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Themed Section: Curative Therapies

Estimating the Clinical Pipeline of Cell and Gene Therapies and Their Potential Economic Impact on the US Healthcare System

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ABSTRACT

Objectives: To estimate, at the indication level, durable gene and cellular therapy new product launches in the United States through 2030, and the number of treated patients.

Methods: A statistical analysis of clinical trials pipeline data and disease incidence and prevalence was conducted to estimate the impact of new cell and gene therapies. We used Citeline's® Pharmaprojects® database to estimate the rates and timing of new product launches, on the basis of the phase of development, duration in phase, and probability of progression. Disease incidence and prevalence data were combined with estimates of market adoption to project the size of reimbursed patient populations.

Results: We project that about 350 000 patients will have been treated with 30 to 60 products by 2030. About half the launches are expected to be in B-cell (CD-19) lymphomas and leukemias.

Conclusions: Cell and gene therapies promise durable clinical benefit from a single treatment course. High upfront reimbursement for these products means that the total costs could exceed what the healthcare system can manage. This creates a need for precision financing solutions and new reimbursement models that can ensure appropriate patient access to needed treatments, increase affordability for payers, and sustain private investment in innovation.

Keywords: cell and gene therapies, drug pipeline, financing healthcare, managed care, pharmaceuticals.

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Introduction

A number of cell and gene therapies, also known as regenerative medicine advanced therapies in the United States and as advanced therapy medicinal products in Europe, are likely to achieve market authorization in the coming years. Hundreds are in development, across numerous indications, with various vectors and methods of administration. These treatments may provide significant—even curative—health benefits from a single administration, thereby improving patient outcomes over the long-term. Many will deliver significant multiyear benefits and some will need to recover substantial upfront development costs from a small number of eligible and treated patients, leading to expected comparatively high upfront single-dose prices—under many scenarios.[1]

Cell and gene therapies present a challenge to existing funding systems designed for reimbursement linked to the frequency and volume of product use; Sovaldi® (sofosbuvir)—although not a gene therapy—and Glybera® (alipogene tiparvovec) are recent examples of a short-duration or single-dose therapy delivering potentially lifetime benefits, and the subsequent uncoupling of the timing of the 2.[2,3] Currently, healthcare systems in the United States and Europe are actively considering this emerging challenge[4] but at varying speeds and in varying ways. For example, the National Institute for Health and Care Excellence in the United Kingdom is seeking to extend existing methods for assessing cost-effectiveness to regenerative medicines[5,6] and to recognize innovation at the same time.[7]

Cell and gene therapies can present financing challenges from different directions. First is the acquisition cost: currently, 2 chimeric antigen receptor T-cell (CAR-T) therapies have been approved—Gilead's Yescarta, for the treatment of relapsed or refractory large B-cell lymphoma, and Novartis' Kymriah, for the treatment of acute lymphoblastic leukemia. They have list prices of $373 000 and $475 000, respectively. Spark Therapeutics' Luxturna, indicated for the treatment of retinal dystrophy,[8] has a list price of $850 000 for a 1-time treatment[9]—although it should be noted that the therapies covered by this analysis will not have the same prices. Another dimension to the financing is that the healthcare system in the United States is not designed for curative, high-cost therapies.[10]

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The focus of the analysis presented in this article is the United States; the context for the cost and financing impact is therefore US payers. Generally, long-term benefit from chronic disease management is matched to smaller time-incremental increases in cost and benefit: how to manage $850 000, for example, for a covered person, where the benefit will come from a lifetime of vision, is not immediately apparent for payers in the United States.

In the United States today, there are known to be several proposed and implemented payment models and risk-sharing schemes.[2,11–13] The current clinical pipeline, however, is deeper than the small number of products currently on the market. Even allowing for trial failures, access restrictions, and so forth, there is a fear that enough new products, for enough patients, at high-enough list prices, will challenge the financial status quo in the United States and elsewhere.

Because of this, it is critical that we understand better what the scale of the potential problem will be. Specifically, of the current clinical pipeline, can we reliably predict the volume and timing of new product launches in the near term? With this, can we also predict the diseases and hence the size of the treated patient population? Being able to understand the scale of these 2 factors will provide the groundwork needed to predict the scale and the probable nature of the cell and gene therapy financing challenges facing payers in the United States.

The aim of this study was to understand the scale of new cell and gene therapies in the United States. The objectives were to estimate (1) the future cell and gene therapy product launches and penetration rate and (2) the predicted size of the eligible and treated patient populations for the products launched.

Methods

The overall design for the analysis is shown in Figure 1. The analysis presented here is based on quantitative modeling. Each iteration of the underlying Monte-Carlo model follows the process illustrated in Figure 1. Data on the existing trials pipeline of cell and gene therapies were extracted from different databases outlined herein, such as clinicaltrials.gov and the Surveillance, Epidemiology, and End Results (SEER) Program database. For use in the modeling process, these data were characterized by product, indication, and disease group. These data were to estimate the duration of each phase of trials and the likelihood of successful completion of each phase. In each iteration of the model, the progress of each drug was forecast on a year-by-year basis until its eventual failure or approval; when a drug was in trials for more than 1 disease, each disease was modeled separately. In the case of approval, data on treatment-eligible incident and prevalent patient populations, together with projections of the penetration rate for the product, were used to estimate the potential number of patients on a year-by-year basis. The results presented represent averages of product approvals, treatable patient populations, and financial burden taken over 10 000 iterations of the model.

Projected Product Launches

In forecasting the number of product launches, we start with the existing pipeline of cell and gene therapy trials. By this we mean the potential new products in development and their trials status (preclinical, phase 1, phase 2, phase 3, under regulatory review by the US Food and Drug Administration, or approved). By applying estimates of the time taken to progress through each level of trials, and probabilities of success (which we define as the probability that a product, on completing one level in the trials process, will initiate a trial at the next level), we forecast the success or failure of each trials program.

Data on the existing trials pipeline were drawn from a number of sources. We started with a sample of drugs from the Pharmaprojects® database from Citeline®[14]; data were filtered for cell and gene therapy on the basis of the plasmid DNA, viral vectors, human gene editing technology, and patient-derived cellular gene therapy products. We included gene replacement therapies, CAR-T therapies, CRISPR-Cas9/ZFN gene editing therapies, and siRNA therapies delivered via lentivirus or adenovirus. We excluded the following on the basis of focusing on durable, potentially curative therapies: siRNA therapies delivered naked, via liposomes, nanoparticles, or in bacteria; vaccines; mRNAs delivered via liposomes or nanoparticles; and oncolytic viruses. Data were extracted in October 2018 and were filtered first to include only active trials in the United States, and then to include only gene therapies as described. As a second stage we identified all drugs that targeted more than 1 disease and broke out each disease as a separate entity. Finally, we used

Figure 1. Schematic of process for predicting cell and gene therapy product launches and penetration rate.

Pharmaprojects, TrialTrove® (another Citeline database), and clinicaltrials.gov to identify trials associated with a particular drug and disease. From this search, we identified 628 products in the clinical pipeline for analysis. Trials were spread across more than 200 diseases, which were aggregated into 11 classes (see the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.014).

Estimates of the duration of the phases of clinical trials were obtained by examining samples of completed trials. From these samples, completion curves were derived for each phase of trials, relating time taken to complete a trial to the number of trials taking that amount of time. These were used probabilistically to forecast whether an active trial would be completed in the current year of forecast.

The same data set of completed trials was used to derive probable success rates for each phase of trials. These data were broken down into 4 groups for the purposes of forecasting: hematological cancers, solid tumors, gene therapies for orphan diseases, and gene therapies for higher prevalence diseases. For these purposes, an orphan disease was defined as one with a US prevalence of less than 200 000.[15] Each of these groups was found to have somewhat different characteristics, which are reflected in the parameters we use in the forecasting process. We should note that although there is a literature on trials success, the data used in their analyses are broadly based and tend to reflect the experience of traditional "small molecule" trials as opposed to those for gene and cell therapies.[16]

Projected Patient Population Size

Oncology data were obtained from the most recent SEER database.[17] For our purposes we defined the treatment-eligible population as those who would not survive 5 years after diagnosis. The most relevant therapies in this analysis are CAR-T and T-cell receptor therapies, which are most likely to be second-line and third-line treatments. Patients who survive longer than 5 years have generally responded well to first-line or second-line therapies. Those with relapsed or refractory disease represent the patient pool who might benefit from CAR-T or T-cell receptor therapies. On average these are about 30% of those diagnosed, although for individual cancers, the proportions range from more than 90% (for lung or pancreatic cancer) to less than 10% (for prostate cancer). The implication is that the potentially treatable pool in oncology is entirely incident—there is no prevalence.

Non-oncology, gene therapy data were obtained through targeted searches of published and online literature on diseases for each disease for which a gene therapy is in our trials pipeline. This is a multiphase process without the benefits of a single registry such as SEER. First, many conditions can be caused by any one of a number of genetic factors—for example, retinitis pigmentosa has more than 100. Most gene therapies, however, address only 1 such factor, and treatment eligibility would be limited to only those whose condition is caused by the specific genetic factor addressed by that treatment. There are also other patient-related factors that may vary by disease or treatment modality; for example, where adeno-associated viruses are used as the delivery vector, the existence of antibodies may eliminate a patient from eligibility. Age may also play a part as might disease severity: some treatments are considered to be suitable only for adults, whereas others may not be appropriate for the aged. In some conditions, only severe cases might be considered for treatment. All these factors, and others in specific instances, go into deriving the expected pool of treatment-eligible patients.

Projected Penetration Rates

Once launched, new products will have market penetration established on the basis of adoption, which comprises 2 factors: the maximum penetration rates achieved for incident cases, including the time taken to reach that ceiling, and the maximum proportion of prevalence cases to be "cleared," and the time taken for that. In diseases with poor prognosis (eg, aggressive cancers), there will be very little backlog because few patients survive. Many cell and gene therapies in development, however, are targeted at chronic conditions. Both uptake and clearance are expected to be lower than 100% because of factors such as other non–cell and gene therapy products in the market, payer-imposed access restrictions, or individual willingness to try new-to-world treatments relative to existing alternatives.

Adoption and market penetration cannot be known reliably for some time for cell and gene therapies. In addition to insufficient real-world data, historical data make a poor foundation for forming assumptions because they will not include cell and gene therapies. Our analyses were based on assumptions that are flexible, but in the base case are maximum penetration rate of new incident cases of 90% in total for all products in an indication, with a 2-year ramp-up to that ceiling from the time of the first product's launch; maximum penetration rate of prevalent cases (the "backlog") of 70%, also in total for all products in an indication with a 5-year time frame to clear. These assumed base-case parameters were formed jointly by the authors, including the MIT NEWDIGS FoCUS Writing Group. The differential penetration rates for incident and prevalent cases reflect a decline based on access restrictions, patient deaths, or other factors that reduce eligibility. The explicit access restriction of all erstwhile eligible patients is a limit on access that reflects (1) access restrictions (eg, by payers, but also clinician prescribing, etc) and (2) likely narrowing of indications relative to what were broad indications listed in clinical trials databases.

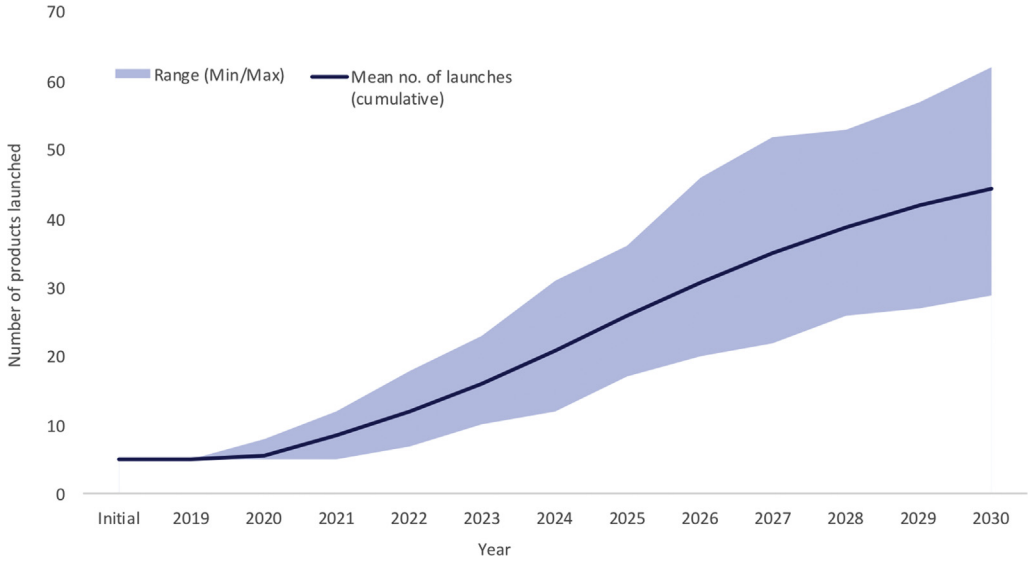
Results

The Citeline Pharmaprojects database provided a pipeline of 628 active, individual, US-based clinical trials programs for durable gene and cellular therapies comprising 211 indications, 335 preclinical studies, 91 phase I studies, 174 phase II studies, and 19 phase III studies. A breakdown of these is shown in the Appendix in Supplemental Materials. The main study results are shown in Figure 2, displaying the rise of total product launches along with the minimum and maximum. The ranges correspond to the most and the least restrictive assumptions. On the basis of our estimated success rates and trial lengths, this pipeline would be expected to lead to between 40 and 50 launches by 2030, with about 12 launching within the next 5 years. Over the duration of the forecast, about half the launches are expected to be in B-cell (CD-19) lymphomas and leukemias.

In total, we project that about 350 000 patients will have been treated with 30 to 60 products by 2030; in 2030, about 50 000 patients per year may be treatable with cell and gene therapies. There is, however, a wide range around estimated eligible patient population numbers largely because of the number of factors involved. Results in terms of annual treated patient population sizes are shown in Figure 3, along with 95% confidence intervals representing variation across all diseases for eligible patient population sizes.

Both the incident and prevalent cases are shown in Figure 3. There is a lump apparent in the prevalent patient population size, reflecting the clearance of the backlog; slightly earlier is the

Figure 2. Predicted cumulative product launches, 2018-2030.



notable increase in incident patients treated as the adoption rate reaches the maximum.

Treated population projections were undertaken at the individual disease level. Tables 1 and 2 present the estimated number of product launches and treated patients aggregated into disease groups: hematology, cardiovascular, immunological, infectious disease, metabolic, musculoskeletal, neurological, hematological cancer, solid tumor cancer, and "other" diseases without an obvious aggregating group. In total, about 350 000 patients will have been treated with up to 60 products by 2030. In 2030 itself, about 50 000 patients per year may be treated with cell and gene therapies.

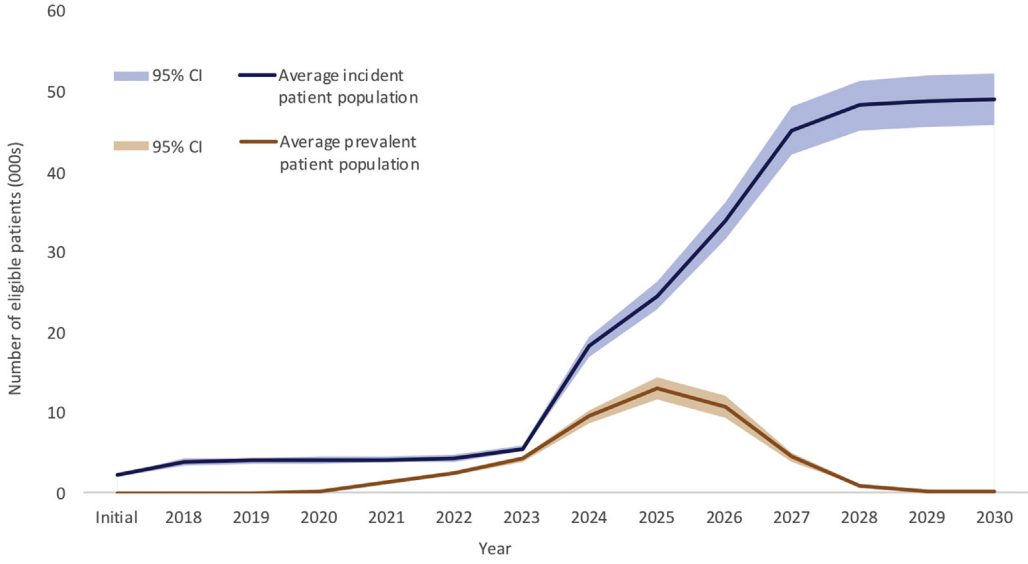
The biggest development can be seen in cancer and hematology; treated patient populations, however, are driven more by total population sizes, but also by the number of prevalent cases. Hematological cancers, for example, have poor prognosis and relatively few prevalent cases; in contrast, hematological and musculoskeletal diseases have higher treated patient populations. In the case of musculoskeletal diseases, this is despite having among the fewest new products launched.

Discussion

The results presented here show that from any given static point, it takes several years for new products to launch, and longer for the total scale of treatments to emerge and stabilize. This is an important result to be understood within the context of existing fears about the total cost impact, and timing of that impact, of cell and gene therapies.

The basis of our analysis of treating the eligible patient population bears some consideration when interpreting the

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



CI indicates confidence interval.

Table 1. Cumulative product launches per year by disease group, 2018-2030.

Indication	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
All indications	*5.0*	*5.6*	*8.4*	*11.9*	*15.9*	*21.2*	*26.4*	*31.1*	*35.7*	*39.5*	*42.8*	*45.4*	*47.3*
Hematological cancer	3.0	3.2	3.6	5.0	7.0	9.6	12.5	15.1	17.5	19.5	21.2	22.4	23.4
Solid tumor cancer	0	0	0	0	0.1	0.3	0.4	0.6	0.8	1.0	1.1	1.2	1.3
Cardiovascular	0	0	0	0.2	0.3	0.4	0.5	0.6	0.6	0.7	0.7	0.8	0.8
Hematology	0	0.1	0.9	1.4	2.0	2.6	3.2	3.7	4.2	4.5	4.9	5.2	5.4
Immunological	0	0	0	0	0	0.1	0.1	0.2	0.3	0.4	0.4	0.5	0.5
Infectious disease	0	0	0	0	0	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2
Metabolic	0	0	0	0.1	0.2	0.5	0.8	1.1	1.5	1.9	2.2	2.4	2.6
Musculoskeletal	0	0	0.2	0.3	0.3	0.6	0.8	1	1.2	1.3	1.4	1.5	1.6
Neurological	0	0.2	0.9	1.5	1.9	2.1	2.3	2.4	2.6	2.8	3	3.2	3.3
Ophthalmological	2	2.1	2.5	2.9	3.4	4.0	4.6	5.1	5.5	5.8	6	6.2	6.3
Other	0	0	0.3	0.5	0.7	0.9	1.1	1.2	1.4	1.5	1.7	1.8	1.9

results. Because we established a ceiling on effective penetration rates, when referring to Tables 1 and 2, we should understand that this is the total penetration rate of all products. That is, in hematological cancers, we see up to 20 000 patients treated cumulatively by 2030 even though, at this point, about 25 products are estimated to have been launched.

This is because the penetration rate applies to the patient population, not the product, with 1 product used in the entire patient population; with 25 products, each product is used in 1/25th of the patient population—but the same total number of patients is treated. This is critical to understand as people seek to better predict the scale and timing of costs of cell and gene therapies; the scale and timing of new product launches is a critical factor, but arguably the more important driver of those costs will be the specific products/indications and the patients treated.

A second important characteristic is that it will be the intersection of products and patient population sizes that ultimately determine the scale of the impact. Many products launching in relatively small diseases will not have the impact that a few products launching in very large diseases will have; Sovaldi is a commonly used example of the latter in particular.[2,18–20] At the same time, the limits on eligibility, uptake, and penetration are likely to be more rigid in large diseases. Although horizon scanning activities for the United States exist, typically the focus is limited to the drug pipeline and not the analysis of the likely successful launches or impact.[21,22] Nevertheless, it remains that understanding the indication and how narrow it is, and the potential restrictions on eligibility and how narrow they might be, is a key component of any analysis.

The third important factor to consider is that the list price is a known point of anxiety with cell and gene therapies. Nevertheless, many will be introduced in diseases with very costly current standards of care, for example, hemophilia, which has costly care related to managing bleeds, providing factor VIII replacement, and so forth, or cancer, where stem cell transplants and expensive drugs may be displaced. In addition to the value that the durability and efficacy of cell and gene therapies will generate, cost offsets will again be a dynamic effect that could limit the ultimate cost impact and there is very little current knowledge from which to draw estimates. A range as simple as average list prices of $500 000 to $4 million per product, for example, leaves hematological cancer treatment costs of between $12.5 billion and $100 billion, which is a significant range.

There are limitations to the analysis, which inescapably relied on many assumptions. An important assumption

Table 2. Number of cumulative treated patients by disease group, 2018-2030.

Indication	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
All indications	*4086*	*8133*	*12 276*	*17 700*	*24 608*	*34 388*	*62 183*	*99 849*	*144 545*	*194 195*	*243 446*	*292 592*	*341 775*
Hematological cancer	3977	7958	11 940	15 922	19 904	24 765	38 680	53 802	69 728	85 773	102 209	118 714	135 222
Solid tumor cancer	0	0	0	0	0	0	0	0	2702	11 896	21 489	31 098	40 707
Cardiovascular	0	0	0	0	0	0	0	183	970	2461	4552	7001	9503
Hematology	0	0	0	15	309	916	1558	1944	2153	2325	2493	2661	2829
Immunological	0	0	0	0	0	0	0	0	0	8	27	52	79
Infectious disease	0	0	0	0	0	0	0	0	0	0	0	0	0
Metabolic	0	0	0	0	6	1356	4277	7005	8189	8677	9096	9528	9951
Musculoskeletal	0	0	0	0	0	0	0	0	0	0	0	0	0
Neurological	0	0	65	1056	3023	5338	15 080	33 810	57 333	79 306	99 412	118 791	138 104
Ophthalmological	110	175	227	278	334	532	873	1213	1406	1501	1576	1649	1722
Other	0	0	44	429	1032	1481	1716	1893	2066	2248	2591	3098	3659

underlying the analysis is that the clinical pipeline is not replenished. In reality, this will not be the case; nevertheless, there is no basis, nor data, for projecting the future clinical pipeline—in terms of products alone, but also the indications in which future development may occur. To attempt to do so would increase substantially the uncertainty in the out-years. Therefore, this analysis is a "snapshot": the current status of the clinical pipeline, rolled out over a 10-year time horizon; new products entering discovery and development would require a longer time horizon than this.

The clear assumptions applied around penetration rate and adoption timelines have been considered. Others, though, underlie most of the parameters listed in Figure 1. Correctly narrowing down the specific reimbursed indication is also a limitation, for example, estimates for oncology assume treatment of relapsed/refractory disease only. To some degree, these limitations have been mitigated by incorporating disease-specific data, particularly around cancer and noncancer data.

Conclusions

Our analysis suggests that by 2030, up to 60 new cell and gene therapies could be launched, treating an expected 350 000 patients cumulatively and about 50 000 patients per year. This is, on the face of it, not an imposing number relative to the US population, or to all disease incidence and prevalence. Nevertheless, this should be considered against the projected prices and total treatment costs of many of these new therapies, which are expected to exceed current average acquisition costs of treatments currently and could create a financial crisis. The interplay of long-term treatment value and the upfront cell and gene therapy costs on the one hand, and access restrictions on the other hand, create a need to consider novel financing options. The MIT NEWDIGS FoCUS Project has been developing precision financing solutions with a broad consortium of stakeholders to mitigate these challenges. The actual product launches and patient uptake will determine the scale of the affordability and financing challenges that payers in the United States will need to face over the next 10 years. We recommend that analyses like these be calibrated continuously and validated against real-world launch data as the clinical pipeline and the cell and gene therapy landscape evolve.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.03.014.

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