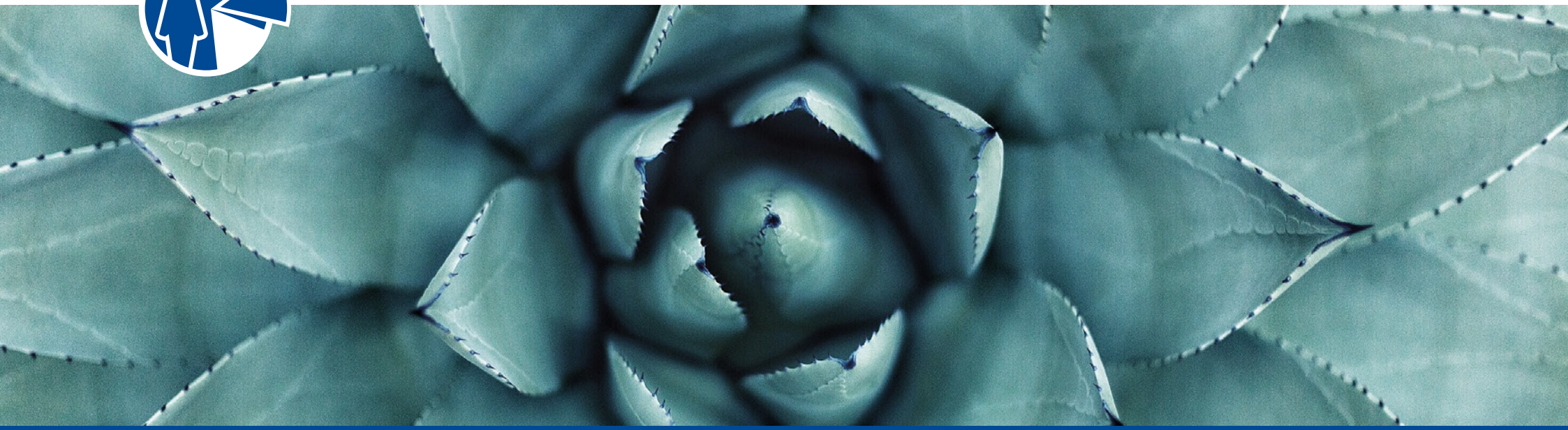
REAL-WORLD ANALYTICS GROUP

Cytel
Shaping the Future
of Drug Development



Innovative Data Science and Real-World Analytics Approaches in Practice

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Deriving Value from the Data Revolution

We are now at the center of a perfect storm where a combination of forces is driving a transformational shift in how drugs are ultimately developed and accessed by patients.

With the rise in digital technologies, there has been an explosion in volume and type of data sources we can obtain from social media data and mobile apps, to wearable sensors and electronic health records and insurance claims data. This data could yield a more robust and complete picture of diseases, the patient journey, and the effectiveness of interventions in the real world to make better drug development, reimbursement, and clinical decisions. However, apart from accessing and curating this data, we also need to harness advanced analytical techniques including sophisticated statistical methods, machine learning, and artificial intelligence to realize the full potential of the opportunity and unlock the insights from this data.

New data sources bring new data dynamics to exploit such as real-time streaming of data, greater longitudinal patient records over time, and of course larger, more representative patient population data. Yet, alongside the opportunities, the new data sources bring inherent challenges to be overcome including lack of standardization, missing data, and variation in quality.

Against this backdrop, is the drive of regulators , notably the FDA with its 21st Century Cures Act,[1] to promote innovative approaches and 'accelerate the discovery, development, and delivery of 21st-century cures'. In 2018, the Framework for FDA's Real-World Evidence Program[2] was launched to explore the use of real-world data and evidence and build an understanding of new data sources and techniques and their fitness for decision-making. The INFORMED initiative[3], described as an "incubator for collaborative oncology regulatory science research" draws on a multi-disciplinary group of experts- from oncologists to statisticians to establish organizational and technical infrastructure for big data analytics and investigate novel evidence generation methods for use in regulatory decision-making.

Despite the promise, there remains a lack of widespread understanding of how data science techniques applied to real-world and other data can be used in practice by sponsors to drive better outcomes. In the 2018 paper "From hype to reality: data science enabling personalized medicine," Frolich et al.[4] articulate the disconnect between the industry discussions about the potential of data science and analytical approaches to transform healthcare, and the applications we see in practice. The authors write, "While during recent years there has been a lot of enthusiasm about the potential of 'big data' and machine learning-based solutions, there exist only few examples that impact current clinical practice. The lack of impact on clinical practice can largely be

attributed to insufficient performance of predictive models, difficulties to interpret complex model predictions, and lack of validation via prospective clinical trials that demonstrate a clear benefit compared to the standard of care."

As technology, data, expertise, and investment in this area continue to unfold, future financial sustainability in pharma is dependent on the ability to utilize data as a critical asset to deliver augmented intelligence in decision-making across the value chain and to leverage advanced analytics/cognitive approaches.

An essential step to moving the data science and real-world evidence promise towards a reality where we can benefit patients is enhancing collaboration and knowledge-sharing.

Advanced analytics applied to complex, large datasets can inform smarter study design and better execution in clinical development from biomarker identification, protocol optimization, physician targeting, patient recruitment, and external control arms. In the world of medical affairs, harnessing real-world data also has enormous potential to demonstrate effectiveness beyond randomized controlled trials from pragmatic clinical trials (PCTs), HEOR support, value demonstration, and formulary placement.

On the following pages, you will see examples of how Cytel's data science and real-world evidence groups have helped clients apply advanced analytical techniques to large, complex historical or real-world data sets to improve their decision-making, accelerate development pathways, and enhance their probability of success.

THE CASE STUDIES

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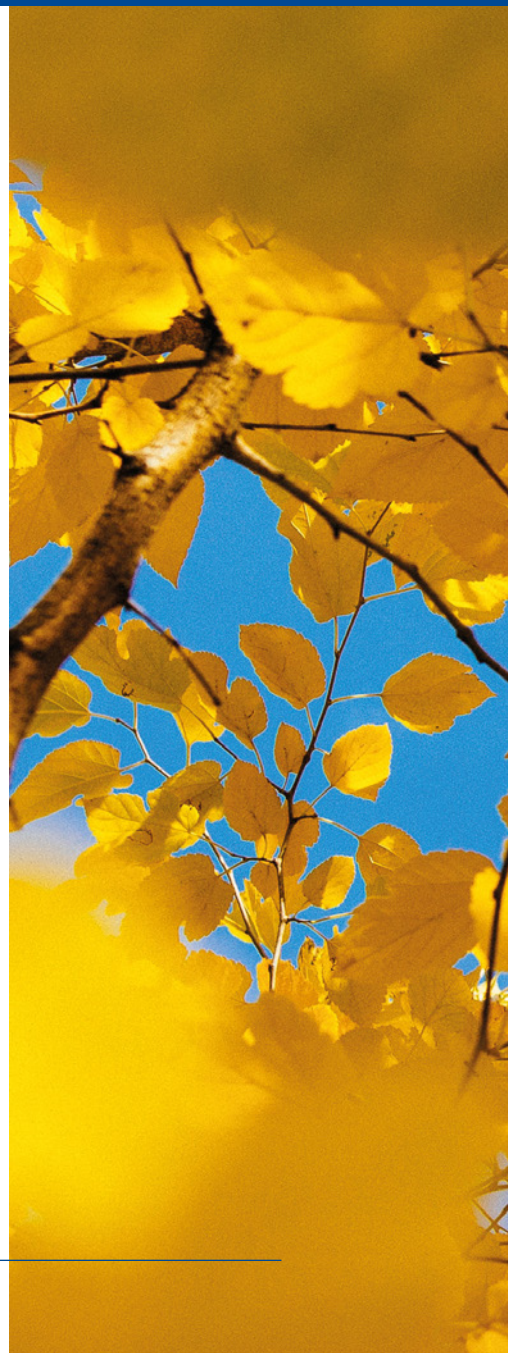
SYNTHETIC CONTROLS: UNLOCKING THE PROMISE OF HISTORICAL AND REAL-WORLD DATA



In place of collecting data from patients recruited for a trial who have been assigned to the control or standard-of-care arm, a synthetic control creates a comparator arm using either real-world datasets such as electronic health records or previous clinical trials. The synthetic control offers a practical, effective way to leverage real-world evidence and has been applied in regulatory approvals.

Development Challenge

Our customer is a specialized biopharmaceutical company, developing novel oncology therapies. Their breakthrough therapy had the potential to be first-in-class for a rare and aggressive hematological cancer and had shown great potential in earlier clinical trials. In areas of high unmet need, it is critical to bring vital new medicines to patients faster, yet conventional development pathways involving multiple stages can be slow, expensive, and inefficient.

In many breakthrough treatment areas, where the patient population is small, or there is overwhelming evidence of efficacy at Phase 2, it has become common for drugs to be approved based on a pivotal single arm trial – however, this is not always optimal. With this in mind, our customer planned a registration pathway based on a single arm registrational study with a comparison to a synthetic control.

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Cytel Solution

Creating a synthetic control requires advanced statistical expertise to effectively distribute the baseline characteristics between the synthetic control arm and the arm receiving the experimental treatment. The client acquired databases from 2 leading cancer centers and planned to combine it with data from 2 earlier clinical trials to form a retrospective trial as a comparison to one of their single arm pivotal trials. They approached Cytel to help identify the best statistical and analytical methods and deliver the analysis based on the acquired real-world data.

Data Cleaning and Curation

- Combine, clean and standardize datasets from the two purchased oncology databases and the two prior clinical trials for the retrospective analysis.

Analyses for Pivotal Trial

- Summarize the data from the cleaned and pooled retrospective dataset
- Divide single arm trial data and retrospective dataset into six groups (by refractory category and ECOG status) and perform a weighted average
- Propensity score matching with bootstrap confidence intervals to equalize the groups and examine the average treatment effect
- Increasingly complex propensity score matching using AIPWCC estimators for survival analysis producing Kaplan-Meier type graphs adjusted for covariates

Analysis for Regulatory Responses and Health Economic Insights

- Create different analyses over the course of several months to respond to EMA regulatory requests
- Examine numbers of post-refractory treatments to inform health economic insights

Outcomes

The outcomes from the analysis showed that the experimental treatment yielded a significant improvement in Objective Response Rate and complete response vs. Standard of Care, Life expectancy increased from 6 months to several years.

The analysis was instrumental in achieving regulatory approval for the experimental treatment and brought a vital new medicine to patients.

LEVERAGING CLAIMS DATA TO SUPPORT COMPETITIVE POSITIONING OF MULTIPLE SCLEROSIS (MS) THERAPY

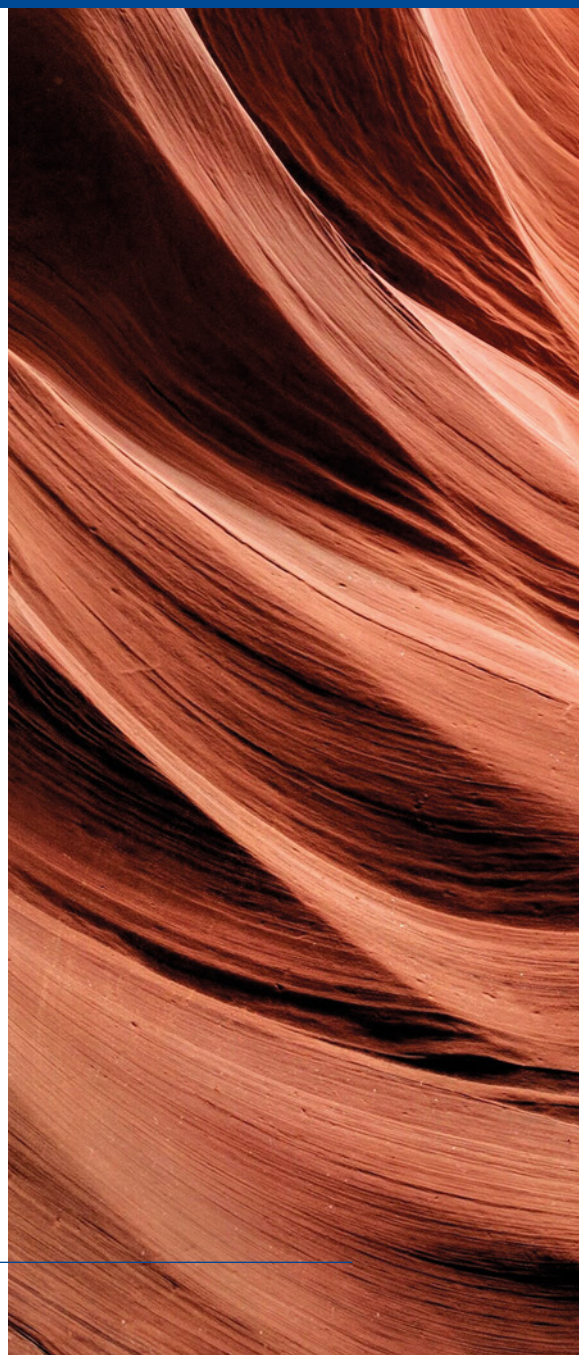
Claims data provides a valuable opportunity to researchers to build a better view of the patient journey, and an understanding of therapy effectiveness in the real world. However, claims data can be complicated and to analyze effectively, organizations need to have the right combination of domain knowledge, technology, expertise to understand the data structures, interrelations, and how the claims data is generated.[5]

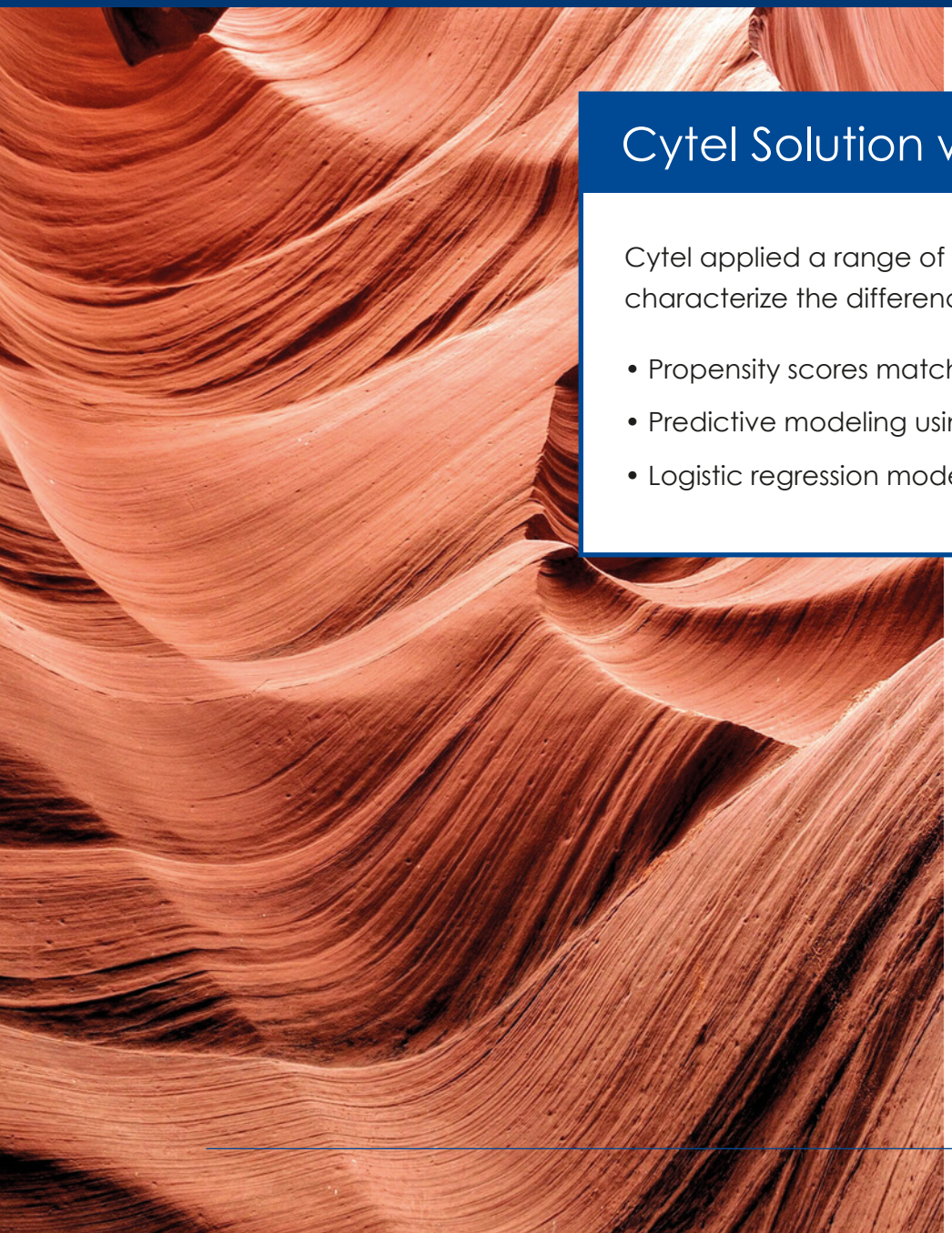
Development Challenge

Healthcare providers are seeking information on the real-world utilization of Interferons (INFs) to inform their use of a specific class of Disease Modifying Therapies (DMTs) to manage relapsing-remitting Multiple Sclerosis.

Our client needed to compare the effectiveness of their therapy versus a competitor in the real world to inform their discussions with payers and support the pricing of their marketed product.

They approached Cytel to conduct a retrospective, observational cohort study of patients identified in the Truven MarketScan® Commercial claims database. The objective of the study is to compare the effectiveness of the client's therapy vs. a competitor by measuring the reduction in relapse and disability progression in relapsing-remitting MS.





Cytel Solution with Advanced Analytical Expertise

Cytel applied a range of techniques to the claims data to produce the analysis and characterize the differences between treatment:

- Propensity scores matching
- Predictive modeling using patient-level information
- Logistic regression modeling

Outcomes

This approach was a more cost-effective and faster solution than conducting a traditional post-marketing observational study.

The client identified differences in effectiveness between their therapy and the alternative in the real-world setting, enabling them to influence payers and justify the pricing.

Abstracts were submitted and accepted for key thought leadership conferences.

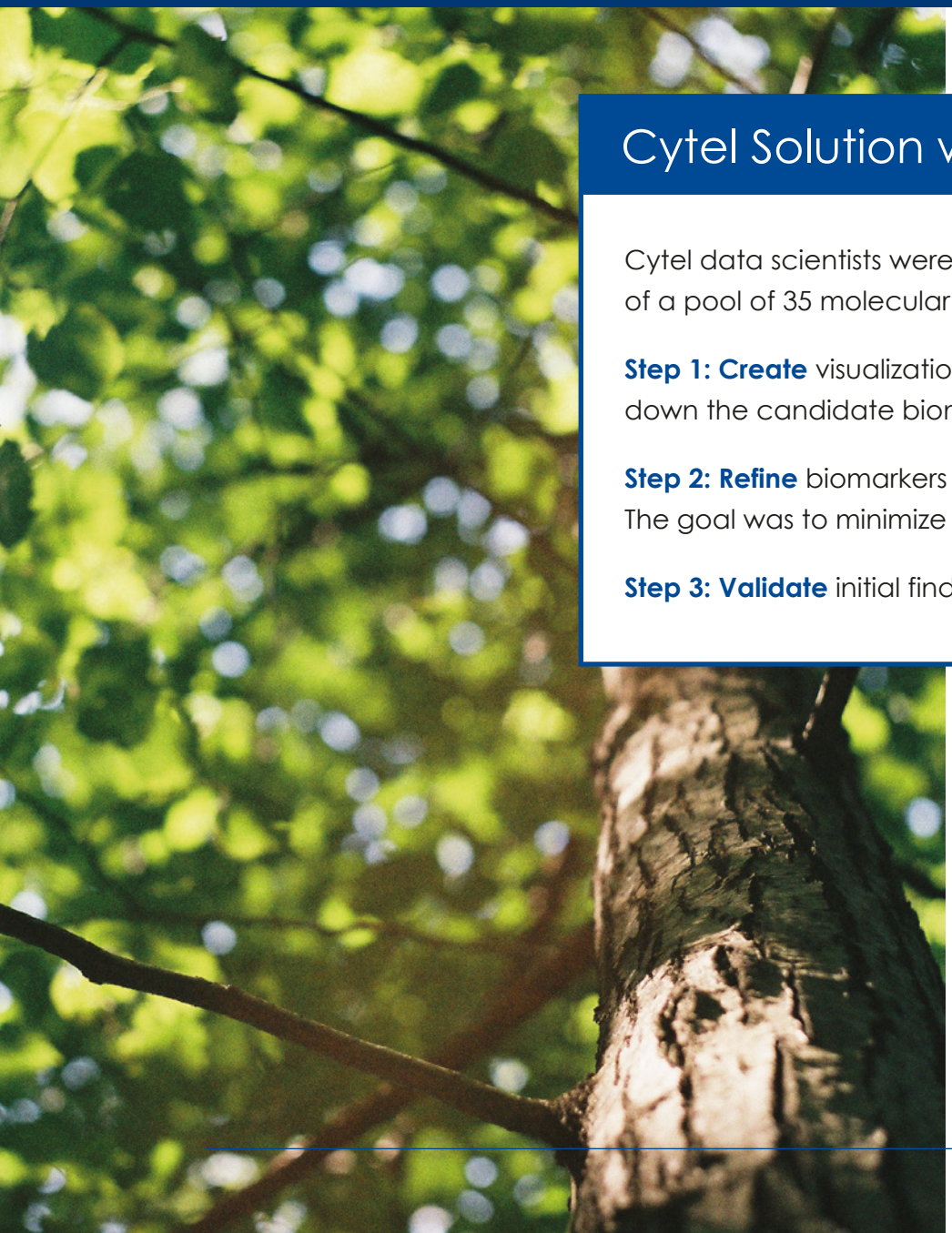
PREDICTIVE BIOMARKER SIGNATURE CHARACTERIZATION

The term biomarker signature describes the behavior of a set of biomarkers that define a signature to maximize the prediction performance. We examine the behavior of specific biomarkers as a set that consistently fluctuate together to maximize the accuracy on predicting the disease-related outcome.

The application of a biomarker signature depends on the prediction problem. A prognostic biomarker signature is used to predict the disease progression, a risk biomarker signature is used to identify sets of subjects that are likely to develop a disease, and a predictive biomarker signature is used to determine the patients that are likely to respond to a particular treatment. Predictive biomarker signatures are used often in oncology to stratify patients with a specific cancer into sub-populations and develop targeted therapies for the diseased population subtypes defined by the biomarker signature.

Development Challenge

Our client was developing a new drug for complex neurodegenerative disease in pre-clinical development. The drug may be only effective for a particular subgroup of patients. Our client needed to generate a hypothesis on the molecular pathway and the targeted drug activity and identify a biomarker signature defining potential response to the new drug.



Cytel Solution with Advanced Analytical Expertise

Cytel data scientists were engaged to narrow down and define the relationship of a pool of 35 molecular variables:

Step 1: Create visualization tools using Principal Component Analysis (PCA) to narrow down the candidate biomarkers.

Step 2: Refine biomarkers further using unsupervised learning clustering algorithms. The goal was to minimize cluster complexity and heterogeneity.

Step 3: Validate initial findings using a new dataset and semi-supervised clustering.

Outcome

The analysis produced a biomarker signature that was provided to the client for in-vivo validation.

Using these techniques, the client was able to improve their chances of targeting the most promising subgroup for their therapy.

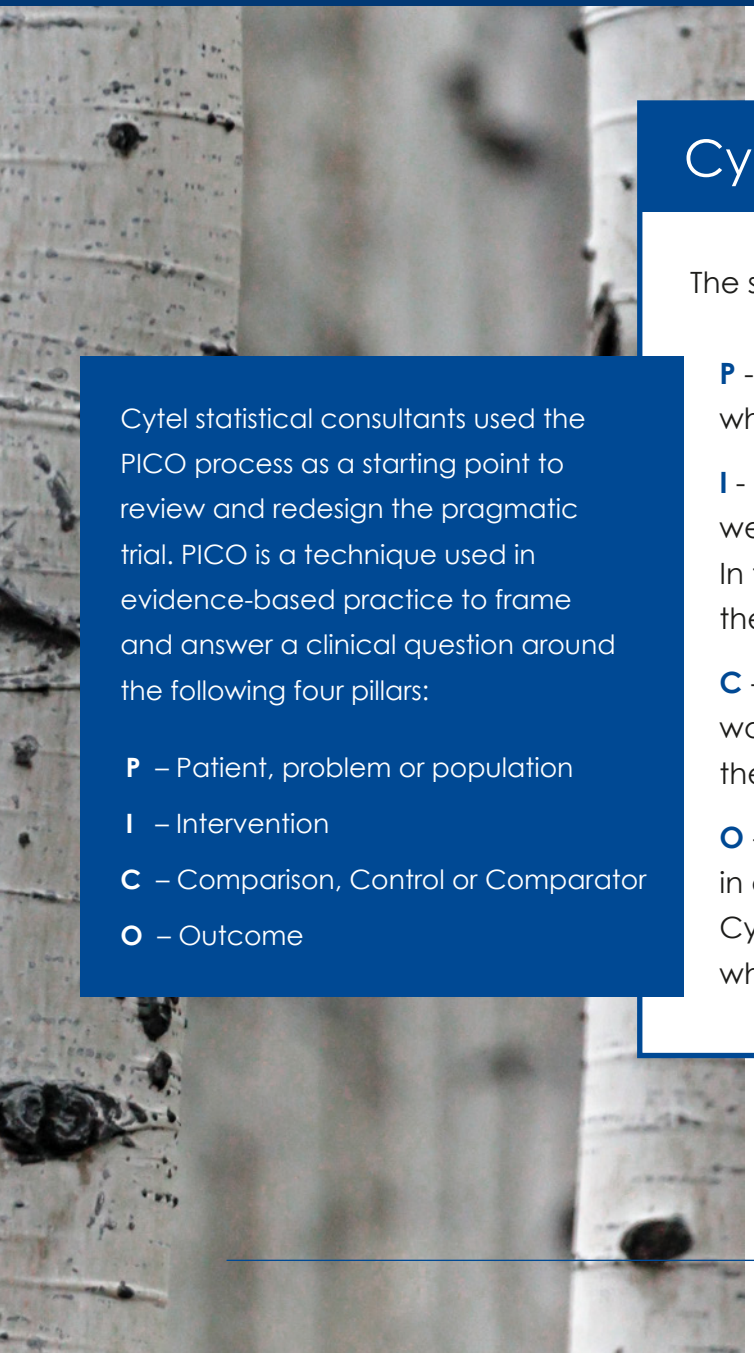
REDESIGNING A PRAGMATIC TRIAL IN ONCOLOGY

Pragmatic trials seek to estimate effectiveness–benefit within routine clinical practice, and answer questions about risk/benefit versus other interventions in the real-world setting.[6]

Development Challenge

Our client has a healthcare clinic which aims to provide low-cost, effective therapies to complement the existing Standard of Care treatment for a range of cancer indications. Through a literature search, they had established that certain approved medicines might demonstrate a positive effect on cancer treatment when taken in combination with conventional therapy approaches. They wished to further assess the effectiveness of a regimen of selected treatments for patients with cancer.

The client planned a pragmatic trial to evaluate the effectiveness of the interventions in the real world setting and produce results to allow general claims to be made. However, at the planning stage for the trial, the local regulatory agency rejected our client's proposed pragmatic design as they considered that several aspects were not sufficiently well controlled. The agency was concerned that bias could be introduced, and so the client approached Cytel for support to redesign the trial.



Cytel statistical consultants used the PICO process as a starting point to review and redesign the pragmatic trial. PICO is a technique used in evidence-based practice to frame and answer a clinical question around the following four pillars:

P – Patient, problem or population

I – Intervention

C – Comparison, Control or Comparator

O – Outcome

Cytel Solution

The strategic consultants worked to redesign the trial addressing these issues:

P - Who precisely are the patients being treated, what cancers do they have, and where do they originate from geographically?

I - It was not sufficiently clear in the original protocol what cancer indications the drugs were being used for specifically, or what combination of therapies was being used. In the redesigned pragmatic trial, Cytel consultants worked with the client to ensure these aspects were clarified.

C - In collaboration with the client, Cytel statistical consultants conducted extensive work to establish what the controls would be-whether historical or concurrent within the trial itself.

O - While in a randomized trial, survival is measured from randomization to death, in a pragmatic trial setting, a different definition of survival needs to be created. Cytel statistical consultants worked to create this definition, as well as specifying when the endpoints would be measured for the historical and concurrent controls.

Outcome

The new trial design robustly addressed the concerns of the local regulatory agency.

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ABOUT CYTEL

As a pioneer in evidence generation, with deep expertise in advanced analytical solutions, Cytel is uniquely equipped to unlock the value from increasingly complex data. Life sciences companies count on Cytel to deliver exceptional insight, minimize trial risk, and accelerate the development of promising new medicines that improve human life. Cytel has specialized teams with expertise in analyzing real-world and novel datasets and creating tailored real-world evidence designs to meet the disparate needs of clinical, medical affairs and market access audiences.

For more information on Cytel, visit **www.cytel.com**

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