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# Innovative Analysis Resolves Liver Toxicity Dilemma

## Challenge

A client had completed several Phase I, II and III clinical trials for an oncology drug leading up to an NDA filing. Efficacy data were promising and the product was moving toward FDA approval. Then came a potential red flag: Elevated liver enzymes were seen in a high percentage of the tested population.

That could put a stop to or delay FDA approval, unless the client could provide an explanation of the liver toxicity and a method to address it. What factors, if any, could predict patient susceptibility to liver enzyme elevation? How could those factors be addressed? Standard statistical methods of analysis were not revealing any answers.

The client turned to Provonix, knowing that Provonix had a good understanding and experience using innovative methods for analysis in the past.

## Action

After taking stock of the current situation and the question that needed to be answered, Provonix chose to analyze the data using a classification tree algorithm. This method is designed to identify prognostic factors that segment the population into different risk-level groups. Classification Tree analysis identifies the most important prognostic factor and corresponding threshold value (for continuous variables) in the whole population and each sub-population thereafter by examining every prognostic factor and all threshold values.

The study team identified the following prognostic factors to evaluate:

- Liver function test baseline values
- Trough concentration
- Age
- Race
- Pharmacogenetics

- Liver metastases at screening
- Use of hepatotoxic drugs
- Use of statins

The classification tree analysis showed that steady-state trough concentration was the most significant predictor of elevated ALT in the whole population. The percentage of patients with elevated ALT and trough concentration levels lower than a threshold value were a third of what was seen in the total population. Fortunately, this was the one predictor that could be modified.

Dosing information now contains recommendations to reduce trough concentrations. Two other prognostic factors were liver function baseline values and age. Doctors can more closely monitor these patients.

## Outcome

Analyzing the data using a categorical method allowed Provonix to create specific high and low risk groups based on the key prognostic factor of trough concentration. As a result of this analysis, changes to the dosing were made, so that trough concentration can be maintained at a safer level. The dosing recommendation changes satisfied the FDA's concerns and the drug was approved for use.

This challenge demonstrated something that we have always known at Provonix: More often than not, data analysis is not a straightforward path. Standard regression models don't work for every problem.

That's why we approach each challenge with an open mind, and a readiness to use whatever innovative or unconventional analytical method is best suited to each individual problem.