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Second-Generation *p*-Values in a High Dimensional Analysis of Prostate Cancer Variants

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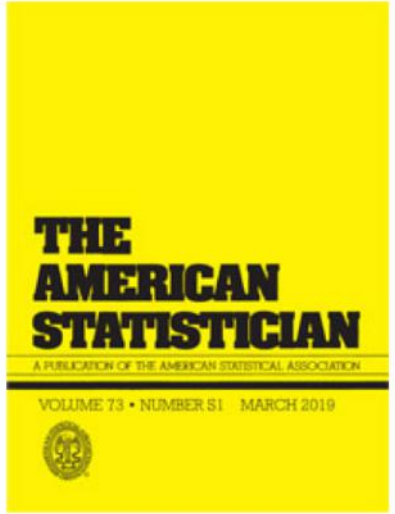

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An Introduction to Second-Generation *p*-Values

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ABSTRACT

Second generation *p*-values preserve the simplicity that has made *p*-values popular while resolving critical flaws that promote misinterpretation of data, distraction by trivial effects, and unreproducible assessments of data. The second-generation *p*-value (SGPV) is an extension that formally accounts for scientific relevance by using a composite null hypothesis that captures null and scientifically trivial effects. Because the majority of spurious findings are small effects that are technically nonnull but practically indistinguishable from the null, the second-generation approach greatly reduces the likelihood of a false discovery. SGPVs promote transparency, rigor and reproducibility of scientific results by a priori identifying which candidate hypotheses are practically meaningful and by providing a more reliable statistical summary of when the data are compatible with the candidate hypotheses or null hypotheses, or when the data are inconclusive. We illustrate the importance of these advances using a dataset of 247,000 single-nucleotide polymorphisms, i.e., genetic markers that are potentially associated with prostate cancer.

ARTICLE HISTORY
Received March 2018
Revised September 2018

KEYWORDS
Likelihood ratios; Null hypothesis; *p*-Value; Statistical evidence

Typical concerns with standard *p*-value approaches

- Statistical significance ≠ clinical or practical significance
- Large *p*-values do not indicate support for the null hypothesis
- *p*-value adjustments for multiple comparisons
  - Often conservative
  - No universal solution
- Ranking findings by *p*-value may miss interesting large effects

Alternatives

- Consider an interval null hypothesis

- Differentiate between when the data support:
  - Only alternative hypotheses
  - Only null hypotheses
  - Null and alternative hypotheses (inconclusive)

- Type I Error rate shrinks as the sample size increases

- Rank findings by clinical and statistical importance

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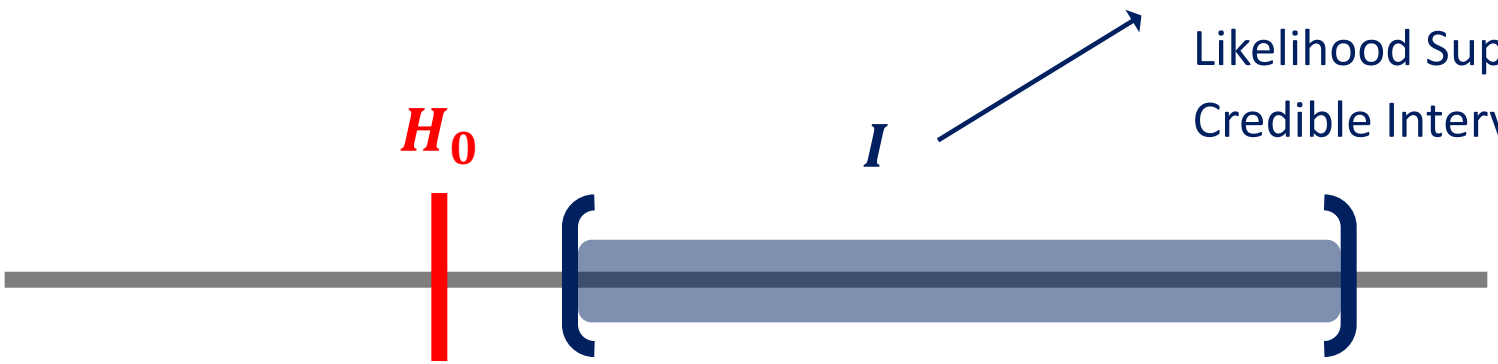
second-generation *p*-value

Introduction to the second-generation *p*-value (SGPV)

Point null hypothesis



Confidence Interval
Likelihood Support Interval
Credible Interval

Introduction to the second-generation *p*-value (SGPV)

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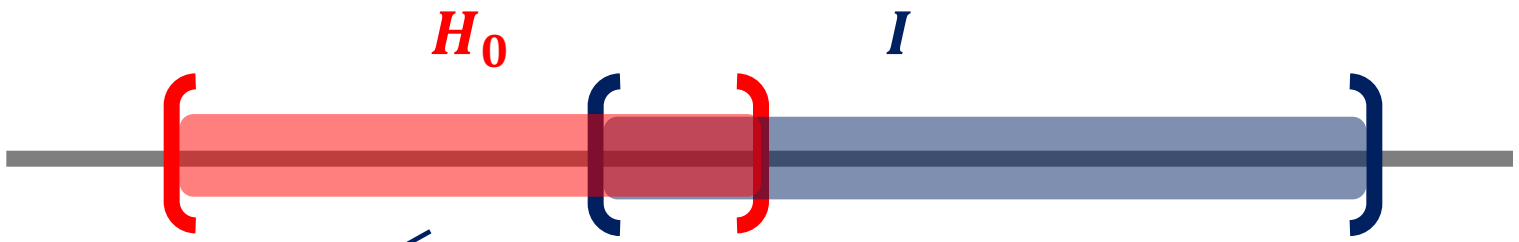
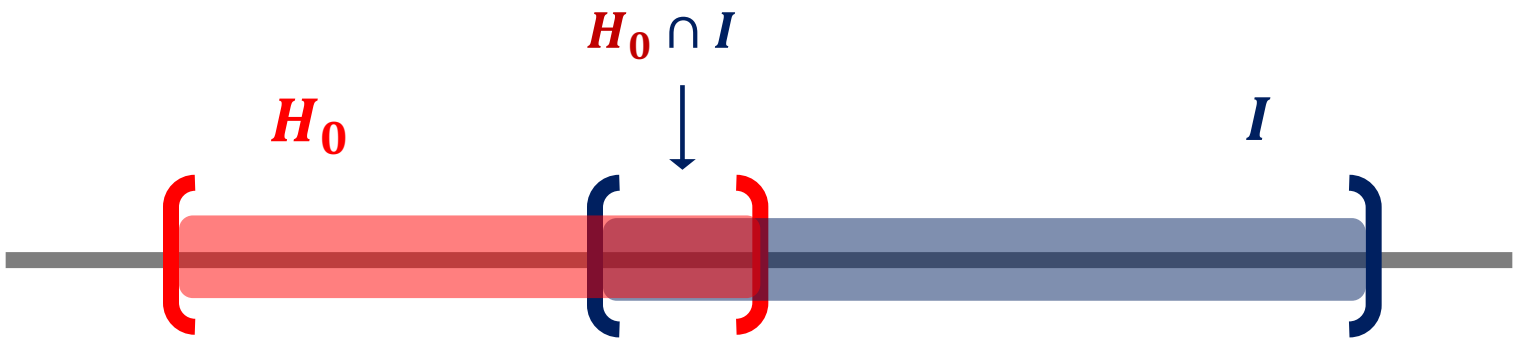
Point null hypothesis

Interval null hypothesis

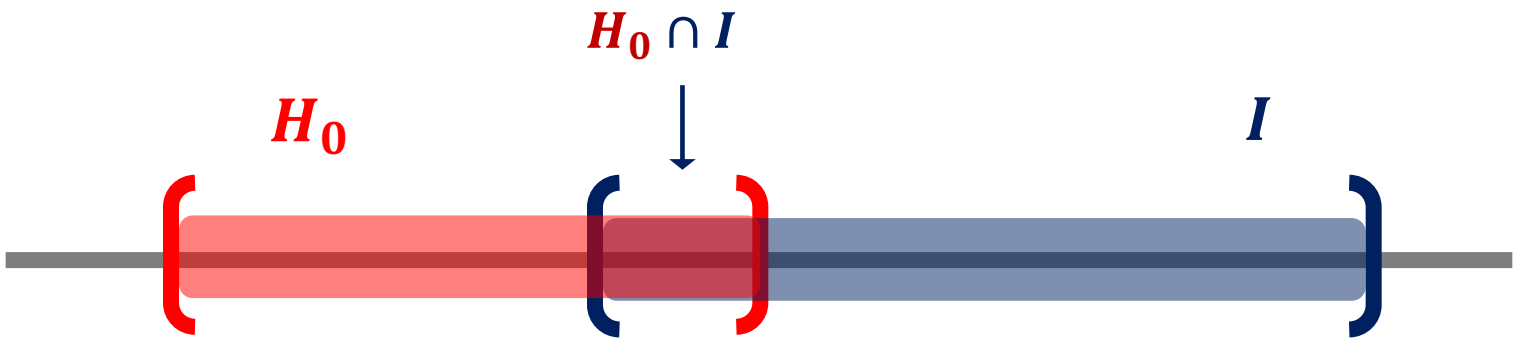


Undetectable
Clinically unimportant/trivial
Measurement error

Introduction to the second-generation *p*-value (SGPV)



Introduction to the second-generation *p*-value (SGPV)



$$p_\delta = \frac{|I \cap H_0|}{|I|} \times \max\left\{\frac{|I|}{2|H_0|}, 1\right\}$$

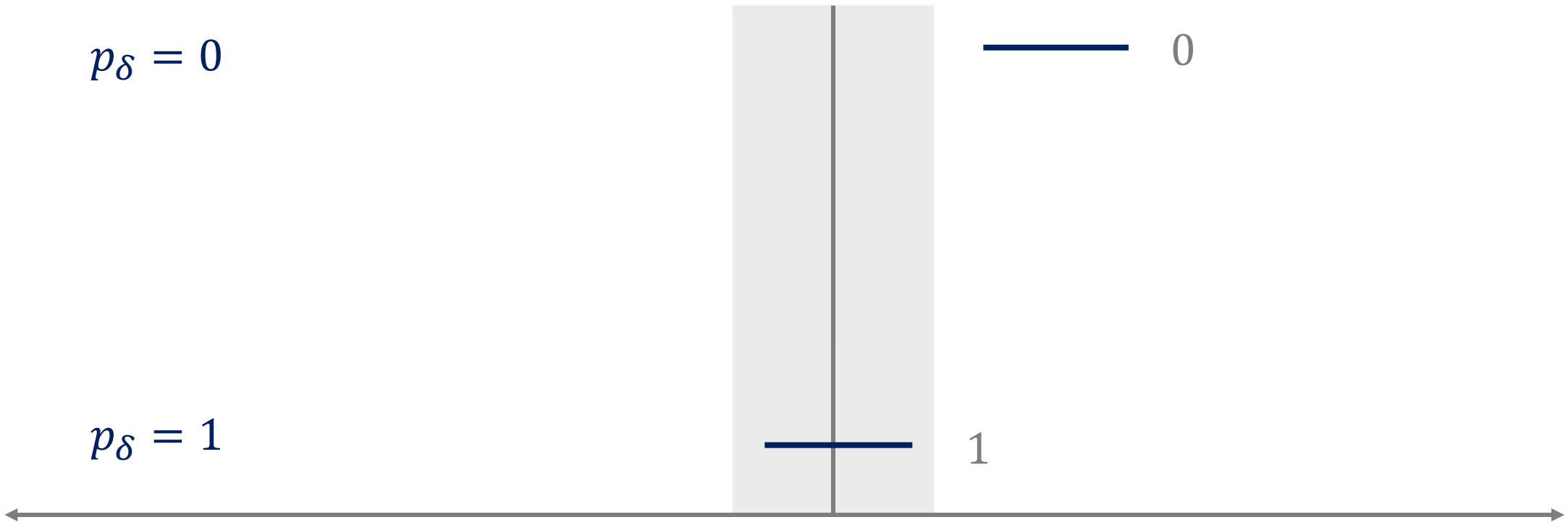
Proportion of data-supported hypotheses that are also null hypotheses

Small-sample correction factor

shrinks proportion towards ½ when $|I|$ is greater than $2|H_0|$

Introduction to the second-generation *p*-value (SGPV)

- Provides a single-number summary of when the data support only null effects, only meaningful alternative effects, or are inconclusive



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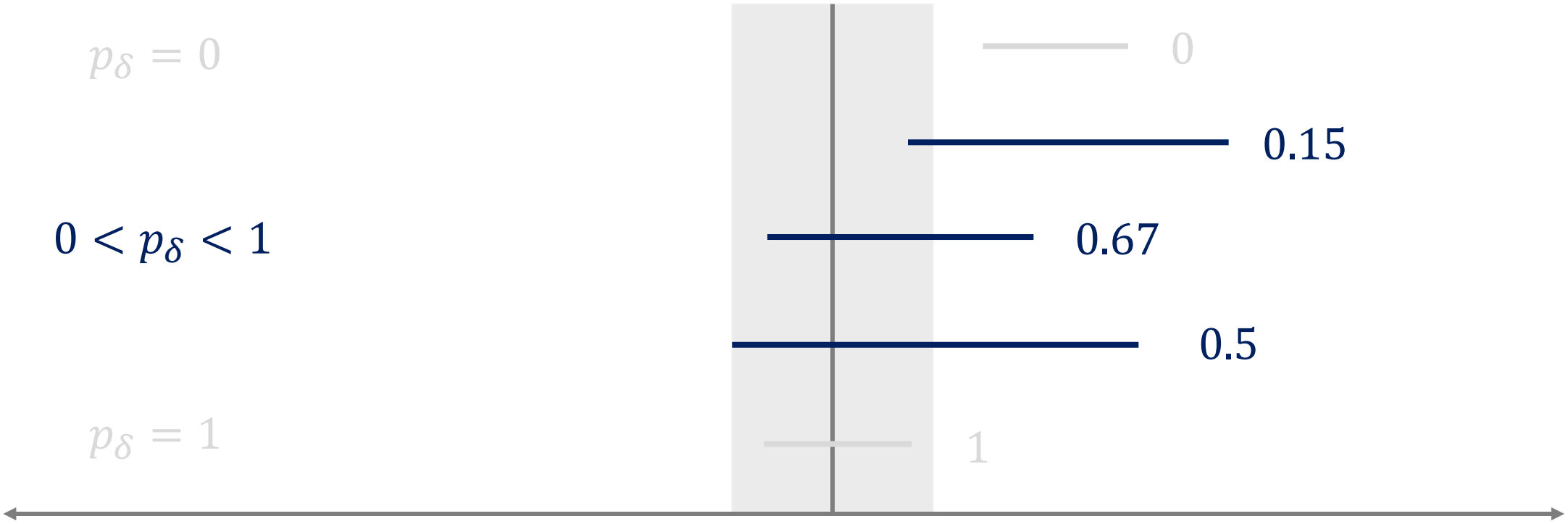
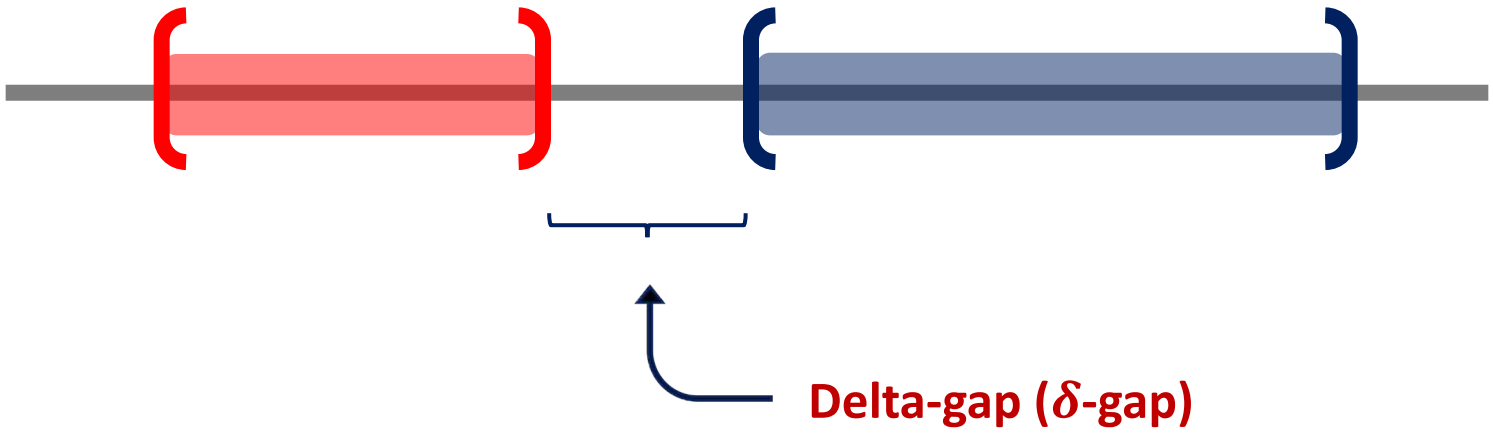


Ranking second-generation *p*-values

- When $p_\delta = 0$, there is a gap between the intervals. The length of that gap is the delta-gap



- Allows refined differentiation among findings

Example with prostate cancer variants

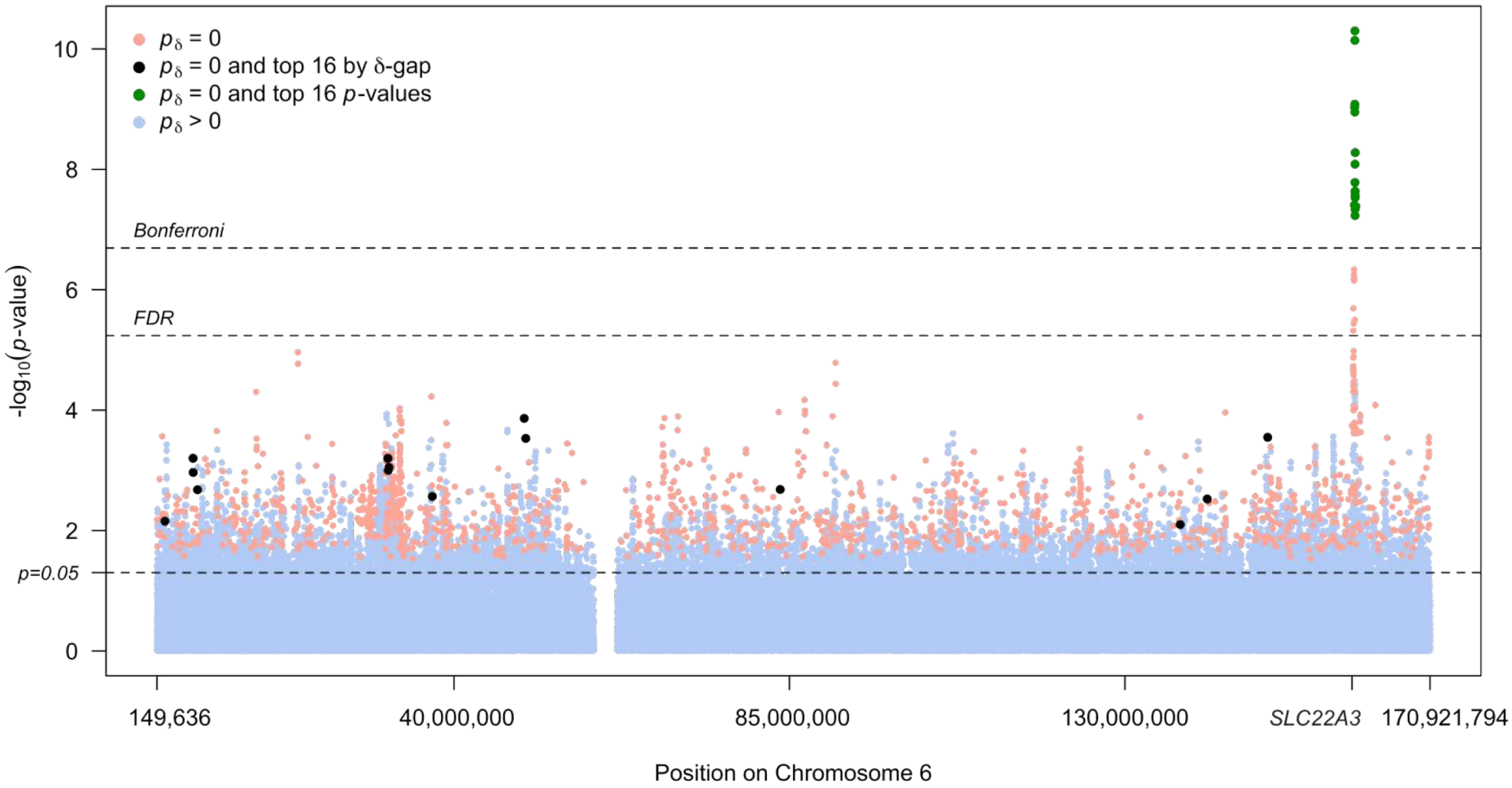
- International Consortium for Prostate Cancer Genetics (Schaid and Chang 2055; ICPCG 2018)

  - $\sim 3{,}900$ subjects ($2{,}500$ cases & $1{,}400$ controls)
  - $\sim 247{,}000$ single-nucleotide polymorphisms (SNPs) from Chromosome 6

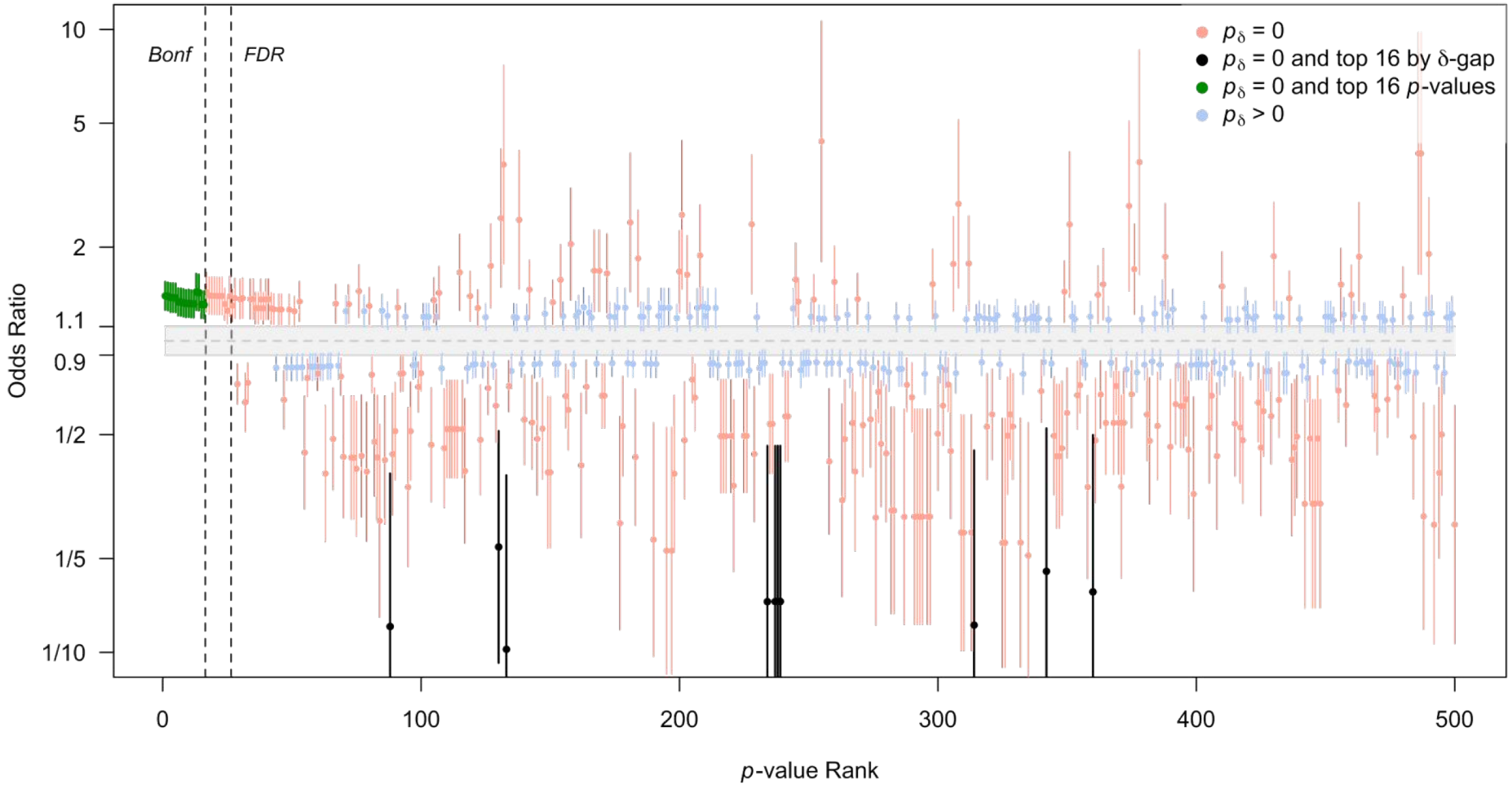
- Goal: Identify 'interesting' SNPs potentially associated with prostate cancer

$$H_0: OR \in [0.9, 1.11]$$

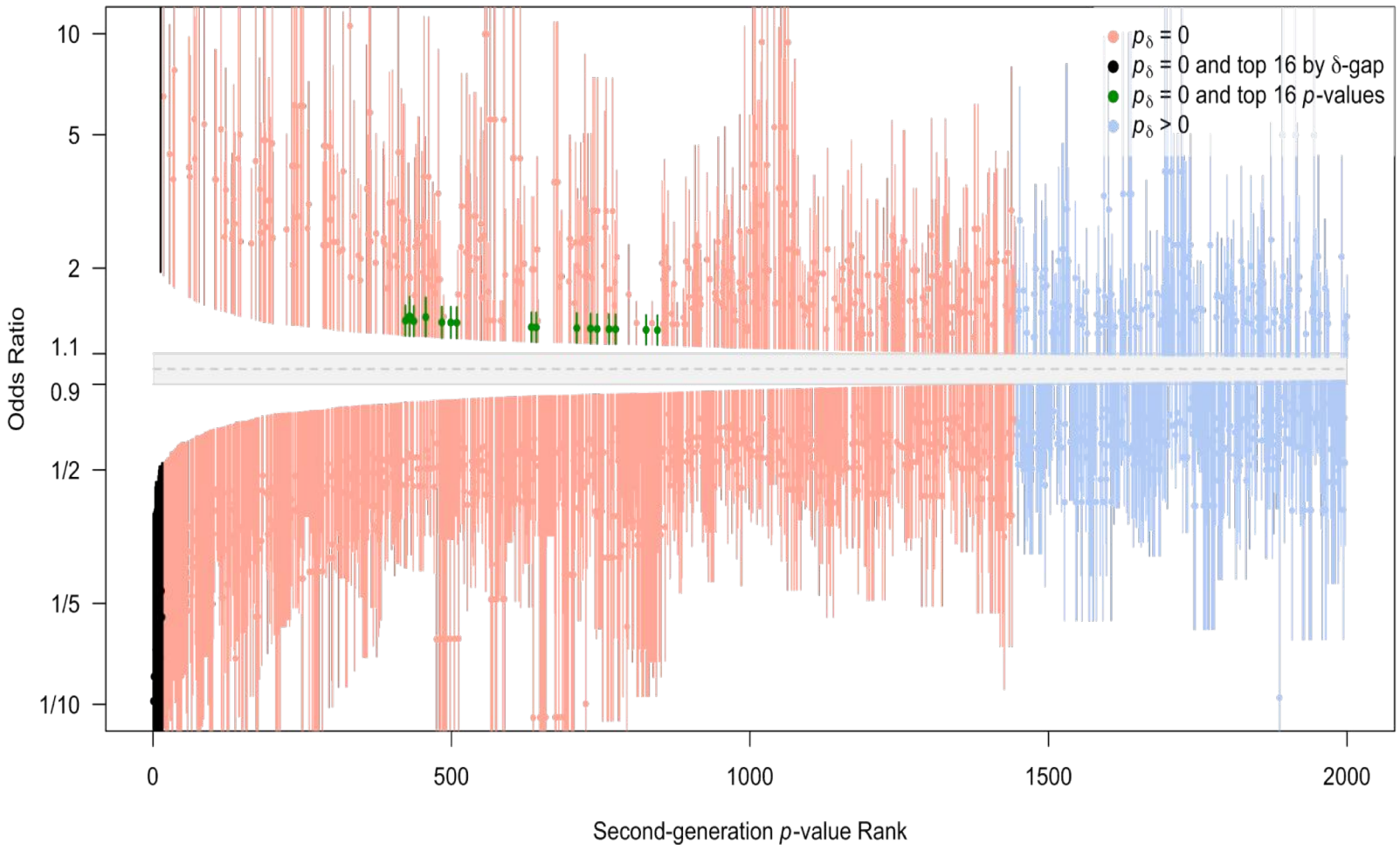
Manhattan Plot



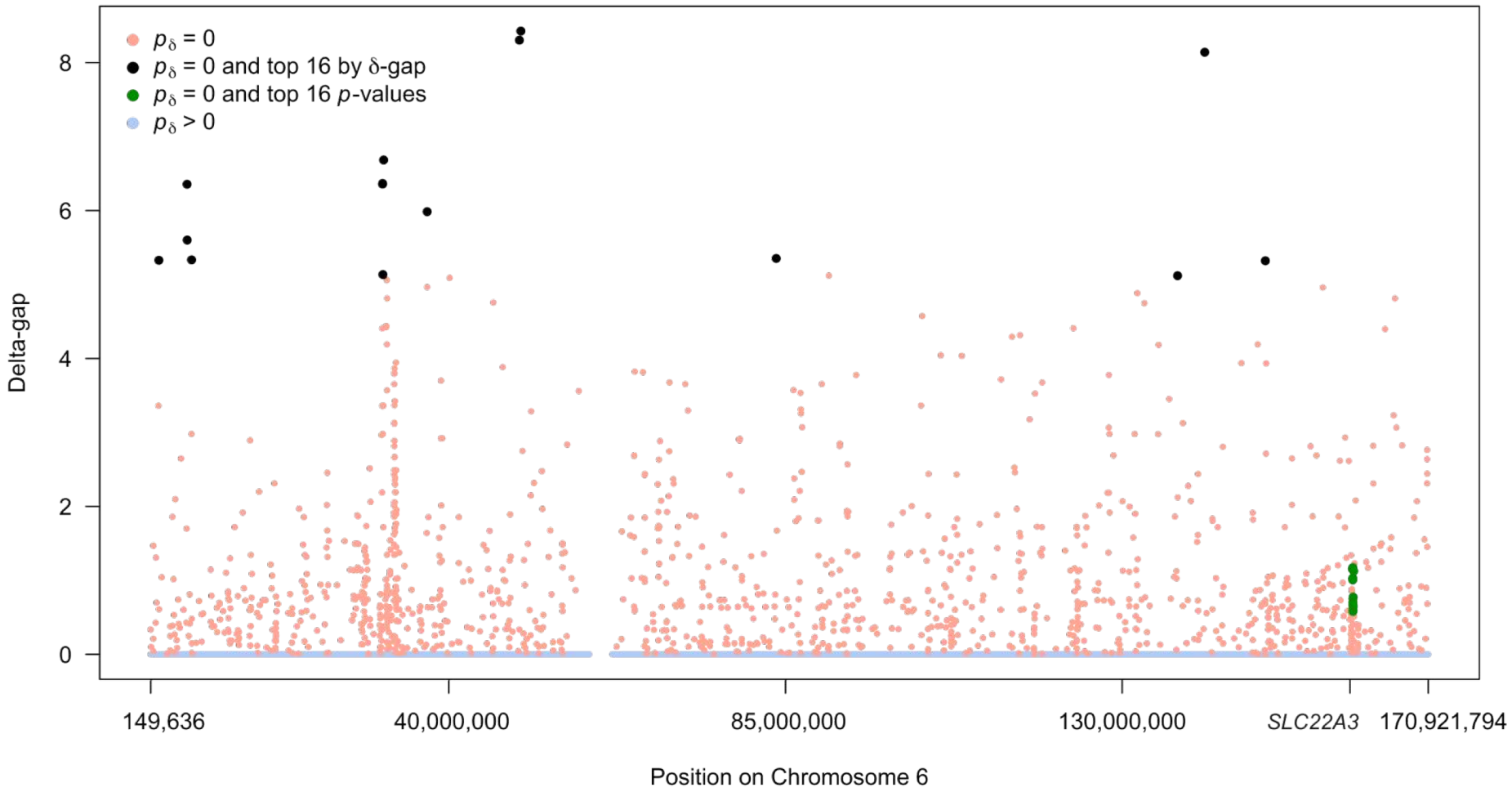
Top 500 support intervals by *p*-value ranking



Top 2,000 support intervals by SGPV ranking



SGPV Manhattan plot



Discussed in papers (Blume et al. 2018, Blume et al. 2019)

- SGPV error rate profile
  - Both Type I and II Error rates converge to 0 with sample size
- False discovery rate profile
  - Maintains FDR improvement associated with multiple comparisons adjustments while lowering the false confirmation rate

Ongoing work

- SGPV false discovery rates (FDR_δ)
  - Estimation methods
  - Rank SGPV findings by FDR_δ

Recommendations

- Report all finding where $p_\delta = 0$ and $p_\delta = 1$ ("discoveries" and "confirmations")
- Identify top findings among those with $p_\delta = 0$ by large delta-gaps or low FDR_δ values
  - ➢ Prioritizes clinical impact over precision
  - ➢ Incorporates reliability of findings

  → Above set of findings is very different from those of classical *p*-value approaches

- R package available at github.com/weltybiostat/sgpv

```
sgpvalue        plotsgpv
sgpower         fdrisk
```

Support and References

TREAT Research Group (Dept. of Thoracic Surgery) and Statistical Evidence in Data Science (SEDS) Lab

- Jeffrey Blume (PI) 🌐 statisticalevidence.com
- Thomas Stewart
- Megan Hollister

Blume JD, Greevy RA, Welty VF, Smith JR, Dupont WD (2019) An Introduction to Second-Generation *p*-Values, The American Statistician, 73:sup1, 157-167, DOI: 10.1080/00031305.2018.1537893

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