

NEW DIGS

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Financing and Reimbursement
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RESEARCH BRIEF

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FoCUS Project
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Updated projection of US durable cell and gene therapies product-indication approvals based on December 2019 development pipeline. Ongoing pipeline modeling by the MIT NEWDIGS FoCUS team projects 10X growth from July 2020 levels, but with large uncertainties.

OBJECTIVE

The FoCUS Pipeline Analysis and Modeling (PAM) initiative seeks to estimate the potential impact of durable cell and gene therapies on the US healthcare system to inform stakeholder decision making to sustainably ensure appropriate patient access to these potentially transformative therapies.

METHODS

PAM uses a Markov Chain Monte Carlo approach with three main inputs: first, a snapshot of the therapy development pipeline including the candidate therapy and its development phase, and indication as defined by condition and genetic target; second, distribution estimates of development phase durations (to project the potential timing of approvals); finally, distribution estimates of development phase/approval success rates (to project the potential number of approvals).

DEFINING THE PIPELINE

Defining the included therapies precisely and transparently is critical. Qualifying therapies were those falling into the modalities below, and which produce or promise to produce durable effects beyond 18 months from treatment:

- Gene replacement therapies both in vivo and ex vivo using viral vectors
- T-cell receptors (TCRs) and immune cells engineered to incorporate chimeric antigen receptors (CARs)

KEY TAKEAWAYS

Using historical success rates and development times, we project that the durable cell and gene therapy pipeline as of December 2019 will yield:

60+ US product-indication approvals are likely by 2030.

- **24 non-oncology product indications** are likely to be approved from the existing clinical pipeline (i.e. excluding preclinical programs).
- **30 product-indications** (some currently in preclinical development) are likely to be approved for monogenic conditions, some of which are currently in development.

Therapies from China might grow the total to 90+ product indications if they seek FDA review.

The broad range of 40 – 90 possible 2030 cumulative product-indication approvals results from the significant uncertainties of both estimating development phase success rate and duration distributions and then using them in a Monte Carlo simulation.

- Gene editing therapies:
 - Zinc finger nucleases (ZFNs)
 - Transcription activator-like effector nucleases (TALENs)
 - CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats)
- Long-acting DNA plasmids

- Mesenchymal stem cell therapies and those utilizing unmodified tumor infiltrating leukocytes are not included in our forecasting set.

Our forecasting set comprises all identified qualifying therapies with active trials or preclinical activity commencing on or before December 31, 2019.

INPUTS

Pipeline snapshot

Therapies were identified primarily using therapeutic class and modality search criteria in the Citeline™ Pharmaprojects™ database¹. Further therapies were identified in the clinicaltrials.gov database using a combination of natural language processing and manual searches and extraction². Clinical trials registered on clinicaltrials.gov were identified where possible for all therapies of interest. Only interventional trials with a known status and development phase were included. Non-oncological therapies in advanced preclinical investigation were identified from the Citeline™ Pharmaprojects™ database for inclusion in our analysis.

Despite registering their trials on clinicaltrials.gov, we believe and assume that originators from China without an international partner or prior international products will limit their programs to local use. We therefore exclude those trials from the main analysis. (Figure 3 and Table 3 below show the scenario results of including originators from China.)

Estimating development phase durations

Because durable cell and gene therapies remain a relatively new and small field, trial duration distributions by development phase were estimated from a larger set of cell and gene therapies. These data were extracted from Pharmaprojects™ and clinicaltrials.gov in September 2018.

Reported start dates and primary end dates were the basis for estimating trial durations by phase: Phase 1, Phase 2 (including Phase 1/2), and Phase 3 (including Phase 2/3). Trials that had not reached a conclusion (completed, terminated or withdrawn) were discarded. Preclinical durations were estimated as the period from the date of first appearance on Pharmaprojects to the date of first clinical trial. Phase-specific distribution functions were used to determine the probability of a trial completing (successfully or not) in each time cycle.

Estimating development phase success

The probability of success distribution estimations for each clinical trial phase used the same extended sample of trials. Additionally, because many trials, particularly in oncology, may address multiple disease states, our sample space was expanded by considering each disease state addressed by such a trial as a separate trial: if a trial addresses lung cancer, breast cancer and colorectal cancer, for the purposes of estimating the probability of success, it is treated as three separate trials.

Each product and indication combination was treated as a distinct program. For each, any phase with at least one trial was identified.

For each such phase, success for the program was defined as (i) commencement of a trial of a more advanced phase or (ii) submission of a New Drug Application (NDA) or a Biologics License Application (BLA). Failure was defined by the absence of these conditions if no trials in the phase remain active. If there were active trials in a phase that has not met the definition of success, that phase for the development program was not included in the calculation of the success probability for that phase.

BRINGING IT ALL TOGETHER

A total of 1,057 development programs for product-indication combinations were included in the forecasting model; there were 586 disease & genetic target pairings and 184 diseases overall (genetic targets are typically antigens in oncology and genes otherwise.) These development programs include 232 preclinical gene therapies and 315 programs originating in China.

Our model uses a Markov Chain Monte Carlo process; within each of the 100,000 Monte Carlo iterations, the Markov state change calculated for each individual development program in each year culminating in either failure or an approval in a year.

For each development program, the year of approval (should it occur) is noted and then summed across all programs to create a product indication approval projection. 100,000 iterations run to create 100,000 independent pipeline projections.

RESULTS

The 100,000 PAM iterations generated the product-indication approval distribution shown in Figure 1. The median of the 100,000 distinct Monte Carlo projections is plotted as the black line.

The median PAM projection is for about 60 cumulative product-indication US approvals by 2030. The 95th percentile projection indicates 74 approvals while the 5th percentile projection indicates 52 approvals (Figure 1).

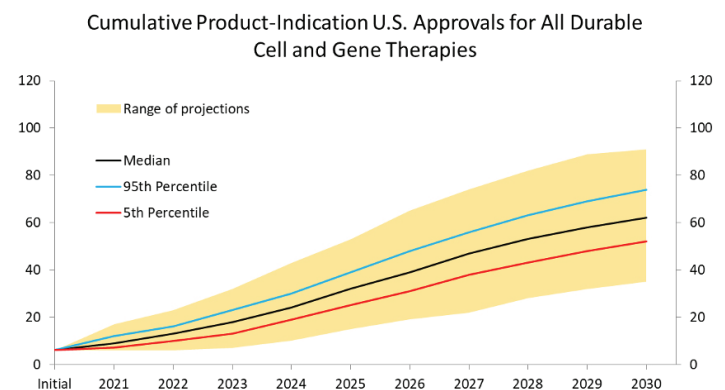


Figure 1. Cumulative (total) product-indication US approvals by year. Includes all conditions, excluding programs originating in China. A single product may receive multiple approvals such as a CAR-T receiving separate approvals for several cancer indications.

Product-indication approvals by therapeutic class are shown in Table 1. Hematological cancer therapies account for 45% of mean 2030 total approvals. All non-cancer therapies make up 52% of mean 2030 cumulative approvals.

	Initial	2021	2022	2023	2025	2030
Cancer, hematological	3	4.1	4.8	6.6	13.4	28.3
Cancer, solid tumor	0	0.0	0.0	0.2	0.7	1.8
Cardiovascular	0	0.0	0.0	0.1	0.1	0.3
Hematology	0	1.2	2.4	3.5	5.1	7.6
Immunological	0	0.0	0.2	0.7	1.6	2.9
Metabolic	0	0.1	0.4	0.9	2.4	6.5
Musculoskeletal	0	0.0	0.0	0.2	0.6	1.6
Neurological	1	1.3	1.5	1.5	2.0	4.2
Ophthalmological	2	2.6	3.2	3.8	4.8	6.7
Other	0	0.2	0.4	0.6	1.2	2.6
Total	6.0	9.6	13.0	17.9	31.9	62.4

Table 1. Mean cumulative product-indication US approvals by therapeutic class. Excludes local programs originating in China.

The subset of non-cancer, monogenic condition (primarily orphan diseases) approvals are shown in Table 2 and Figure 2. A high proportion of these approvals are for pediatric onset conditions – suggesting a need to expand the national newborn testing program to provide rapid, appropriate patient access.

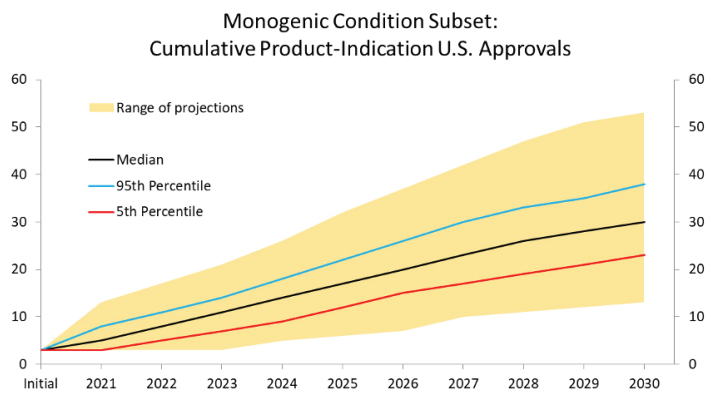


Figure 2. Cumulative (total) product-indication US approvals by year (monogenic conditions)

	Initial	2021	2022	2023	2025	2030
Cardiovascular	0	0.0	0.0	0.0	0.1	0.2
Hematology	0	1.2	2.4	3.4	5.1	7.6
Immunological	0	0.0	0.2	0.7	1.6	2.8
Metabolic	0	0.1	0.4	0.9	2.3	5.9
Musculoskeletal	0	0.0	0.0	0.2	0.6	1.5
Neurological	1	1.3	1.4	1.5	1.9	3.7
Ophthalmological	2	2.6	3.2	3.7	4.7	6.3
Other	0	0.0	0.1	0.2	0.7	2.0
Total	3.0	5.3	7.8	10.7	17.1	30.0

Table 2. Monogenic conditions subset: Median cumulative product-indication US approvals by therapeutic class. (Excludes programs originating in China).

STRUCTURAL UNCERTAINTY SCENARIOS

The main results above reflect the structural scope of the starting assumptions. Alternative scopes are imaginable.

Excluding preclinical programs due to uncertainty

First, the impact of excluding non-cancer preclinical programs was examined. The main results include these programs to estimate pipeline replenishment and new indication expansion. But these programs have highly uncertain success rates and preclinical durations. Excluding them may therefore produce a more conservative, lower forecast. Table 4 shows mean cumulative product-indication US approvals by therapeutic class when excluding preclinical programs. A comparison with Table 1 shows that around 25% of the non-cancer mean forecast approvals came from preclinical developments.

	Initial	2021	2022	2023	2025	2030
Cardiovascular	0	0.0	0.0	0.0	0.1	0.2
Hematology	0	1.2	2.4	3.4	5.0	6.8
Immunological	0	0.0	0.2	0.6	1.5	2.3
Metabolic	0	0.1	0.4	0.9	2.0	3.7
Musculoskeletal	0	0.0	0.0	0.1	0.5	0.8
Neurological	1	1.3	1.5	1.5	1.7	2.1
Ophthalmological	2	2.6	3.2	3.7	4.7	5.7
Other	0	0.2	0.4	0.6	1.0	1.6
Total	3.0	5.5	8.1	11.0	16.5	23.4

Table 4. Cumulative mean aggregate approvals of gene therapies by therapeutic class (excluding preclinical developments and programs originating in China).

INCLUDING PROGRAMS ORIGINATING IN CHINA

Second, consider the impact of including vs excluding the programs originating in China. Figure 3 and Table 3 show the product-indication approval forecast of approvals when those programs are included. Comparison with Figure 1 and Table 1 indicates that more than 91% of the overall increase in approvals comes from oncology (primarily CAR-Ts or TCRs) with 97% of that oncology increase coming from treatments for hematological cancers. Market saturation and patent issues may also limit the interest of the Chinese developers in the US market. Thus, while the model forecasts the potential for 30+ additional approvals, the upside may be far lower.

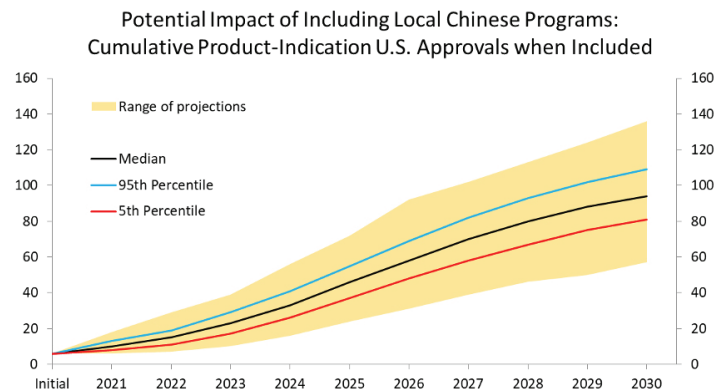


Figure 3. Cumulative (total) product-indication US approvals by year when including therapies originating in China.

	Initial	2021	2022	2023	2025	2030
Cancer, hematological	3	4.7	6.4	10.5	25.1	57.0
Cancer, solid tumor	0	0.0	0.1	0.3	1.1	2.6
Cardiovascular	0	0.0	0.1	0.3	0.5	0.7
Hematology	0	1.2	2.4	3.5	5.3	8.0
Immunological	0	0.0	0.3	0.7	1.9	3.4
Metabolic	0	0.1	0.4	0.9	2.4	6.5
Musculoskeletal	0	0.0	0.0	0.2	0.6	1.6
Neurological	1	1.3	1.5	1.7	2.4	5.0
Ophthalmological	2	2.8	3.6	4.2	5.3	7.3
Other	0	0.2	0.4	0.6	1.2	2.6
Total	6.0	10.4	15.1	22.8	45.8	94.5

Table 3. Cumulative mean aggregate approvals by therapeutic class (including therapies originating in China).

WHAT THIS MEANS

These PAM results suggest that while uncertain, the number of US approved cell and gene therapies by 2030 can be reasonably bounded. There is notable stochastic uncertainty in the estimates – but the greater factor is understanding the scope of programs being included in the model. The scope of the forecasting question and the estimation uncertainty of the parameters are both critical to interpreting these projections.

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