

Finding Needles in the Same Haystack: Comparing Designated Medical Event Versus Untargeted Approaches in Signal Identification

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BACKGROUND AND OBJECTIVES

- Signal identification (SI) using tree-based scan statistics (TBSS) screens many health outcomes simultaneously rather than testing one prespecified outcome at a time. Because many outcomes are evaluated simultaneously, the method adjusts for multiplicity, which can reduce power to detect true signals.
- Prior SI analyses used broad, untargeted outcome trees that can identify unexpected safety signals across a wider outcome spectrum. However, broader screening increases multiplicity (lowering power for a given outcome) and can increase the number of alerts requiring clinical review.
- A more targeted approach limits screening to serious outcomes of regulatory interest, such as designated medical events (DMEs). A DME targeted tree may improve signal identification and reduce triage burden by evaluating fewer, clinically important outcomes, but it may miss signals outside the curated tree.

Two ways to search for safety signals within the same Haystack

Untargeted tree

142,758 outcome groupings

- Broad surveillance
- Potentially lower power
- More alerts

DME targeted tree

5,535 outcome groupings

- Focused surveillance
- Potentially higher power
- Fewer alerts

OBJECTIVE

To compare signal identification using an untargeted ICD-10-CM outcome tree versus a targeted screening for serious DMEs among adults initiating semaglutide (Ozempic®) versus empagliflozin.

METHODS

Using the Sentinel Distributed Database, we identified new users of subcutaneous semaglutide (Ozempic® only) and empagliflozin among non-pregnant adults with type 2 diabetes. Semaglutide (Ozempic®) initiators were 1:1 propensity score (PS) matched to empagliflozin initiators. We assessed incident outcomes through 183 days after treatment initiation, using a 400-day washout period to exclude non-incident outcomes, and compared alerts from unconditional Bernoulli TBSS using an untargeted ICD-10-CM tree versus a DME tree (Table 1). The DME tree was based on the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) DME lists, supplemented with additional clinically important events of special interest.

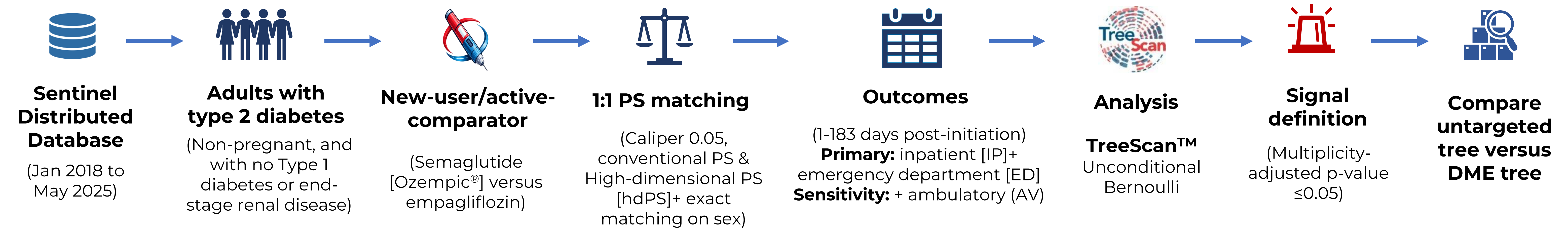


Table 1. Comparison of outcome trees used for signal identification

Feature	Untargeted tree	DME targeted tree
Tree content and source	Broad hierarchical ICD-10-CM tree, excluding cancer, pregnancy, congenital malformations, and external causes of morbidity	Curated ICD-10-CM tree based on FDA and EMA DME lists, supplemented with other clinically important events
Tree levels assessed	Levels 3-5	Levels 3-5
Outcome groupings screened	142,758	5,535
Primary purpose	Broad hypothesis generation	Targeted hypothesis generation for serious safety outcomes
Main trade-off	Broader coverage, but greater multiplicity and review burden	Fewer outcomes and lower review burden, but potential to miss signals outside the curated tree

CONCLUSION

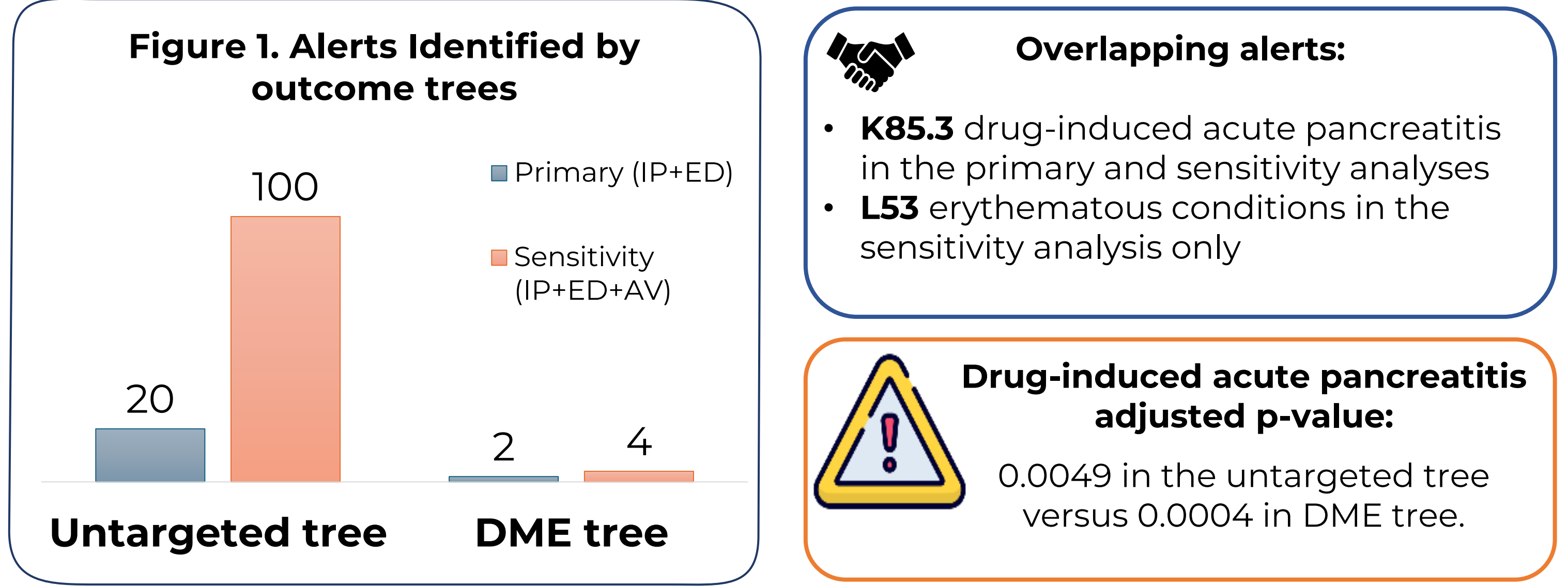
- The choice of outcome tree substantially affects the number and types of alerts identified.
- Untargeted tree-based scan statistics support broad hypothesis generation and the discovery of unexpected signals.
- The DME tree supports targeted hypothesis generation for serious safety outcomes and may yield smaller multiplicity-adjusted p-values for overlapping alerts because fewer outcomes are evaluated.
- The two approaches may be used complementarily, balancing outcome coverage, statistical efficiency, and clinical review capacity according to the study objective.

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RESULTS

- The untargeted tree identified more alerts than the DME targeted tree in both analyses: **20** versus **2** in the primary IP+ED analysis and **100** versus **4** in the sensitivity IP+ED+AV analysis (Figure 1).
- Drug-induced acute pancreatitis**, a known risk, was the only overlapping alert in the primary analysis. Its multiplicity-adjusted p-value was smaller in the DME tree than in the untargeted tree: 0.0004 versus 0.0049.
- Most additional untargeted-tree alerts reflected **gastrointestinal events**, **electrolyte/mineral imbalances**, and **non-specific adverse event** codes not included in the DME tree.
- In the sensitivity analysis, **erythematous skin conditions** were also identified by **both trees**, with the same minimum observable p-value of 0.0001.



Points to Consider

- The alerts identified are potential signals, not confirmed safety associations.
- Including ambulatory visits broadens the signal profile but may capture outpatient care and healthcare contact associated with treatment initiation rather than true safety signals.