TRIANGLE INSIGHTS GROUP by Valerís

Biopharmaceutical forecasting has never been more complex-or more critical-as companies face unprecedented policy volatility, evolving diagnostic and access landscapes, and rapidly intensifying competition across therapeutic areas. This three-chapter series brings together Triangle Insights Group's latest perspectives on how to build forecasts that are credible, defensible, and strategically actionable.

Triangle Insights Group (TIG) has published a series of articles that address:

» How shifting payer behavior and evolving legislative dynamics are reshaping market access assumptions

» Methodologies for rare disease forecasting, where archetype-driven approaches help manage high uncertainty and small-data environments

» Strategies for establishing early differentiation in crowded oncology landscapes, where positioning can influence value as much as clinical outcomes

Together, these perspectives provide a practical playbook for forecasting in an era where uncertainty is the norm-helping teams anticipate change, strengthen decision-making, and uncover opportunity across some of the most complex markets in healthcare.

Forecasting Rare Disease: The Benefits of a Market Archetype Approach

Seizing Early Advantage in a Crowded Oncology Market

Forecasting Through an Uncertain Access Environment: Building Credible, Defensible Assumptions in a Volatile Policy Era

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Forecasting Rare Disease:
The Benefits of a Market Archetype Approach

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NOVEMBER 2025

WHITE PAPER

Introduction

Forecasting the commercial potential of rare disease assets is high stakes. Small differences in assumptions have an outsized impact on forecasted revenues due to small patient populations. Unique rare disease forecasting challenges include:

- **Limited Published Epidemiology:** Existing prevalence estimates are often outdated and subject to sample bias (e.g., based on advocacy cohorts or centers of excellence), which can over- or under-represent undiagnosed, less engaged, or milder patient segments. In many cases, estimates capture only a subset of a heterogeneous disease, limiting their utility for commercial planning
- **Evolving Diagnosis & Treatment Dynamics:** Rates of diagnosis and treatment can shift rapidly in response to new product launches, updated clinical guidelines, heightened provider awareness, and expanded access to genetic or biomarker testing. These fluctuations complicate forecasting and require continuous assumption validation
- **Influence of Access Dynamics:** The access environment (e.g., payer policies, site-of-care limitations, infrastructure constraints) can materially accelerate or constrain uptake. Small changes in coverage criteria or utilization management can meaningfully alter the realized patient population

These challenges make it difficult to develop a credible picture of today's diagnosed and treated populations and tomorrow's addressable opportunity. Forecasts must not only interpret and reconcile fragmented literature and claims data but also anticipate how patient awareness, diagnostic pathways, and activation strategies will evolve.

Key questions include:

- *What is the true size of the addressable patient pool? What share remains undiagnosed, concentrated in centers of excellence, or sitting on the sidelines due to lack of effective treatment?*
- *Where are patients dropping out of the journey, and why? Is it during the diagnostic odyssey, accessing specialists, adopting advanced treatment, or continuing with treatment?*
- *Which strategic levers, whether through awareness, diagnostic support, patient activation, and/or evidence generation, will be essential to unlock growth and drive the commercial opportunity?*
- *How might payer behavior (e.g., outcomes uncertainty, UM, evidence expectations) create inflection points that can be incorporated into modeling accurately and at the correct time?*

Without addressing these questions rigorously, forecasts may be misaligned with strategy, complicating alignment on asset value and organizational resourcing.

Market Archetype Approach to Rare Disease Forecasting

Approaching rare disease forecasting from an archetype approach allows us to focus assumptions and sensitivities on the core levers relevant to the target indications.

Diagnosis-Limited Archetype

Key characteristics:

- Misdiagnosed or undiagnosed due to low awareness or limited access to diagnostics, often with no specific diagnostic code available
- Even when diagnosed, patients often absorb the burden of educating their care team
- May be genetically driven but are often later onset and less severe in presentation
- Symptomatic patients are managed with generics or intensive self-care routines

Core Challenge:
Estimating the latent patient pool and modeling how awareness campaigns, diagnostic tools, and referral pathway improvements can expand the market.

Illustrative Analogs

- **Transthyretin amyloidosis (ATTR):** Awareness and noninvasive diagnostic tools (PYP scans, genetic testing) dramatically increased diagnosed prevalence once effective therapies emerged
- **Alpha-1 antitrypsin deficiency (AATD):** Growth has been driven by targeted HCP education and expanded screening programs
- **Lysosomal storage disorders (e.g., Fabry, Pompe):** Also historically underdiagnosed, newborn screening and genetic testing has expanded identified patients

Constrained Growth Archetype

Key characteristics:

- Established diagnosed population based on genetic testing, or clear diagnostic criteria
- Uptake constrained by lack of screening, utilization in subsets, or access restraints
- Health system capacity constraints related to gene therapy adoption (e.g., center accreditation, bed availability, conditioning regimen, historic failures)

Core Challenge:
Developing high impact strategies to counter constraining forces and modeling impact on adoption

Illustrative Analogs

- **Duchenne muscular dystrophy (DMD):** Although most patients are identified through established diagnostic pathways, early therapies demonstrated limited efficacy, and payer skepticism regarding cost–benefit slowed adoption and constrained initial market growth
- **Spinal muscular atrophy (SMA):** The introduction of gene and antisense therapies rapidly expanded the treated population; while newborn screening and access barriers initially constrained uptake, these challenges have largely been mitigated over time
- **Sickle-cell disease (SCD):** Newborn screening has increased diagnosis rates, but adoption of gene therapies remains limited by treatment infrastructure, access constraints, and uncertainty around long-term outcomes, while other therapeutics face hurdles related to dosing burden, modest efficacy, and payer resistance

Mature Market Archetype

Key characteristics:

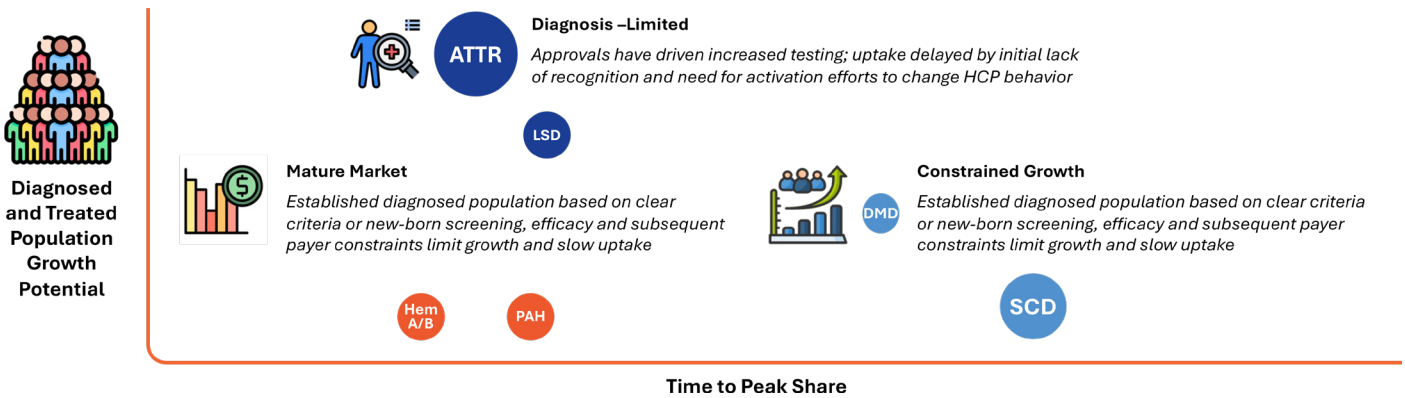
- High diagnosis and treatment rates driven by long-standing awareness, established diagnostic pathways, and multiple available therapies
- Market growth driven primarily by differentiation among late entrants rather than expansion of the patient pool
- Rebate walls and formulary entrenchment can create payer challenges for late entrants attempting to define differentiation

Core Challenge: Identifying credible levers for differentiation - improved tolerability, convenience, combination potential, or evidence in underserved patient subsets - to capture share in a well-defined market

Illustrative Analogs

- **Pulmonary arterial hypertension (PAH):** A mature market shaped by decades of commercial activity; late entrants are primarily differentiated through novel delivery modalities (e.g., oral, inhaled) and combination strategies. Growth has plateaued as most eligible patients are already treated
- **Hemophilia A/B:** A market with near-universal diagnosis and well-established care infrastructure. Successive innovation waves have emphasized treatment convenience and durability, with uptake delayed as HCPs and payers awaited real-world evidence from switching studies and indirect treatment comparisons
- **Paroxysmal nocturnal hemoglobinuria (PNH):** Soliris (Alexion) defined the market; later entrants like Ultomiris leveraged extended dosing intervals and improved convenience rather than new patient growth, while biosimilar and complement-pathway competition now focus on pricing and administration advantage

Figure 1. Rare Disease Market Growth and Penetration by Archetype



The Triangle Insights Group Approach: Building a Defensible, Insights-Driven View of Rare Disease Opportunity

Capturing value in rare disease markets requires more than epidemiology and optimism. At Triangle Insights Group, we blend quantitative rigor, analog-driven benchmarks, and strategic commercial insight to build a credible, investor-ready view of a commercial opportunity as well as a roadmap to realize it.

Our approach translates ambiguity into advantage, delivering actionable outputs that connect forecast potential directly to launch strategy, resource allocation, and organizational focus:

- **Patient Journey & Diagnostic Pathway Mapping:** Granular analysis of where patients fall out of the journey, who influences progression, and what interventions can accelerate diagnosis and treatment, enabling smarter investment and higher yield on activation spend
- **Commercial Opportunity Assessment and Forecasting:** Robust models that synthesize published epidemiology, real-world claims, and registry insights,

  all pressure-tested through relevant analogs to anticipate growth trajectories, adoption dynamics, and barriers to uptake. Outputs include realistic adoption curves and evidence-based assumptions informed by targeted market research
- **Market Access landscape:** Enabled by our proprietary Policy Reporter database, identifies detailed review of access policies for the competitive set and/or analogs to understand relationship between clinical data package, label, pricing, and utilization management likely to influence product positioning and market share
- **Commercial Lever Prioritization & Launch Roadmap:** A quantified view of which levers matter most and when. We provide a prioritized roadmap to focus commercial resources where they will drive measurable acceleration in adoption and unlock full market value

In rare disease, opportunity is defined not only by the asset, but by the ecosystem. This is inclusive of diagnostics, infrastructure, payer behavior, awareness, and real-world evidence. Triangle Insights helps clients see that ecosystem clearly, forecast credibly, and invest intelligently.

Organizations seeking to strengthen their rare disease strategy, validate market potential, or prepare for launch are encouraged to engage with our partner team. Reach out to learn how Triangle Insights can offer customized support for strategic needs in rare disease and adjacent therapeutic areas.

Figure 2. From Data to Direction: A Rare Disease Commercial Assessment Framework

TRIANGLE INSIGHTS GROUP by Valerís

Seizing Early Advantage in a Crowded Oncology Market

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WHITE PAPER

Introduction

The oncology landscape is expanding at an unprecedented pace. Major scientific breakthroughs are opening new frontiers and simultaneously crowding the pipeline. Forces driving this surge include:

> **Newly druggable targets**. KRAS, once considered undruggable, now has more over 50 inhibitors in development, transforming a single target into one of the most competitive spaces in oncology.

> **Rapid expansion of antibody-drug conjugates (ADCs).** Over 430 ADC clinical trials are active worldwide, creating intense clustering across solid tumor indications.

> **Proliferation of rare driver-mutation therapies.** Programs initially designed for rare driver mutation subpopulations are expanding through pan-tumor strategies, multiplying competitors across tumor types.

> **Acceleration in next-generation immunotherapy.** More than 100 bispecific antibodies—many engaging CD3 to drive T-cell activity—are in testing, adding another wave of mechanism-level competition.

Together, these advances are blurring traditional lines of differentiation. With multiple agents pursuing similar mechanisms, late entrants in particular face steeper hurdles to define where they fit and why they matter.

Analogs Analysis: Differentiation of late entrants

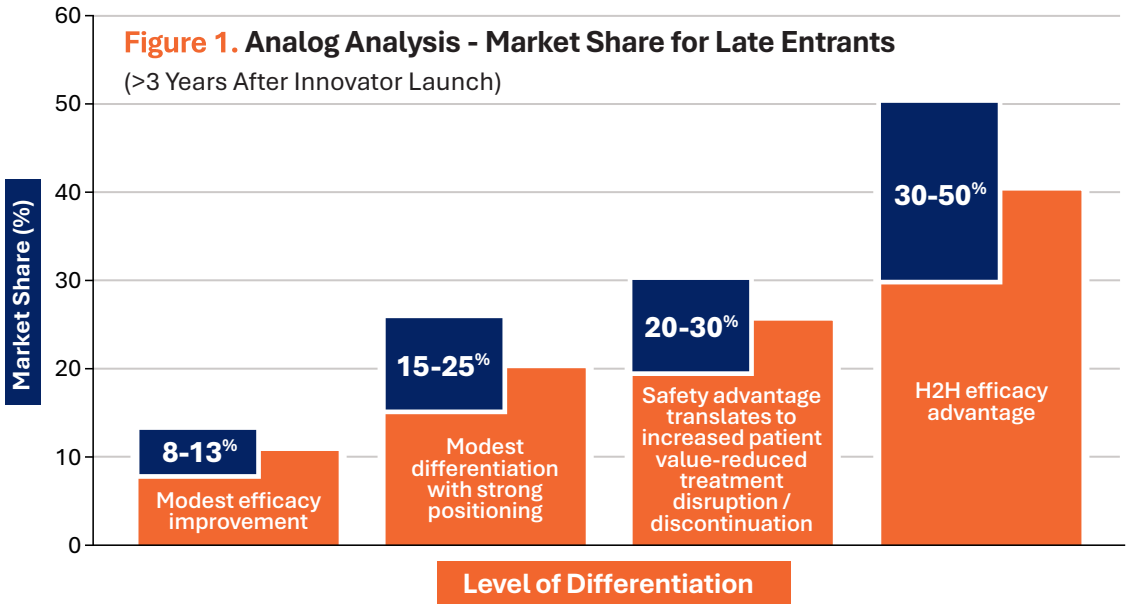
Efficacy proven in H2H studies versus a timely, relevant standard of care

When efficacy differences are modest, head-to-head data against the current standard of care become essential. Alecensa (alectinib) demonstrated superiority over crizotinib in ALK-positive NSCLC driving rapid adoption and dominant market share. In contrast, Alunbrig (brigatinib) entered later with demonstrated improvement over crizotinib, but not meaningfully challenge alectinib, which had become the reference treatment.

Safety and tolerability linked to treatment continuity

A clear safety advantage can shift share when it enables patients to stay on therapy longer without compromising efficacy. Calquence (acalabrutinib) cut rates of atrial fibrillation nearly in half versus Imbruvica (ibrutinib) and reduced discontinuations due to adverse events by nearly 7%. This tangible link between tolerability and outcomes drove Calquence adoption.

Even when a late entry doesn't offer a major jump in clinical outcomes, success is still possible—but it increasingly depends on how well the product is positioned, requiring a compelling story for key opinion leaders and payers, and effective communication of the commercial narrative. In a crowded indication where the outcome gains may be more incremental, marketing and positioning become the accelerant for share capture.



Early Pipeline Agents: Claiming Positioning Drives Value

Early-stage oncology companies demonstrate that deliberate, visible positioning—highlighting target, patient population, and potential differentiation—can generate investor confidence, attract clinical attention, and accelerate market awareness well before regulatory readouts.

Revolution Medicines (RVMD) — Strong positioning drives $11 B valuation
Revolution Medicines' lead asset, daraxonrasib, targets multiple RAS mutations. By positioning itself as tackling historically "undruggable" cancers with broad potential, the company has commanded a market cap of over $11 B even before pivotal trial results.

Nuvalent (NUVL) — Early narrative elevates valuation vs. peers
Nuvalent is developing next-generation ROS1 and ALK inhibitors. Even in early clinical stages, strong messaging around CNS penetration, resistance profiles, and potential differentiation has helped the company achieve a valuation of ~$6.7 B—roughly four times higher than Nuvation Bio (~$1.6 B), which has a marketed ROS1 therapy.

Merus N.V. — Clear positioning leads to multi billion-dollar acquisition
Merus focused on its bispecific antibody petosemtamab for head-and-neck cancer, emphasizing a high-need indication with promising early data. The company's visible positioning narrative contributed to an ~$8 B acquisition before commercialization.

TIG Approach to Early Positioning

Early positioning is critical for success in crowded oncology markets. TIG's approach combines deep competitive insight with structured cross-functional alignment to ensure assets claim meaningful territory before pivotal readouts.

Figure 2. From Data to Direction: An Oncology Assessment Framework

1 Competitor Positioning Map

Objective: Identify the white space and crowded positioning territories where early positioning and evidence generation will be required.

Methods: Intensive analysis of competitor data, commercial messaging, and medical narratives

Output: Competitor Positioning Map.

2 Asset Differentiation and Positioning Territory

Objective: Understand the differentiating features to inform clinical and commercial messaging and shape the narrative for market and investor audiences.

Methods: Analyze the client's asset to identify unique attributes and the potential benefits they provide relative to the competitive set.

Output: Early positioning statement

3 Evidence Priorities

Objective: Building from desired positioning territory, identify evidence generation and publication strategies to ensure ownership of white space and competitive areas

Method: Collaborative cross-functional workshops

Output: Evidence generation priorities designed to support the ideal positioning and strengthen the value proposition

By combining competitor insight, asset differentiation, and cross-functional alignment, TIG ensures that early-stage oncology programs can strategically claim positioning territories, guide evidence generation, and maximize both investor and clinical interest well ahead of regulatory milestones.

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Forecasting Through an Uncertain Access Environment – Building Credible, Defensible Assumptions in a Volatile Policy Era

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WHITE PAPER

Introduction

Pharmaceutical forecasting has always required navigating uncertainty, but today's access environment introduces a level of volatility that fundamentally changes how assumptions must be built, stress-tested, and communicated. Emerging legislation, shifts in payer behavior, and new commercial models—spanning the IRA, O3B Act proposals, MFN frameworks, direct-to-consumer discounting, and cash-pay channels—are just a few of the many factors reshaping how products are priced, reimbursed, and adopted.

Forecasts that once relied on historical analogs or stable policy norms now require explicit scenario planning and meaningful policy fluency. Triangle Insights Group (TIG) uses an approach grounded in continuous tracking of legislation and payer policy, disciplined methods for translating those signals into forecast inputs, and proprietary data from Policy Reporter that connects historical policy patterns to emerging access dynamics. The result is a forward-looking and defensible forecast that anticipates and quantifies variability rather than reacting to it.

The Access Environment Has Entered a New Phase of Volatility

Several structural shifts are now directly influencing pricing, coverage, UM, and uptake:

Channel/distribution shifts

Channel control (white bagging, brown bagging, site-of-care mandates) along with mandates for direct-to-patient models, particularly in categories with high out-of-pocket burden (e.g., dermatology, obesity, migraine) directly impact gross-to-net. These models, along with alternative purchasing models (e.g., Walmart, Amazon, Cost Plus), introduce uncertainty in channel mix, patient behavior, and payer response—requiring scenarios that explore where net revenue may erode or accelerate.

IRA: Structured uncertainty and evolving negotiation thresholds

While IRA timelines are known, the drivers of final negotiation outcomes remain fluid. Forecasters must consider therapeutic-area dynamics, competitive density, indicative analog discount trends, and early CMS interpretation signals. Rather than treating IRA as a fixed assumption, TIG builds bounded scenarios informed by past negotiation patterns and category-specific precedent.

Tariffs and MFN pricing proposals

Tariffs on APIs, evolving trade policies, and periodic reintroduction of MFN models influence list price strategy, global reference pricing, and gross-to-net erosion. We track these shifts as they emerge and translate them into probability-weighted pricing paths.

Evolving payer behavior

Shifts in 340B expansion, Medicaid/ACA coverage, and payer consolidation and integration affect both time-to-access and the intensity of UM. These behaviors must be understood within their policy context and tested for how they shape RWE needs, coverage quality, step edits, and adherence.

TIG's Methodology: Translating Policy Signals into Forecast Inputs

TIG pairs real-time policy monitoring—powered by our proprietary Policy Reporter database—with structured forecasting methods that convert evolving legislation, payer actions, and access signals into measurable assumptions. This ensures the forecast reflects the access reality a product will face, not a hypothetical landscape.

Using Policy Reporter, we anchor assumptions in how payers and regulators are behaving today. Active legislation, benefit design changes, Medicaid dynamics, and channel steering trends are translated into quantitative inputs that shape the forecast's core assumptions.

TIG focuses on four access levers most likely to influence performance:

1. Coverage & Restrictions: Anticipated formulary placement, PA criteria, step edits, and how these evolve with shifting policy pressure.
2. Channel Utilization: Movement between medical and pharmacy benefit, cash-pay and DTC dynamics, and how Medicaid policy influences site-of-care and access points.
3. Patient Affordability: Cost-sharing rules, accumulator/maximizer activity, and state affordability programs that influence adherence and persistence.
4. Rebate & Discount Pressure: Policy-driven contracting constraints, evolving payer demands, and the net pricing environment.

We model baseline and alternative scenarios—such as tightening Medicaid rules, increased channel steering, or affordability mandates—to show how different policy trajectories shift uptake, adherence, and net revenue. This produces a forecast that is analytically rigorous and grounded in real-time policy intelligence.

Forecasting in a Policy-Volatile Era

Today's access environment demands forecasts that are flexible, transparent about uncertainty, and built with deep policy fluency. TIG combines:

- Real-time policy and payer monitoring
- Proprietary Policy Reporter analytics
- Disciplined, scenario-based modeling
- Cross-functional forecasting expertise

to help clients build forecasts that are credible, adaptable, and resilient—even as the access environment changes faster than traditional forecasting cycles can keep up.

Case Example: Using Payer Management Archetyping to Strengthen Forecast Assumptions

A top-20 pharmaceutical company sought to understand how a novel, new-to-market asset would be managed in a highly competitive therapy area—an essential input for building their launch forecast.

TIG collaborated with the client to identify analog products with parallel pricing strategies, evidence profiles, and competitive pressures. Using Payer Management Archetyping (PMA) and Policy Reporter data, we evaluated for each analog:

- Formulary restrictions across payers, channels, and integrated MCO/PBMs
- Approved vs. rejected claims and how these differed by archetype
- Evolution of payer restrictiveness as markets matured
- Unexpected disconnects between high restrictiveness and low claims rejection (and vice-versa)

The analysis revealed surprising variance across specific payers and channel-integrated entities—variance that would have materially altered early uptake assumptions had it not been identified.

By integrating PMA findings into the forecasting workstream, the client was able to:

- Re-segment accounts based on actual behavior rather than broad payer categories
- Adjust access and GTN assumptions for high-risk archetypes
- Refine early uptake curves to reflect likely UM intensity
- Align pricing, value, and PIE strategies ahead of launch

The result was a far more defensible forecast, with access assumptions grounded in historical behavior rather than generic expectations.