Is today's pharmaceutical commercial model going extinct?

7 ways one-time therapies disrupt drug commercialization

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CRA Charles River Associates

The volume and pace of scientific advancement in gene and cell therapy has increased significantly in recent years. Breakthrough treatments such as Kymriah™ (acute lymphoblastic leukemia), Luxturna™ (hereditary vision loss), and other similar novel cell and gene therapy options are significantly improving treatment outcomes, and in some cases providing cures via one-time treatment to rare diseases previously considered untreatable.

While these one-time therapies, particularly when curative, have the potential to be beneficial to patients with serious life-threatening diseases, a number of characteristics differentiate them from conventional chronic therapies:

- One-time therapies typically treat an existing prevalent pool of patients at launch.
- One-time therapies typically have treatment regimens of significantly shorter duration relative to chronic therapies.
- The available patient population diminishes, sometimes rapidly, over the course of the curative therapy lifecycle as the pre-launch patient prevalent pool is depleted.

In this paper, we aim to present 7 disruptions and some mitigation strategies related to one-time therapies:

1. Increased emphasis on order of market entry
2. Increased value of real-world efficacy in target patient population
3. Increased need for focused, but flexible development platforms
4. Increased value of development partnerships and alliances
5. Re-evaluation of commercial team structure/size
6. Elevated importance of product marketing and value communication
7. Entrance into novel strategic commercialization partnerships

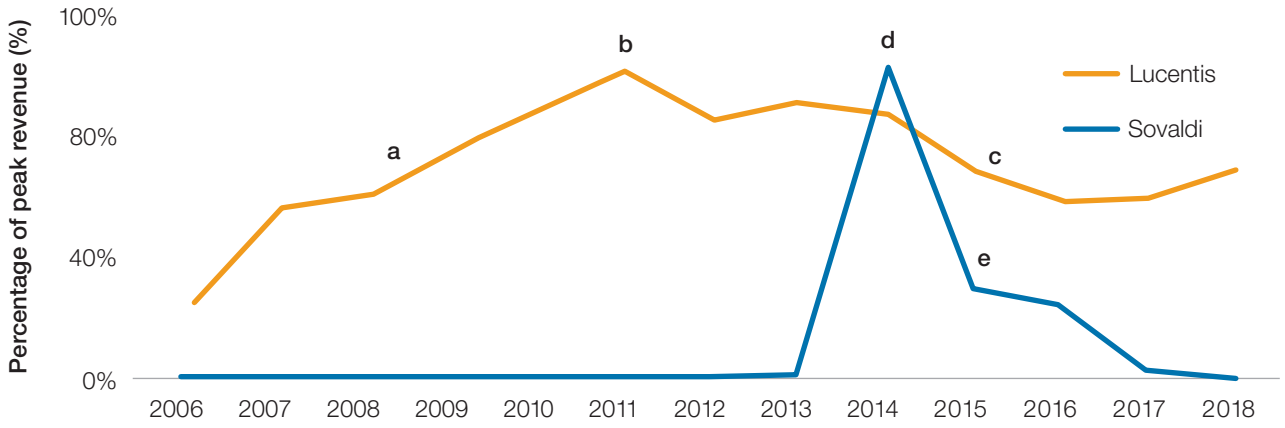
Challenge posed by the one-time therapy lifecycle and the reimbursement model implications

For most chronic therapies, peak sales typically occur several years (~3–5 years) after launch as product adoption increases. Once achieved, peak sales typically can be sustained for 5–10 years and are followed by revenue decline as more competitors enter and/or the product loses patent protection. This lifecycle curve is typical for chronic therapies and has become the primary basis for manufacturer investment and commercial planning.

For one-time therapies, however, patients are treated over a shorter period (vs. chronic therapies) and the treatable patient population diminishes over time. As a result, product revenue potential declines over time, sometimes very rapidly. To mitigate against the compressed commercial viability of these therapies, and account for their expected long-term benefits, manufacturers frequently price one-time therapies at a substantial premium relative to chronic therapies. The high cost associated with these therapies poses a significant challenge to manufacturers' commercial business models and payer reimbursement models since all tend to be based on the typical lifecycle of chronic therapies.

The differences in the product lifecycle under the current payer reimbursement model are exemplified in the comparison of Sovaldi,™ a curative therapy for hepatitis C, to Lucentis,™ a chronic therapy with various indications such as wet age-related macular degeneration (AMD).

Figure 1: Percentage of peak US revenue comparison for Lucentis vs. Sovaldi



Note: Revenue depicted is US only. Lucentis revenue is for its wet AMD indication only.[1]

Chronic therapy – Lucentis

a. **Growth phase:** at launch; characterized by low initial adoption
b. **Peak sales:** increased adoption over time
c. **Decline:** revenue declines due to competitive/generic entry

One-time therapy – Sovaldi

d. **Peak sales:** at launch or close to launch due to pre-launch patient prevalent pool
e. **Sharp decline:** due to depletion of patient pool, perhaps exacerbated by competitive entry

Due to these differences and the large up-front financial outlays required by payers, one-time therapies represent a disruptive challenge to payers' existing reimbursement model.

Consultants with Charles River Associates (CRA) interviewed US national and regional payers covering ~75 million commercial lives regarding one-time therapies. All the interviewees stated that they believe the potential budget impact of one-time therapies merits a new way of thinking about payment. With over 800 one-time therapies in development, (some targeting mass market indications like cardiac failure), these payers believed that maintaining the current reimbursement model as the default model for one-time therapies will be unsustainable.

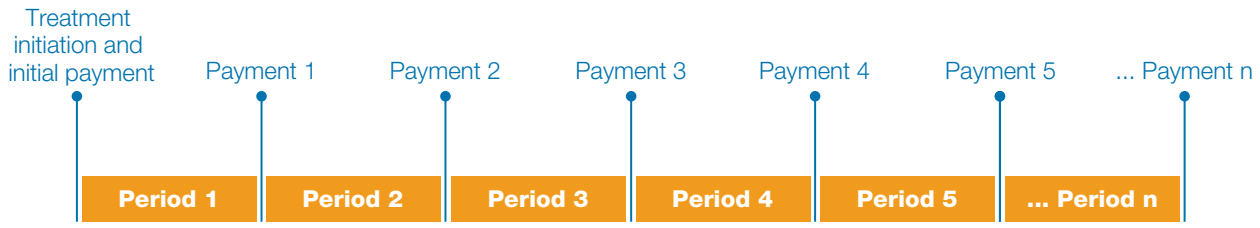
Figure 2: Sample one-time therapies currently in development and their indications

Product	Manufacturer	Indication	Development phase
RT-100	Renova Therapeutics, Inc.	Heart failure and reduced ejection fraction	3
AVXS-101	Novartis Pharmaceuticals Corporation	Spinal muscular atrophy	3
ADXS11-001	Advaxis, Inc.	Metastatic cervical cancer	3
GT-AADC	PTC Therapeutics, Inc.	Aromatic L-amino acid decarboxylase deficiency	3
LentiGlobin	bluebird bio, Inc.	ß-thalassemia	3
OTL-200	Orchard Therapeutics plc	Metachromatic leukodystrophy	3

The three alternative payment models explored in CRA's interviews were annuity payments, outcomes-based arrangements, and government/third-party funded risk pools. Effective payment mechanisms may be characterized by a single model or a combination of these models, as appropriate, and depending on the disease.

Annuity payments: In this model, payers would make payments to manufacturers over a fixed period of time for each patient that receives the one-time therapy. For example, a $1 million therapy could be divided into 10 inflation-adjusted payments of approximately $100,000 for each treated patient. Structuring the payments this way would help mitigate the high up-front cost that would otherwise be associated with the therapy.

Figure 3: Annuity payment model



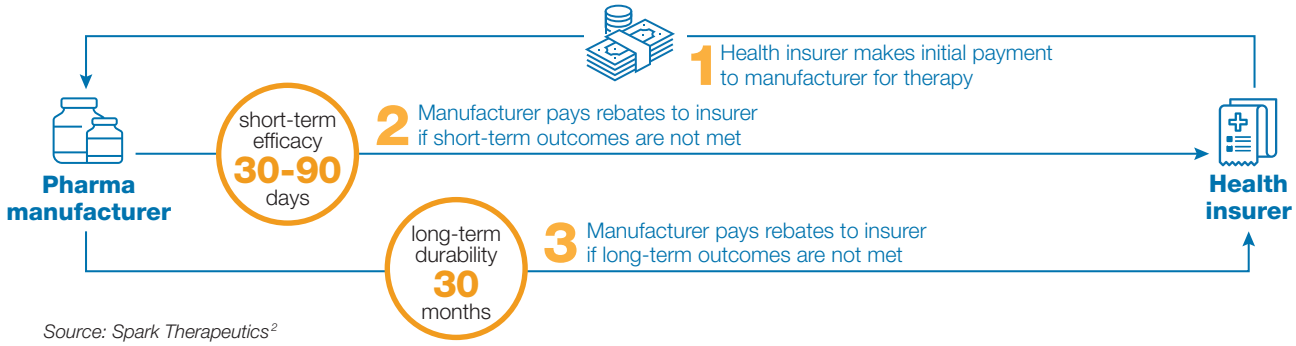
Note: Number of payments (n) to be agreed upon by the payer and manufacturer

While annuity payments help reduce the burden of a high up-front treatment cost, the model also would flatten the one-time therapy revenue peak and mitigate the resulting spike in payer budgets. However, it will likely create a need for new reporting capabilities to track and monitor payments such as Medicaid best price. It would likely also require new legislative policies to allow for state Medicaid budgets to undertake a long-term liability. This model also raises the issue around patient turnover and which entity is responsible for the payment if a patient switches insurance plans.

Outcomes-based arrangements: In this model, payers would make payments to manufacturers based on the ability of the therapy to meet specific clinical targets at pre-defined time periods. If the end points are not met, all or some portion of the cost of therapy would not be reimbursed or would be paid back as a rebate. These types of agreements help to minimize the cost of unsuccessful treatments and mitigate data-related concerns about the cost-effectiveness of one-time therapies. Within the last two years, manufacturers such as Novartis Pharmaceuticals Corporation and Spark Therapeutics, Inc. have announced innovative contracting programs dependent upon patient outcomes with a commitment to improving patient access.

While this model can eliminate the cost of non/sub-optimally responsive patients to payers, the challenge is identifying outcomes that are measurable, durable, and expected to mirror clinical trials. This model is dependent on patient show rates for follow-up appointments. Additionally, successful execution of outcomes arrangements will require logistical and organizational investments to support the definition, management, and tracking of patient outcomes. In some cases, outcomes are not easily measureable on a patient-by-patient basis, further challenging implementation of an outcomes-based arrangement.

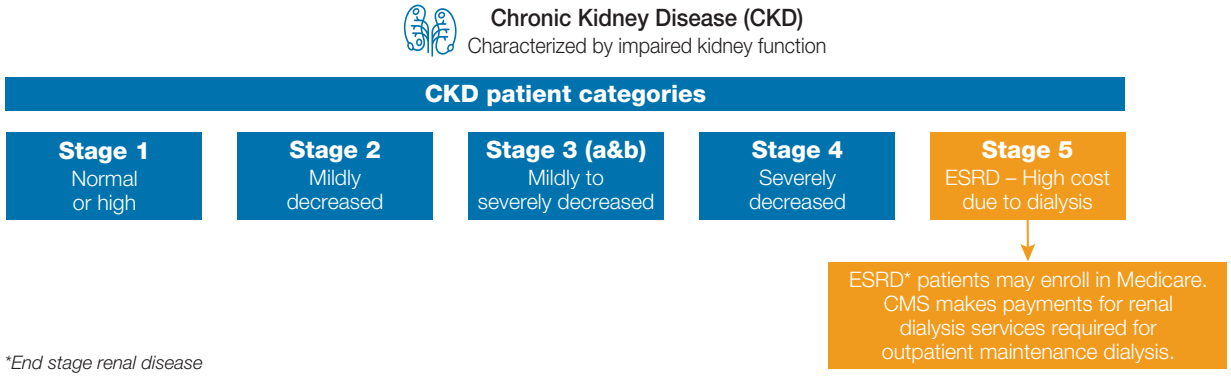
Figure 4: Spark outcomes-based arrangement



Source: Spark Therapeutics[2]

Government/third-party funded risk pools: In this model, the government or a third party would set up a fund that pays for the cost of one-time therapies. The fund(s) could be established by therapeutic/disease area, and would allow payers to carve out the cost of one-time therapies and keep patient premiums at reasonable levels.

Figure 5: Risk pool



**End stage renal disease*

For manufacturers, inclusion in the pool would mean one-time therapies are reimbursed by a public or private entity with concentrated buying power, which would place downward pricing pressure on manufacturers. Additionally, this also likely would require new and potentially costly reporting capabilities to track payments.

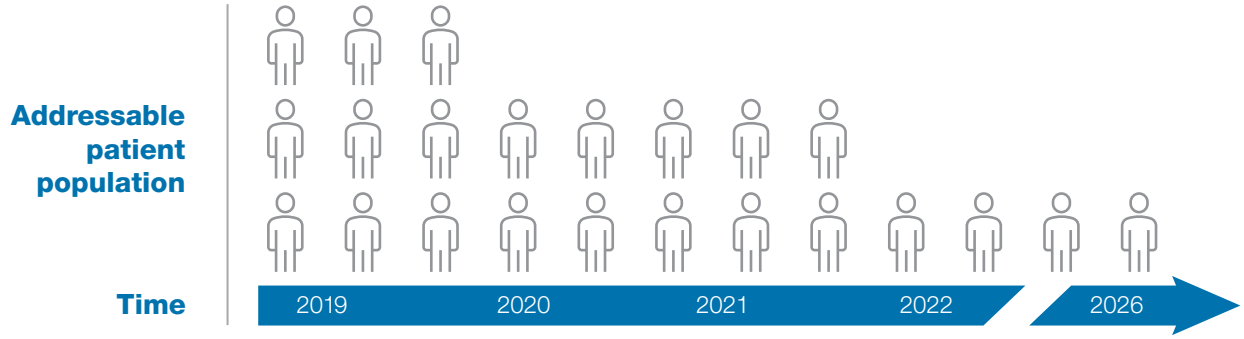
Commercial model disruptions

Development

With the entry of more one-time therapies and adoption of alternative reimbursement models to pay for these therapies, there are implications for how manufacturers develop one-time therapies.

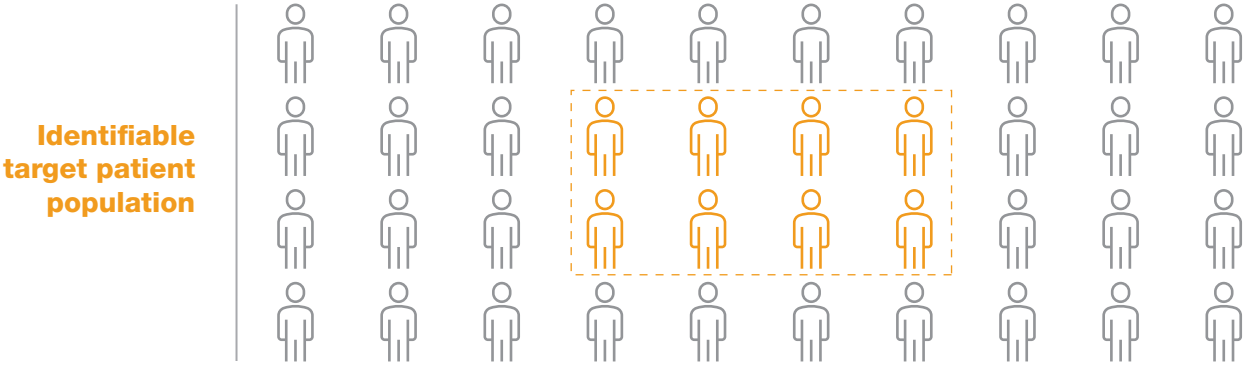
1. **Increased emphasis on order of market entry**: Due to the curative nature of one-time therapies, the pool of prevalent patients is finite and constantly diminishing, thus the significance of being first, or very early to market, greatly increases.

Figure 6: Addressable patients decline over time



2. **Increased value of real-world efficacy in target patient population**: With the adoption of reimbursement models that lengthen the payment cycle, the link between reimbursement and demonstrated clinical value in real-world setting is greater. Thus, there is a significantly higher premium on identifying the 'right patient' and clinical outcomes in the development phase.

Figure 7: Identifiable target patient population



In first-line non-small cell lung cancer (NSCLC), Keytruda™ utilized a companion diagnostic that successfully allowed it to identify the subset of patients that would respond well to treatment.[3] All potential Keytruda patients must be tested for presence and level of PD-L1 expression (tumor proportion score ≥50%) to determine eligibility for the treatment. Contrastingly, Bristol-Myers Squibb opted to target a broad patient population, without the requirement for patients to be high PD-L1 expressors. Trial failure results for Bristol-Myers Squibb suggest that the enrolled patient population may have been too broad. A successful mechanism of outcomes predictability can allow manufacturers to more accurately develop and implement outcomes-based agreements if such a payment model were desirable.

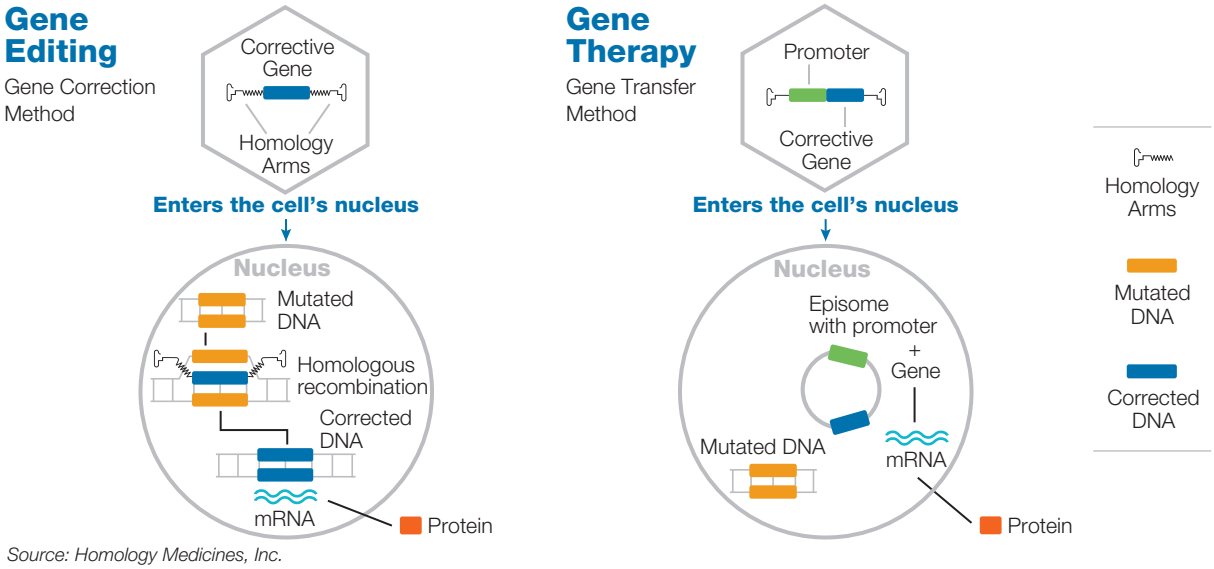
Figure 8: Outcomes predictability

Product	Manufacturer	Diagnostic regulatory status	First line monotherapy pivotal trial outcome
KEYTRUDA	Merck & Co., Inc.	Companion	Significantly greater response rates for high PD-L1 expressors
OPDIVO™	Bristol-Myers Squibb	Complementary	Failure to meet primary end point

3. **Increased need for focused, but flexible development platforms**: With higher stakes associated with order of entry of one-time therapies and potentially shorter peak sales phase, the ability to quickly shift development resources will become more valuable. Manufacturers will need to have deep domain knowledge of their platform and its attributes while maintaining a broad perspective on potential applications so that they can pivot quickly if a target disease area becomes less attractive for any reason such as increased competition.

   For example, Homology Medicines, Inc. has developed a platform based on human hematopoietic stem cell-derived adeno-associated virus vectors (AAVHSCs) with applications in both gene editing and gene therapy and the "potential to enable gene correction in a majority of diseases."[4]

Figure 9: Homology development platform

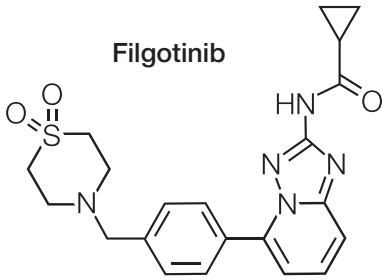


Source: Homology Medicines, Inc.

4. **Increased value of development partnerships and alliances**: Investing in partnerships with other development stakeholders such as academic research centers and other manufacturers will facilitate access to inorganic opportunities (e.g., licensing and asset acquisitions) and enhance speed to market.

   For example, Galápagos NV and Gilead entered into a global partnership in the development of the highly selective JAK1 inhibitor, filgotinib, which has potential benefits across multiple disease areas (e.g., RA, Crohn's disease, and ankylosing spondylitis).[5] As a clinical-stage biotechnology company, Galápagos NV can leverage Gilead's robust regulatory, manufacturing, and marketing capabilities to improve commercialization of the filgotinib asset. Learnings from this partnership will allow Galápagos NV to build a fully integrated infrastructure that supports their development platform.

Figure 10: Gilead and Galápagos NV partnership



Commercialization

Manufacturers of one-time therapies need to re-evaluate their commercial objectives and identify how best to allocate resources to compete in the emerging one-time therapy landscape.

5. **Re-evaluation of commercial team structure/size**: Due to the depletion of the pre-launch patient prevalent pool and the subsequent reduction in revenue, the structure and size of commercial teams must evolve for successful one-time therapy commercialization.

   Due to short revenue cycles, manufacturers will need commercial teams to ramp up and down more quickly to profitably launch their therapies. A portfolio strategy focused on a single therapeutic area or platform would be an advantage so a commercial team could launch multiple products before the team moves to other opportunities. Additionally, once the pre-launch prevalent patient pool is depleted, commercial teams will need to shift their focus to patient finding techniques that leverage data to direct field efforts.

   Furthermore, current roles in commercial organizations will need to be re-evaluated. For example, since many one-time therapies are administered at large centers of excellence, physician targets are likely to be clustered, meaning traditional sales resources such as field sales representatives and medical science liaisons may not be deployed in the same manner as they are for chronic therapies.

   Additionally, differences in the value chain of one-time therapies relative to chronic therapies may command a shift in investments. For example, one-time therapies may require substantially greater investments in distribution logistics, especially compared to pills used to treat chronic diseases.

6. **Elevated importance of product marketing and value communication**: Due to the finite patient pool and potential adoption of more outcomes-based agreements, the value of clinical evidence and a patient-centric marketing mix in driving commercial success in the form of traction and buy-in with key stakeholders will likely be greater for one-time therapies.

   To this end, manufacturers need to:

   - Develop and communicate the product value story early to ensure rapid formulary placement and reimbursement,
   - Identify the relevant key stakeholders and the most appropriate channels for reaching them, and
   - Engage the patient community to continually assess unmet needs.

7. **Entrance into novel strategic commercialization partnerships**: Successful commercialization of one-time therapies will require strong strategic partnerships with a variety of stakeholders; investing in the right relationships will likely be a significant determinant of success.

   Manufacturers need to simultaneously evaluate the role of current stakeholders in the emerging one-time therapy landscape (e.g., collaborating with payers on evidence needs for outcomes-based agreement ahead of launch), while also identifying new stakeholders that can facilitate speed-to-market and successful launches (e.g., centers of excellence with scientific expertise in one-time treatments that can help train physicians and drive adoption).

   Overall, identifying and investing in the strategic partnerships in line with manufacturer objectives will be more crucial for successful one-time therapy commercialization.

Recap

The recent entry of multiple one-time therapies is already placing the existing payer reimbursement model under pressure and altering the product lifecycle for manufacturers of one-time therapies. The unsustainability of today's reimbursement model will likely be exacerbated as more one-time therapies enter the market.

Consequently, manufacturers need to rethink their current approach to product development and commercialization in order to successfully compete in the future one-time therapy landscape where deferred payments, outcome-based agreements and/or pricing pressure become established norms, and the value of being early to market is greatly increased.

Positioning within this landscape will require changes to the current approach to developing and commercializing one-time therapies. Specifically, the rewards for investing in one-time therapies will accrue to manufacturers who:

- Are first/early to market,
- Identify the right patients for their therapies and demonstrate value through real-world evidence generation,
- Engage in strategic partnerships and alliances, and
- Consider innovative payment models and design their commercial teams to support business priorities.

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Notes

1 *EvaluatePharma*. Data from March 12, 2019.

2 Spark Therapeutics Announces First-of-their-kind Programs to Improve Patient Access to LUXTURNA™ (voretigene neparvovec-rzyl), a One-time Gene Therapy Treatment, Spark Therapeutics, January 3, 2018, news release, available at: http://ir.sparktx.com/news-re- leases/news-release-details/spark-therapeutics-announces-first-their-kind-programs-improve.

3 Jan Trøst Jørgensen and Karsten Bork Nielsen, "Companion and complementary diagnostics for first-line immune checkpoint inhibitor treatment in non-small cell lung cancer," *Translational Lung Cancer Research*, vol. 7, Suppl 2 (2018): S95-S99. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5943227/.

4 Technology Platform, Homology Medicines Inc., available at https://www.homologymedicines.com/technology.

5 Galapagos and Gilead Announce Global Partnership to Develop Filgotinib for the Treatment of Rheumatoid Arthritis and Other Inflammatory Diseases, Business News Wire, December 17, 2016, news release, available at https://www.businesswire.com/news/home/20151216006495/en/Galapagos-Gilead-Announce-Global-Partnership-Develop-Filgotinib.