Exploratory subgroup analysis: Post-hoc subgroup identification in clinical trials

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EMA Expert Workshop 2014

Outline

Exploratory subgroup analysis

Guideline-driven and principle-driven approaches

Key principles of subgroup identification

Analytic subgroup search procedures, complexity control, adjustment for selection bias, biomarker screening, reproducibility assessment

Case study

Phase III development program in patients with nosocomial pneumonia

Exploratory subgroup analysis

Subgroup analysis

Subgroup analysis approaches

Several classification schemes proposed in clinical trial literature (Varadhan et al., 2013; Lipkovich and Dmitrienko, 2014b)

Simplified classification scheme

Confirmatory subgroup analysis relies on a small set of well defined patient subgroups

Exploratory subgroup analysis focuses on a large set of loosely defined patient subgroups

Applications of exploratory subgroup analysis

Scenario 1 (positive trial)

Assess consistency of treatment effects across key subgroups

Scenario 2 (positive trial)

Analyze subgroups in a post-hoc manner to (1) exclude a subgroup due to lack of efficacy or (2) focus on a subgroup without safety issues

Add a subgroup with enhanced treatment effect

Scenario 3 (negative trial)

Discover subgroups with enhanced efficacy profile

Applications of exploratory subgroup analysis

Scenario 1 (positive trial)

Consistency assessment

Scenario 2 (positive trial)

Post-hoc subgroup identification

Scenario 3 (negative trial)

Post-hoc subgroup identification

Post-hoc subgroup identification

Guideline-driven approaches

Multiple sets of guidelines attempt to improve credibility of exploratory subgroup analysis

Checklist with 25 rules (Brookes et al., 2001), checklist with 21 rules (Rothwell, 2005), checklist with 11 rules (Sun et al., 2010)

Main rule: Proceed with caution

Principle-driven approaches

Subgroup identification ought to be based on specific operationalizable principles

Post-hoc subgroup identification

Key idea

Utilize recent developments in machine learning and data mining to pre-specify a subgroup exploration strategy

Principles of subgroup identification

Define an analytic subgroup search procedure

Control complexity of search space

Perform reliable inferences in selected subgroups

Key principles of subgroup identification

Analytic subgroup search procedures

Haphazard/unplanned subgroup exploration leads to spurious results

Tools used in subgroup search algorithms

Recursive partitioning algorithms with pre-specified rules for subgroup generation to select the most relevant subgroups (e.g., partitioning rules based on maximum differential treatment effect)

Key principles of subgroup identification

Complexity control

Unconstrained (greedy) subgroup search creates a very large search space, which hinders the assessment of clinical relevance

Tools for reducing the size of search space

Efficient subgroup pruning rules to choose child subgroups in recursive partitioning algorithms

Key principles of subgroup identification

Reliable inferences and interpretation

Unadjusted treatment effects in subgroups are misleading due to “optimism bias”

Tools for performing reliable inferences

Resampling- or cross-validation-based adjustments (p-value adjustment and “honest” treatment effect estimates) to perform reliable inferences in subgroups

Subgroup identification methods

Global outcome modeling

Virtual Twins method (Foster et al., 2011), Bayesian subgroup search (Xu et al., 2014)

Global treatment effect modeling

CART-based (Classification And Regression Trees) methods, e.g., Interaction Trees method (Su et al., 2009)

Local modeling

Responder Identification method (Kehl and Ulm, 2006), SIDES method (Lipkovich et al., 2011)

Local modeling

Subgroup Identification based on Differential Effect Search (SIDES)

Recursive partitioning-based subgroup identification method which provides a multivariate assessment of biomarkers, employs complexity control and accounts for selection bias

SIDEScreen method

Extension of original SIDES method with efficient biomarker screening for complex settings, e.g., > 100 biomarkers (Lipkovich and Dmitrienko, 2014a)

Case study

Phase III program in pneumonia patients

Clinical trial database

Total sample size: 1289 patients

Primary endpoint: All-cause mortality at 28 days

Overall outcome: Slightly negative treatment effect in overall patient population

Exploratory objective

Identify biomarkers that help predict positive treatment response

Reference

Dmitrienko et al. (2014)

Phase III program in pneumonia patients

Main challenge

Candidate set included 26 biomarkers (mostly demographic and clinical variables)

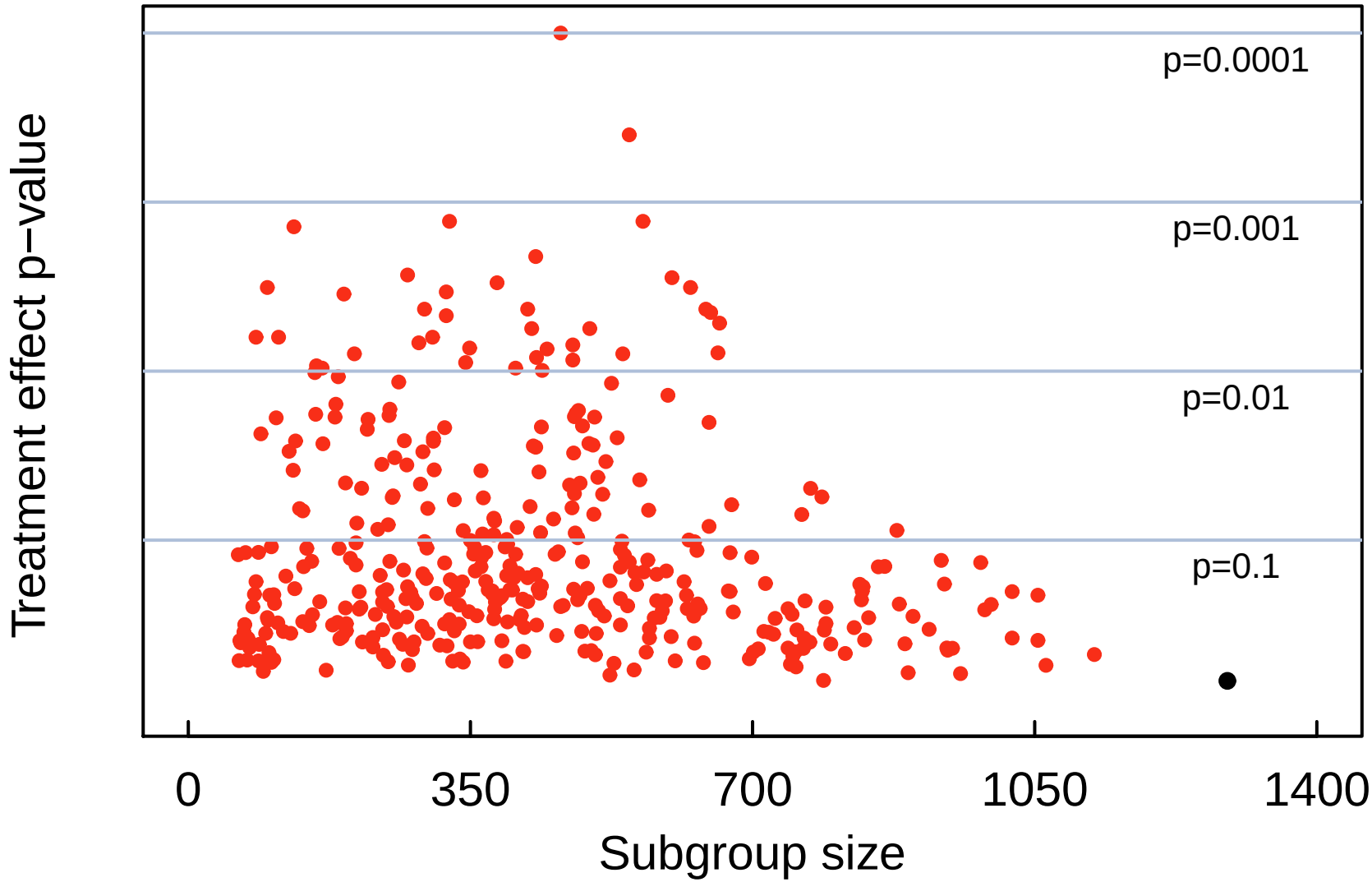
Large set of candidate biomarkers created a vast search space

SIDES-based subgroup search

Aggressive pruning rules to reduce the search space

Biomarker screens to filter out non-informative (noise) biomarkers and focus on best predictors of treatment response

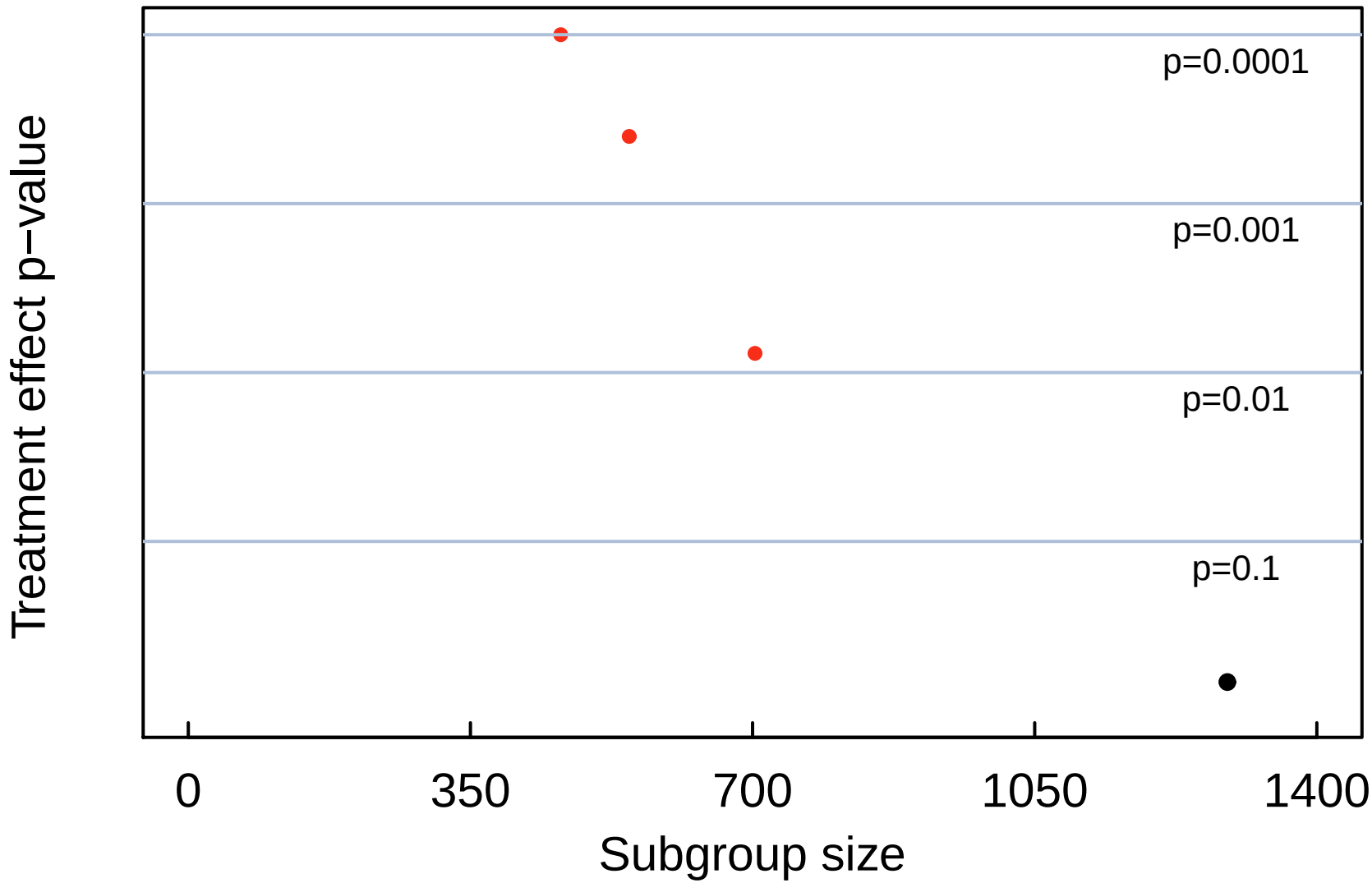
Greedy subgroup search (390 subgroups)



Black dot: Overall patient population

Red dots: Patient subgroups

Efficient subgroup search (3 subgroups)



Black dot: Overall patient population

Red dots: Patient subgroups

Phase III program in pneumonia patients

Selected patient subgroup

Serum creatinine clearance > 67 mL/min

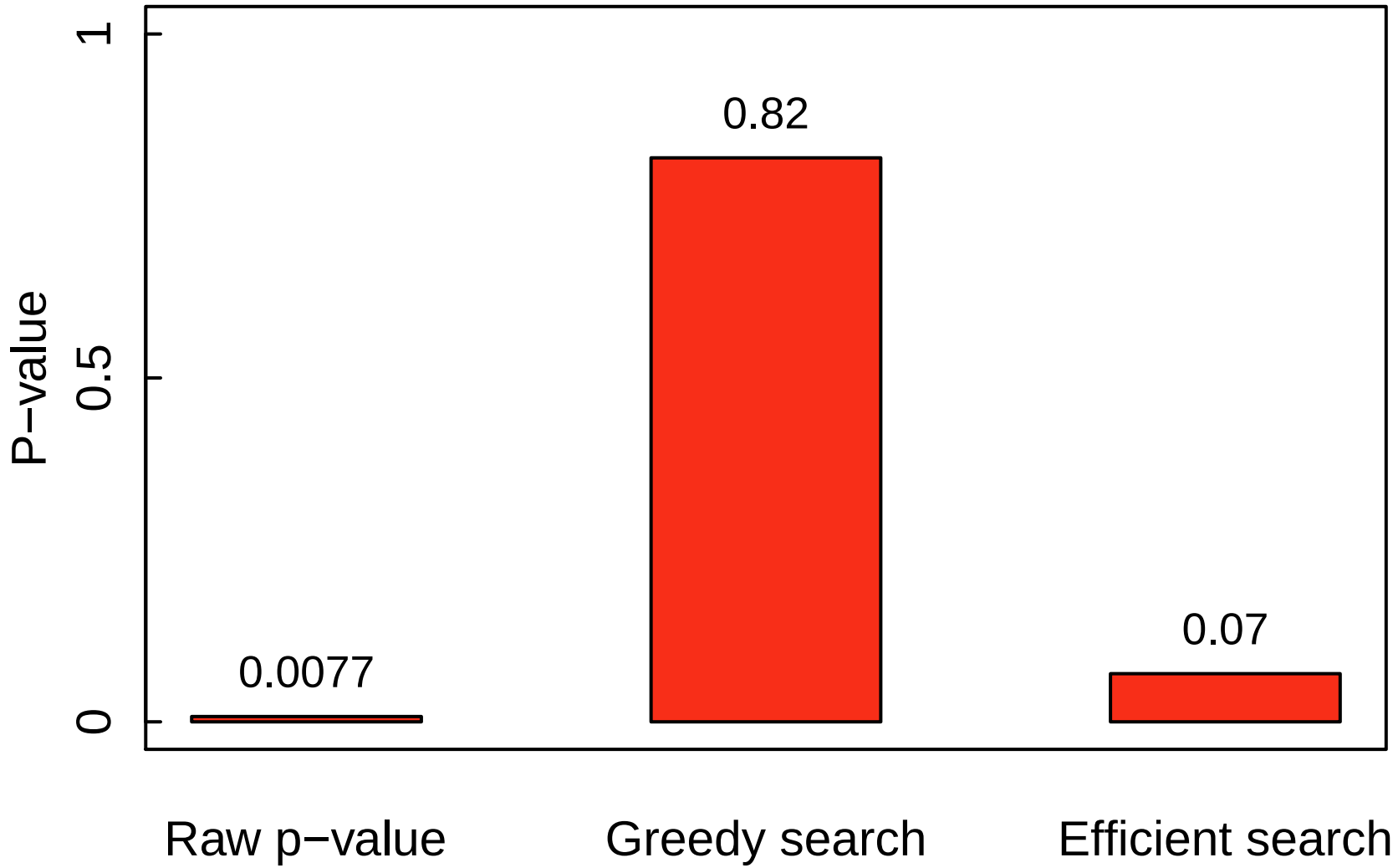
Sample size: 352 patients

Raw treatment effect p-value: $p = 0.0077$

Adjustment for selection bias

Adjusted treatment effect p-values were computed using a resampling-based method

Treatment effect p-values



Efficient subgroup search: Lower multiplicity burden due to reduced search space

Additional important considerations

Adjustment for optimism bias

Cross-validation to derive honest (bias-adjusted) estimates of treatment effects in selected patient subgroups

Reproducibility assessment

“Learn and confirm” method to assess the likelihood of replicating results in another clinical trial

Summary

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Principled-based approach to post-hoc subgroup identification

Analytic subgroup search procedures for examining all relevant patient subgroups to find subsets of overall population with desirable characteristics

Statistical methods

Multiple methods have been developed with available software implementation

Web site: http://biopharmnet.com/wiki/Subgroup_Analysis

References

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