$127	$188	$272
SKYSONA	-	-	-	-	-	$1	$1	$3	$8	$11	$13
LIBMELDY*	-	-	-	-	-	-	$4	$14	$52	$104	$154
ROCTAVIAN*	-	-	-	-	-	-	$22	$242	$502	$762	$1,031
UPSTAZA*	-	-	-	-	-	-	$16	$40	$80	$111	$133
RNA Targeting											
KYNAMRO	$1	-	-	-	-	-	-	-	-	-	-
EXONDYS 51	$5	$155	$301	$381	$422	$454	$491	$496	$420	$376	$310
SPINRAZA	$5	$884	$1,724	$2,097	$2,052	$1,905	$1,753	$1,557	$1,431	$1,420	$1,453
TEGSEDI	-	-	$2	$41	$100	$55	$47	$72	$82	$88	$91
ONPATTRO	-	-	$13	$166	$306	$475	$583	$754	$860	$903	$972
WAYLIVRA*	-	-	-	$1	$26	$4	$15	$29	$43	$54	$64
GIVLAARI	-	-	-	$0	$55	$128	$181	$286	$384	$467	$538
VYONDYS 53	-	-	-	-	$43	$90	$130	$154	$191	$207	$233
OXLUMO	-	-	-	-	$0	$60	$118	$190	$258	$302	$346
VILTEPSO	-	-	-	-	$23	$78	$189	$281	$347	$390	$429
LEQVIO	-	-	-	-	-	$12	$244	$587	$896	$1,268	$1,847
AMONDYS 45	-	-	-	-	-	$69	$190	$207	$216	$245	$246
AMVUTTRA	-	-	-	-	-	-	$32	$198	$477	$936	$1,376
Total Sales	$11	$1,055	$2,411	$3,873	$5,113	$6,479	$8,210	$10,396	$12,723	$15,203	$17,832

*Source: Wedbush Securities; Evaluate Pharma, WW sales; *only approved in the EU; **Marketing application subsequently withdrawn.*

Questions & Answers

Q: How soon before we see CGT in major practice? Currently, there are only a handful of approved CGT treatments in the US and EU. The FDA currently lists 17 gene therapy treatments approved. As per a few different sources, there are between 2,000 and 3,000 CGT programs currently in various stages of development. **We are extremely early on the adoption S curve of CGT and likely won't fully accelerate for 2 years.**

CGT encompasses three major categories of treatments, RNA Therapy, Cell Therapy, and Gene Therapy. Each area is progressing fast, but each area has different hurdles. RNA therapy has

been developed and approved faster than gene therapy as it does not change the DNA of the patient but rather how cells interact with the rest of the body. Genetic therapies are the hardest to implement. Genetic therapies permanently change the patients DNA so those have been the slowest to progress, but with CRISPR CaaS9 and tools like it, their development trajectory has accelerated.

Technically the Pfizer and Moderna COVID vaccines were mRNA vaccines, so if you include those in CGT then the actual revenue from CGT has already taken off quite considerably.

Q: What are the key points of differentiation companies weigh in selecting manufacturing partners (ex: advantages of TMO vs DHR)?

CGT has a unique set of challenges compared to small-molecule development, including a unique production and treatment plan for each different CGT therapy. This requires a close alignment between the therapy developers and the CDMOs early in the development process. This is because developers are not only testing the therapies' safety and efficacy during the clinical trial process but also testing production and treatment methods. CMOs are impossible for CGT due to this constraint, making CDMOs the default in CGT.

The big CDMOs, namely Thermo Fisher (TMO), Danaher (DNR), Samsung Biologics (207940.KS), Lonza (LOON:SWX), and Catalant(CTLT), are the first ones to take on these large production and development challenges. Each company has been pouring billions of dollars into capex and talent development over the last few years in anticipation of this huge increase in demand for both development and production within CGT. Many have signed partnership agreements with therapy development companies for specific therapy programs. Each CDMO is trying to differentiate itself with slightly different regional focuses, but right now, the major issue in the industry is capacity constraints. There is a lack of production capacity to meet the near-term needs of the CGT industry.

With the onset of COVID-19 and the associated mRNA vaccines that were developed to treat it, the CDMO's capacity has been overwhelmed. Based on current industry discussions, it doesn't look like capacity constraints will come into balance until at least 2024. Part of the constraint is driven by a lack of talent in the CMC (Chemistry, Manufacturing, and Controls) discipline which will take time to address. You can't just throw a bunch of capex at the talent shortage overnight.

Smaller specialty companies that provide one or two critical pieces of the CGT production or delivery process have also arisen to fill a very specific need for CGT developers. Examples of these companies are Maxcyte (MXCT) with electroporation, Repligen (RGEN) with filtration & chromatography, Orgenesis (ORGS)/Lonza (LOON:SWX) with decentralized production, and Biolife (BLFS)/Cryoport (CYRY) with cold storage & logistics. These specialty CGT companies are poised for enormous growth over the next 3 to 5 years.

Q: What factors are impacting the revenue ramp (patient pop, modality, etc.) for a drug as it moves from clinic to commercial for various stakeholder groups (drug sponsor, CDMO, etc.)?

The major issue with CGT in terms of revenue ramp has been having a robust program in place that covers patients, payments, and production. Having a well-established program with all aspects of the process in place is a must for a successful CGT launch. Payments in particular are a huge hurdle as the costs of these curative CGT treatments are massive (see next Q&A).

Q: What will be the options for paying the high price for CGT?

As already noted, CGT is a curative treatment for disease. This in turn is different from the historical treatment options available for genetic diseases, which are usually treated over a lifetime via prescription drugs. The costs are shifting from paying a small amount every month over a lifetime to paying a large amount all at once, with many costing over a million dollars per treatment. Thus, the payment plans and options must adapt to this major shift.

There have been several proposed payment options, even some with a "Netflix Subscription Model." Currently, Yescarta and Kymriah are using the traditional model which is having Medicare and/or Private Insurers cover the massive bills. With the current small number of approved CGT treatments, it's probably ok to use the traditional payment model, but what happens when 30-40 more indications and treatments get approved and patient numbers skyrocket?

There will be a point in the near future when the traditional Medicare/Private Insurers will push back and no longer cover new CGT treatments. At that point the states, federal government, drug developers, and nonprofits likely need to step in with a new payment model. It will be some type of pay as you go or pay over time model where a debtor and payer system is set up (potentially a government backed system like student debt) to allow payments to be made upfront to developers and then paid for by patients and insurers over time.

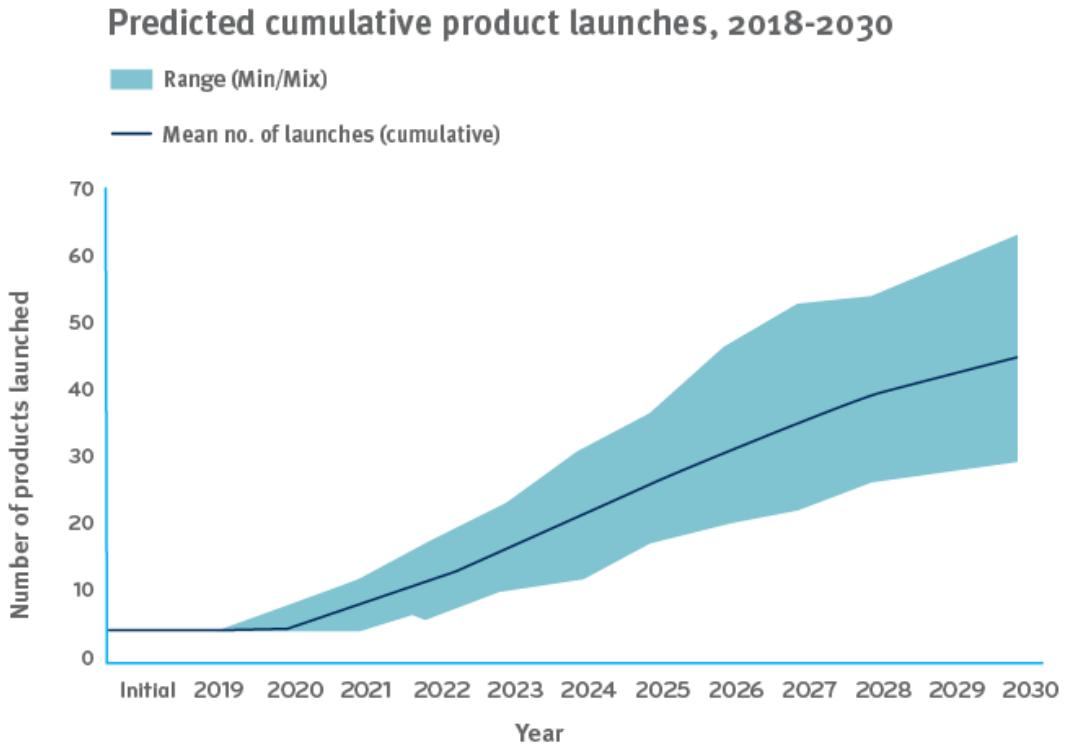
Q: What are the advantages and disadvantages of the different vectors/modalities given the way the data is trending?

The big question for a while was "is Ex-Vivo gene therapy a viable treatment type" due to some early data around issues with safety and efficacy as well as questions around production controls. The issues around safety and efficacy for the most part have been resolved with recent data from Vertex and CRISPR Therapeutics showing high safety and efficacy of Ex-Vivo treatments. Production issues are still being worked out for Ex-Vivo as the fact that a patient's cells are extracted, stored, treated, and then reinserted into them has extremely high resource and technology requirements.

Overall RNA therapies have smaller hurdles and will continue to progress fast. In-vivo and ex-vivo genetic treatments are getting very close to making it over the high regulatory hurdles put in place and we should see a few receive FDA approval in 2023.

Q: What is a realistic manufacturing capacity outlook vs 2026 TAM expectations for CGT production?

Post COVID, there will be a shift taking resources from supporting COVID mRNA vaccines to supporting CGT development. While that will help alleviate some of the CDMO production capacity constraints, the total industry production capacity and constraints will really depend on approval timing. With so many programs currently in development and zero historical capacity before 2018, there is a huge guessing game going on right now by CDMOs to determine the capacity that will be needed. The number of approved and launched CGT therapies in 2025 could be 20 or it could be 50. That is a huge dispersion in needed capacity.



My guess is the production capacity will remain constrained for the next 3–5 year until the industry gets a better handle on the exact timing of treatment approvals and production ramps.

Q: Will one pathway (Ex Vivo/In Vivo) or Vector (Virus delivery type) become the dominant CGT methodology?

In the near term a mix of pathways and vectors will be developed. Within CGT, each part of the body and cell type requires unique specifications. Every therapy has many nuances in terms of cell delivery, production, and treatment timing. Different pathways and vectors will be used, each having specific advantages and disadvantages.

Ex-Vivo vs In-Vivo debate is still a hot topic within the industry. Both methods have specific positives and negatives. Right now Ex-Vivo has higher safety risks and treatment costs more,

but as Ex-Vivo makes progress with CRISPR CaaS9 and advanced gene editing tools we will see costs come down and safety increase.

Q: What are the new trends in CGT development that could become large and impactful in the next 3-5 years?

The current technology can be considered generation 1 of CGT. These are treatments that use stem cells and RNA therapy for very targeted but narrow treatments. Generation 2 is on the horizon with Gene Editing starting with the CRISPR CaaS-9 breakthrough. These are treatments that directly edit genes in our DNA. Generation 3 is already being worked on which could include technologies like Gene Writing and Base Editing that are both extremely efficient and more productive ways to apply gene editing. These generation 3 treatment's will change almost anything you want within the human DNA. Most of the next 10 years will be focused on curing simple genetic diseases with very targeted genetic abnormalities, after that it will open up to more complex diseases, cancers, and then lifespan improvements.

Conclusions

1. CGT production processes are much more resource intensive from both a capital and talent perspective than traditional small molecules production. To date, most of the global pharmaceutical production has been small molecules that have well-established protocols and vast capacities. CGT production is completely different, not only are there many new-process steps but each therapy has unique production requirements. Ex-Vivo CGT in particular requires the extraction of a person's cells, onsite/offsite treatment, and then reinsertion of cells back into the patient all in a controlled environment to avoid cellular damage. This is a big hurdle that current CDMOs are still working through. Many specialty suppliers will mint fortunes if they succeed in supporting CGT markets like Ex-vivo CGT.

2. CRISPR/CaaS9 was just the beginning of Gene Editing. Many new techniques have already been developed that will improve on the CRISPR/CaaS9 technique. Developers are now using advanced editing tools like High Fidelity CRISPR, CaaS Clover, and other gene editing techniques that have better efficiency and less chance of nicking off target genes.

3. CGT therapy causes a permanent change to a person's DNA, and is thus a cure for genetically based diseases, whereas small molecules are mostly just long-term treatments of diseases, not cures. The long-term TAM of CGT is probably enormous, as most future biomedical research will include some knowledge of CGT or its application. We are so early in the development phase that we can barely even conceptualize the potential long-term applications of the technology. **CGT permanently solves the core medical issues embedded in our human DNA while everything else is a metaphoric "band aid."**

4. COVID-19 had significant repercussions on CGT development, which were both negative and positive. On the positive side, due to the fact that two of the major vaccines used in the US were mRNA-based vaccines, it has accelerated the general acceptance of these types of

therapies by the public. Due to the massive production needs of the mRNA Vaccines, significant investment has flowed into facilities, equipment, and talent to support their rollout. That capacity and talent will eventually shift from COVID vaccines to similar CGT development and production programs starting in 2023. On the negative side, CGT development was slowed during COVID years (2020–2022) due to the need to focus resources on mRNA vaccines. An example of this is that the FDA slowed decision making on several CGT programs during those years as they grappled with COVID drug approvals. **As COVID winds down in 2023, CGT is poised for an explosive period of growth due to refocus of production capacity, availability of talent, and removal of FDA constraints.**

5. Services will play a huge part in the valve chain required for scaling CGT treatments. Due to the added steps in the treatment and monitoring process for CGT, additional services businesses will be required to support the treatment process that previously did not exist. These services will include CROs, software services, logistics services, and laboratory equipment sales.

Investment Takeaways

- CGT production demand is likely to increase 3-5x over the next few years as approvals and launches begin to accelerate. CGT speciality providers, services, CROs and makers of devices that support production and development are about to see a huge surge in demand. Speciality CDMOs focused on CGT will also see a huge increase in volume and demand. Long: Any of these CGT speciality companies or CDMOs will likely be a homerun. Deep Sail Capital is long Maxcyte (MXCT), Biolife Solutions (BLFS), and Clearpoint Neuro (CLPT).

- The cost of these therapies will eventually be paid as these curative treatments will be demanded by those affected by them. In most cases, these treatments will change people's lives for the better. There are huge implications for health insurers and potentially society to cover the high costs of these treatments. Keep an eye on the following: If you own any health insurers, CGT payment should be at the top of mind.

- Biopharmaceutical Development companies historically have a very high hit or miss rate with individual small molecules, known as "hit risk." In my opinion, hit risk is less about efficacy in CGT and more about safety and delivery. We know the genetic markers that cause specific diseases and what genes that need to be replaced. Clinical trials in gene editing are not a matter of if it will work but rather can we get it to work safely. Due to this, very targeted simple genetic diseases (ones with one known gene target)

with large patient populations could be seen to have less "hit risk" than small molecules. For most indications, the first approved CGT treatment will take the entire market, as there is little room for two or more treatments. Long: Leaders in gene editing targeting simple genetic diseases with large-patient populations. Note: I don't invest in drug developers, so I haven't spent any time on individual companies.

Top 5 Read, Listen, Watch

1. **GEN Podcast Series (Listen) Best Episode: Alternatives to CRISPR CaaS9**
2. **American Society of Cell & Gene Therapy Quarterly Update (Q1, Q2) (Read)**
3. **Jennifer Douda Nobel Lecture on CRISPR CaaS9 (Watch)**
4. **Estimating the Clinical Pipeline of Cell and Gene Therapies (Read)**
5. **Cell & Gene Podcast (Listen) Best Episode: Best Practices for Partnering with a CDMO**

Final Thought

Cell and Gene Therapy is clearly on a trajectory for significant growth in the next few years. **I think on average investors are underappreciating the rapidly approaching S curve growth in CGT production. The pick and shovels of the industry are extremely well positioned to benefit from this trend.**

So how far can CGT go? It remains to be seen but putting together a logical progression of advancements and there is a reasonable path to some extremely exciting applications over the next 50 years. Potential applications of CGT include life extension, elimination of cancer, elimination of genetic diseases, reengineering our food chain, designer babies, bringing back extinct animals, and industrial applications to combat climate change. The different applications of CGT will each follow different timelines, as humanity will have to grapple with ethical questions that will slow progress in certain areas. We are currently living in a time of great change due to the Cambrian explosion of technological advances in CGT akin to that of the change that occurred due to the invention of the microprocessor. The societal impacts of this change will likely not be clear for many years, as the early focus of CGT will be ridding humanity of simple genetic diseases. Once we get past that first stage of CGT (10–15 years), the focus will shift to more secondary goals that are ethically in a gray area. I hope humanity has the patience and caution to move slowly as we develop what will be some truthly powerful technology to change humanity at its core.