Paying for Cures
How to use the Individual Indication Workbook

The individual Indication Worksheet provides a step-by-step approach to the financial management of a specific durable cell or gene therapy (CGT). The workbook contains four distinct worksheets:

Population Estimator
- Estimates incidence and prevalence by plan size and type.

Market Adjustment
- Adjusts population estimates to those that likely will be treated.

Therapy Impact Model
- Projects financial impact to your plan.

Solution Prioritization Tool
- Matches finance tools to organizational needs.

Once you select a specific disease for analysis, the worksheets build upon each other to suggest potential financial tool(s) that may facilitate patient access and financial stability. The worksheets include a limited description of inputs and required data. Additional detail and background are provided below for enhanced understanding.

Population Estimator

The population estimator tool allows you to determine the incidence and prevalence of patients within your plan for a condition that may be treated by CGT.

Step 1: Indication selection

Cell and gene therapies are categorized by therapeutic class, disease, and subpopulation. The options presented represent diseases and subpopulations with CGT products that have been FDA-approved or are in clinical trials. Subpopulations are defined by the gene of interest in the clinical trial. If "ALL" is selected as the subpopulation, the worksheet will present data for all individuals with the condition. If a specific gene is used to identify the subpopulation, the incidence and prevalence numbers on the worksheet will be limited to those with the gene of interest for which there is one or more products in development.

For purposes of this worksheet, incidence includes the onset of a disease as well as the 'tipping point' of a condition for CGT treatment. For example, the CAR-T therapies are currently used as

a cancer treatment after other courses of treatment have been tried and failed. Incidence numbers for the CAR-T therapy are projected based on numbers of individuals with the cancer for whom other treatments have not worked; they have reached a 'tipping point' to treat with a CAR-T therapy.

Step 2: Payer type adjustment

The incidence and prevalence numbers provided in step 1 are based on the demographics of the total US 2020 census population (General Population). The Population Estimator tool allows for further segmentation by Medicare, Medicaid, or Not Medicare or Medicaid. Commercial plans, self-funded employer benefits, the Veterans Administration, Federal Employee Health Benefits, correctional health services, Tricare, the uninsured, Indian Health Services, and all other categories of lives not included in Medicare or Medicaid are represented by "Not Medicare or Medicaid."

Incidence and prevalence differ by payer types, as select diseases are more commonly associated with the age demographic characteristic of Medicare or Medicaid. For example, cancers are more frequently found in those over age 65 while genetic orphan diseases are often diagnosed at birth, an age demographic of Medicaid. These distributions are approximations, however, as age distributions by disease are not available outside of the SEER cancer registry. Selecting a payer type does provide a better representation of incidence and prevalence estimates for the tool user.

Step 3: Population size adjustment

This section of the Population Estimator Tool allows you to use FoCUS's clinically relevant incidence and prevalence estimates by payer type, applying simple population ratios to get the potential number of patients in your plan for individual product indications. Table 1 presents the number of lives by payer category. Worksheet users should apply the number of lives by each line of business for the best results.

Table 1 Lives by Payer Category for Population Model

Payer Category	Lives based on US 2020 census
Medicaid	70,225,000
Medicare	63,200,000
Not Medicaid or Medicare	198,075,000
US Population	331,500,000

Market Adjustment

The Market Adjustment Tool will help you assess the number of patients meeting FDA label treatment criteria that will likely be treated with CGT products. Numerous factors beyond treatment eligibility will influence a product's use. Treatment decisions based on the disease severity, alternative treatments, insurance coverage, and/or other factors heavily influence the CGT's market penetration. The speed of adoption of the new cell or gene therapy is influenced by many of these same factors, as well as market adoption factors that are similarly seen with chronic disease treatments.

Step 1: Market penetration adjustment

Market penetration refers to the number of individuals likely to be treated, divided by the number of treatment-eligible individuals. In practice, the 'likely to be treated' population is expected to be smaller than the 'treatable' population.

For diseases with severe consequences, the likely treated/treatable percentage is anticipated to be high, subject to any challenges in identifying appropriate patients. For diseases with less severe or more long-term consequences, only a small percentage of eligible patients may be treated. Using an appropriate modifier is vital for any analysis, as the total eligible population may substantially overestimate the number of patients treated.

There is no simple way to anticipate an appropriate market penetration percentage, unfortunately, as market penetration is influenced by multiple factors that will vary in significance by disease. The Market Adjustment tool provides disease-specific data for select factors that will influence market penetration.

- Age at onset; is the diagnosis in infancy, nearing the end of life, or in between?
- Impact on life expectancy; can an individual live with the disease or is life expectancy greatly shortened?
- Therapeutic options; are there alternative treatments? Are they sufficiently effective?
- Therapeutic costs; will the overall cost of care be lessened by the new treatment?
- Symptoms; how do the symptoms impact the quality of life for the patient? What is the impact on the patient's family as caregivers, if any?

Market penetration will be a disease-specific percentage as used in the FoCUS pipeline analysis model unless modified in this section of the worksheet. Modifying the percent of patients seeking treatment will adjust the plan specific incidence and prevalence rates.

Illustration of Market Penetration Adjustments:

Spinal Muscular Atrophy, Type I, Medicaid plan of 500,000 lives

Your Medicaid plan of 500,000 lives has been projected to encounter 135 newly diagnosed patients each year.

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Therapeutic class	Disease	Sub population	Total US Incidence Estimate	Total US Prevalence Estimate
Neurological	Muscular atrophy, spinal	SMN1	270	160
			Incidence - Medicaid	Prevalence - Medicaid
		Plan Type Medicaid	135	80
		Plan type rate per 100,000 lives	0.2	0.1
500,000		Plan specific patient volumes	1.0	0.6

The workbook will present variables that impact speed and extent of market penetration and adoption for SMA1 CGT:

Muscular atrophy, spinal			SMN1	
Age at onset	Impact on life expectancy	Therapeutic options	Therapeutic Cost (annual)	Symptoms
Genetic (SMN1) Type 1 - birth Type 2 - infancy Type 3 - 18 months - adolescence Type 4 - early adulthood	 Type 1 - 1-2 years Type 2 - early adulthood Type 3 - normal Type 4 - normal	Spinraza (nusinirsen) Zolgensma (onasemnogene abeparvovec-xioi) Evrysdi (risdiplam)	$375,000 ($750,000 first year), then $340,000, $2,100,000 $100,000 - $340,000 (<15lb - 44lb)	Atrophy of skeletal muscles

You would consider the following questions in adjusting the market penetration percentage:

1. To what degree would the therapy's impact on life expectancy promote product demand?
2. To what degree would symptom severity and impact on quality of life promote product demand?
3. To what degree would inadequate alternative treatments or high costs for current standard of care promote product demand

Your assessment determines:

- The disease is life threatening.
- The gene therapy is potentially curative.
- Alternative therapies are not curative.
- The prevalence of the disease is low due to potential mortality.

The default market penetration rate was 90% for incidence and 80% for prevalence. Based on your knowledge of payers and providers in the community, you adjust the rate to 100% for incidence. You adjust prevalence to 50% based on the assumption patients forgoing treatment upon diagnosis may have special circumstances for delaying treatment.

Sickle cell disease, Medicaid plan of 500,000 lives

Your Medicaid plan of 500,000 lives has been projected to encounter 504 newly diagnosed treatment eligible individuals each year. Your plan is projected to be providing health benefits to over 6,000 treatment eligible individuals living with sickle cell disease.

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Therapeutic class	Disease	Sub population		Total US Incidence Estimate	Total US Prevalence Estimate
Hematology	Sickle cell disease	HBB		792	12,825
				Incidence - Medicaid	Prevalence - Medicaid
			Plan Type Medicaid	504	6,075
			Plan type rate per 100,000 lives	0.7	8.7
500,000			Plan specific patient volumes	3.6	43.3

The workbook will present variables that impact speed and extent of market penetration and adoption for sickle cell disease with a genetic defect of the HBB gene:

Sickle cell disease			HBB	
Age at onset	Impact on life expectancy	Therapeutic options	Therapeutic Cost (annual)	Symptoms
Genetic (HBB, BCL11A) Diagnosis:	54 years	Prophylactic penicillin up to age 5 Hydroxyurea, blood transfusion Allogeneic bone marrow transplantation Endari (L-glutamine) Adakveo (Crizanlizumab) Oxbryta (Voxelotor)	$322-$2,251, $? $892,700 $14,571-$43,714 $36,770-$147,082 (20kg-80kg) $165,240	Anemia, repeated infections, periodic episodes of pain

You would consider the following questions in adjusting the market penetration percentage:

1. To what degree would the therapy's impact on life expectancy promote product demand?
2. To what degree would symptom severity and impact on quality of life promote product demand?
3. To what degree would inadequate alternative treatments or high costs for current standard of care promote product demand

Your assessment determines:

- The disease lowers life expectancy.
- Individuals living with the disease have alternative treatments available.
- Quality of life is limited by symptoms
- Prior damage to organ systems cannot be reversed with treatment.

The default market penetration rate was 80% for incidence and 75% for prevalence. Based on your knowledge of payers and providers in the community, you maintain the penetration rate at 80% for incidence. You adjust prevalence to 70% based on your organization's cost of claims per year for sickle cell patients is below the national average, suggesting good clinical management with current therapies.

Cancer, B-cell lymphoma, Medicare plan

The FoCUS model for market penetration analysis cannot be applied to cancer products in the pipeline due to variability in the age of onset, treatment options, etc. Therefore, the workbooks' market penetration analysis for these diseases will display:

> *"The degree of variability in patient demographic and disease profiles nullifies the ability to use the market penetration concepts applied in gene therapy for this indication."*

FoCUS advises you to apply your own assumptions for defining a market penetration rate.

Step 2: Uptake/adoption curve adjustment

The product uptake or adoption curve reflects how quickly patients are likely to be treated and will receive treatment. The default assumption is that 100% of likely-to-be-treated patients are treated each year. Step 2 in the worksheet allows the user to alter that assumption and adjust for local

market conditions that may impact the speed of uptake, such as payer coverage decisions, provider availability, local market access, etc.

If the worksheet's default disease specific assumption is applied to market penetration, only newly diagnosed patients will be treated in subsequent years. Alternatively, you may customize a ramp-up rate of treatment by indicating the percentage of incident patients that will be treated each year until 100% of the market penetration rate is met. Incident patients that are not treated in the year of their diagnosis are added to the prevalent population. You can set the treatment rate for the pool of prevalent patients by defining the number of years it would take to treat the entire prevalent population. You may modify the number of individuals remaining eligible in the prevalent pool year to year. One reason to modify the individuals remaining untreated in the prevalent pool to less than 100% may be if a disease has a high mortality rate.

Therapy Impact Modeling Tool

The Therapy Impact Modeling Tool leverages the information from the Population Estimator and Market Adjustment Tools to estimate the potential financial impact of the selected therapy on your business. It lays out a) the estimated cost of therapy in aggregate and PMPM by year, b) the 'likely maximum cost' at the 5% and 95% model intervals, and c) the cost of treating one patient (important for smaller plans that infrequently have these patients).

Step 1: Therapy cost assumptions

Step 1 of the model addresses cost inputs. Users may assess the costs of the therapy alone or may bring in additional considerations such as additional costs, cost offsets, and contract-related adjustments.

Product cost: The default for product cost depends on the model's assignment of the product into one of seven therapeutic categories. The costs for each category are based on observations of current market prices where available. If no existing CGT comparable exists, the model uses prices from existing treatments for this condition. Table 2 provides the default price categories. You may override the default cost assigned within the worksheet.

Table 2 Default price points for therapy impact modeling

Therapeutic Category	Price per patient treated
Ultra-orphan	$2,500,000
Orphan	$800,000
Ophthalmological (genetic)	$800,000
High prevalence	$500,000
CAR-T/TCR	$400,000
Ophthalmological (non-genetic)	$100,000
Osteoarthritis	$50,000

Associated costs: Associated costs expand the financial impact of a new CGT product. Potential costs include pre-therapy preparation and work-up, post-therapy care, travel costs, etc.

Contract-related adjustments: Various contract arrangements may potentially offset payer costs for the therapy. Such offsets include rebates and secondary insurance (stop loss or reinsurance) payments. The modeling tool provides an area for entering funds that offset costs. You should consider how the timing of offset payments may impact financial management of costs.

Step 2: Financial risk assessment

This section of the worksheet provides the annual cost of the therapy in aggregate and as a per member per month (PMPM) cost based on the adoption rate and cost assumptions entered into the model. The worksheet reports the 95th percentile of patient volumes, therapy costs, and PMPM in order to illustrate the 'likely maximum cost.' Finally, the cost of treating one patient (important for smaller plans that infrequently have these patients) is presented as total cost and PMPM impact for the plan.

Patient volumes and corresponding financial impacts will vary with the disease incidence and prevalence. You can freeze results within the worksheet to an even distribution of lives. You can also recalculate the values to give insight into the likely range of actuarial volatility.

Solution Prioritization Tool

The Solution Prioritization Tool is intended as an aide to help you narrow the Precision Financing Solutions identified by the FoCUS Consortium for addressing different financing risks. It asks you to consider the expected financial impact of the therapy and your organization's preferences in managing the cost. Based on the assessment choices you make; the Solution Prioritization Tool will suggest potential preferred financing solutions.

Step 1: Payer financial assessment

The worksheet's questions ask you to consider the three key areas of risk for CGT – Actuarial, Payment Timing, and Performance. Yes or no responses to these questions will reflect your concerns for considering your organization's perspective of risk.

Step 2: Needs determination and potential solutions

Building on the considerations in step 1, the three questions in step 2 will drive recommendations of potential financial models that fit your organization's cost management strategy for the selected gene or cell therapy.

A table in this worksheet lists the financial solutions and considerations for implementing each solution. Your organization may or may not have the internal capabilities to move forward with the potential solution. Building these capabilities internally may not be efficient for all payer organizations to serve patients or to establish contracts with treating providers and developers. Market solutions are emerging to efficiently address these required capabilities. Based on the service you require, FoCUS has created a Supplier Evaluation template to aid in obtaining that service.

ABOUT FOCUS

The Tufts Medical Center NEWDIGS consortium FoCUS Project (Financing and Reimbursement of Cures in the US) seeks to collaboratively address the need for new, innovative financing and reimbursement models for durable and potentially curable therapies that ensure patient access and sustainability for all stakeholders. Our mission is to deliver an understanding of financial challenges created by these therapies leading to system-wide, implementable precision financing models. This multi-stakeholder effort gathers developers, providers, regulators, patient advocacy groups, payers from all segments of the US healthcare system, and academics working in healthcare policy, financing, and reimbursement in this endeavor.

About NEWDIGS

The NEW Drug Development ParadIGmS (NEWDIGS) Initiative at Tufts Medical Center is an international "think and do tank" dedicated to delivering more value faster to patients, in ways that work for all stakeholders. NEWDIGS designs, evaluates, and initiates advancements that are too complex and cross-cutting to be addressed by a single organization or market sector. Its members include global leaders from patient advocacy, payer organizations, biopharmaceutical companies, regulatory agencies, clinical care, academic research, and investment firms.

For more resources and tools to help you make cell and gene therapies accessible and sustainable systemwide, visit **newdigs.tuftsmedicalcenter.org/payingforcures**