VANDERBILT UNIVERSITY

DEPARTMENT OF BIOSTATISTICS

False Discovery Rates for Second-Generation *p*-Values in Large-Scale Inference

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Outline

- Metrics of statistical evidence
- False discovery rate (FDR) review
- Second-generation p-value (SGPV) introduction
- FDR for SGPV
- Examples
- Take home message

Metrics of statistical evidence

Metric	Statistic(s)	Example(s)
Strength of evidence	M	*Test result* p-value
Propensity for study to yield misleading evidence	$\Pr(M \in \Gamma \mid H_0)$ $\Pr(M \notin \Gamma \mid H_1)$	*Sensitivity, specificity* Type I error Type II error Type S error
Propensity for observed results to be misleading*	$\Pr(H_0 \mid M \in \Gamma)$ $\Pr(H_1 \mid M \notin \Gamma)$	*PPV, NPV* FDR FNR

* dependent on prevalence/prior, $\Pr(H_0)$

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False discovery rate

- Large-scale inference

	Null	Non-null	**Total**
Reject	V	$V - R$	R
Inconclusive	U	$N - R - U$	$N - R$
Total	N_0	$N - N_0$	N

- *False discovery proportion* (FDP):

$$FDP = Q = \begin{cases} V/R & \text{if } R > 0 \\ 0 & \text{if } R = 0 \end{cases}$$

False discovery rate

- *False discovery rate* (FDR) is the expected false discovery proportion

$$FDR = E[Q] = E\left[\frac{V}{R} \mid R > 0\right] \cdot \Pr(R > 0) + E[0] \cdot \Pr(R = 0)$$

False discovery rate

- *False discovery rate* (FDR) is the expected false discovery proportion

$$FDR = E[Q] = \underbrace{E\left[\frac{V}{R} \mid R > 0\right]}_{pFDR} \cdot \Pr(R > 0)$$

the "*positive false discovery rate*"

False discovery rate

- Probabilistic interpretation of the pFDR (Storey 2003):

$$pFDR(\Gamma) \;=\; E\left[\frac{V}{R} \mid R > 0; \Gamma\right] \;=\; \Pr(H_0 = 0 \mid M \in \Gamma)$$

under a given set of assumptions

False discovery rate

- Probabilistic interpretation of the pFDR (Storey 2003):

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under a given set of assumptions

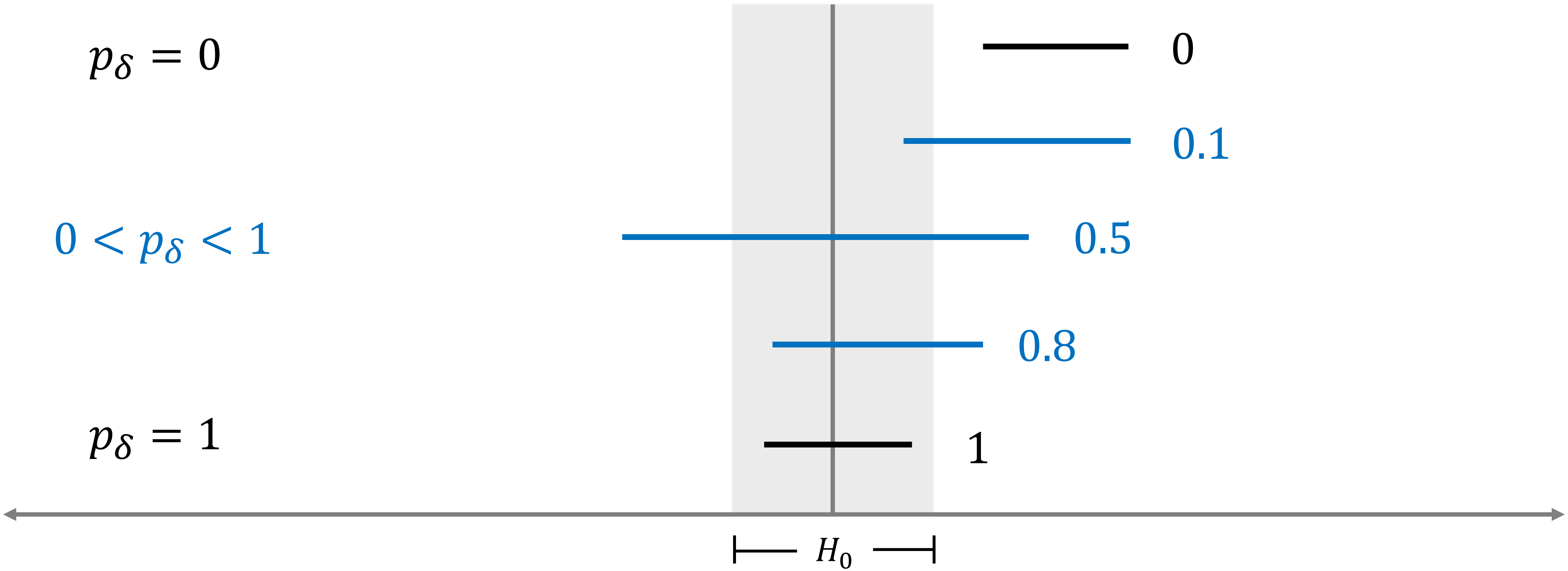
Second-generation p-value

- Interval null hypothesis
  - Clinically unimportant/trivial, undetectable, measurement error, etc.

- Differentiates between when the data support:
  - Alternative hypothesis
  - Null hypothesis
  - Both, to some degree or strictly inconclusive

Second-generation p-value

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



Second-generation p-value

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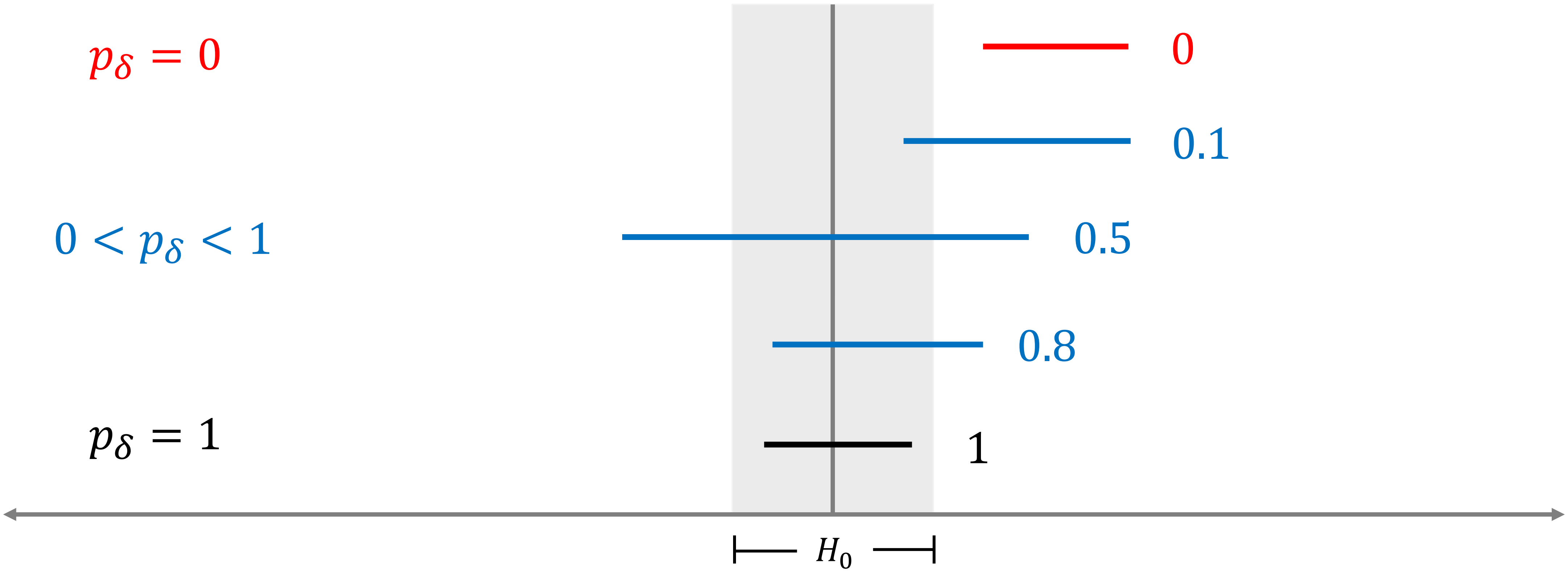

SGPV FDR

- $pFDR_\delta = \Pr(H_0 \mid p_\delta = 0)$

$$= \frac{\Pr(p_\delta = 0 \mid H_0) \cdot P(H_0)}{\Pr(p_\delta = 0)}$$

$$= \left[1 + \frac{P(p_\delta = 0 \mid H_1)}{P(p_\delta = 0 \mid H_0)} \ \frac{P(H_1)}{P(H_0)}\right]^{-1}$$

SGPV FDR

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Estimation?

$$= \left[1 + \frac{P(p_\delta = 0 \mid H_1)}{P(p_\delta = 0 \mid H_0)} \; \frac{P(H_1)}{P(H_0)}\right]^{-1}$$

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Estimation?

$$= \left[1 + \underbrace{\frac{P(p_\delta = 0 \mid H_1)}{P(p_\delta = 0 \mid H_0)}}^{\text{“power”}} \cdot 1 \right]^{-1}$$

SGPV FDR

- $pFDR_\delta = \Pr(H_0 \mid p_\delta = 0)$

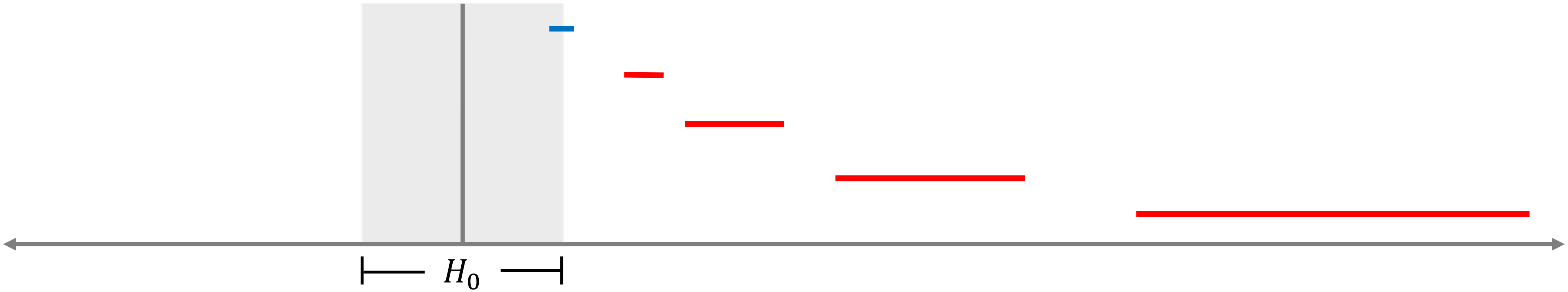
$$= \frac{\Pr(p_\delta = 0 \mid H_0) \cdot P(H_0)}{\Pr(p_\delta = 0)}$$

Estimation?

$$= \left[1 + \underbrace{\overbrace{\frac{P(p_\delta = 0 \mid H_1)}{P(p_\delta = 0 \mid H_0)}}^{\text{"power"}}}_{\text{"type I error"}} \cdot 1 \right]^{-1}$$

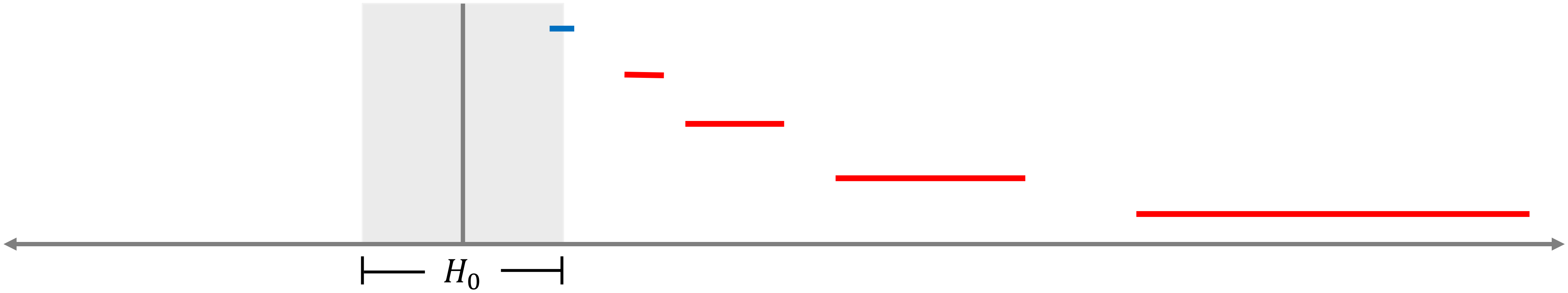
SGPV FDR

$\hat{\theta}$	$\hat{\sigma}/\sqrt{n}$	p-value	SGPV	std. err for pFDR estimate	p-value pFDR	sgpv pFDR
1	0.125	1.3 x10^-15	0.5			
2	0.25	1.3 x10^-15	0			
6	0.75	1.3 x10^-15	0			
12	1.5	1.3 x10^-15	0			
24	3	1.3 x10^-15	0			



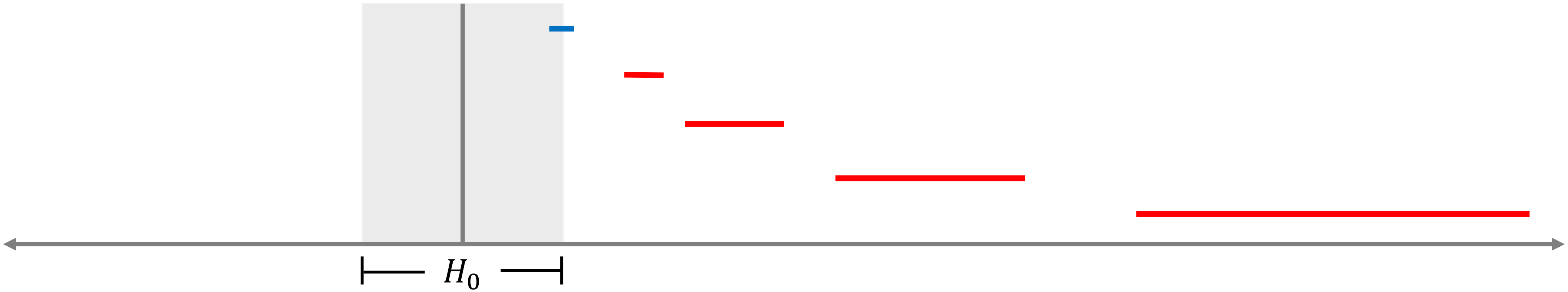
SGPV FDR

$\hat{\theta}$	$\hat{\sigma}/\sqrt{n}$	p-value	SGPV	std. err for pFDR estimate	p-value pFDR	sgpv pFDR
1	0.125	1.3 x10^-15	0.5	0.125	0.048	NA
2	0.25	1.3 x10^-15	0	0.25	0.048	2.6 x 10^-09
6	0.75	1.3 x10^-15	0	0.75	0.048	9.9 x10^-04
12	1.5	1.3 x10^-15	0	1.5	0.048	8.5 x10^-03
24	3	1.3 x10^-15	0	3	0.048	2.1 x10^-02



SGPV FDR

$\hat{\theta}$	$\hat{\sigma}/\sqrt{n}$	p-value	SGPV	std. err for pFDR estimate	p-value pFDR	sgpv pFDR
1	0.125	1.3 x10^-15	0.5	1.125	0.2574	NA
2	0.25	1.3 x10^-15	0	1.125	0.1046	0.03
6	0.75	1.3 x10^-15	0	1.125	0.0476	0.0044
12	1.5	1.3 x10^-15	0	1.125	0.0476	0.0044
24	3	1.3 x10^-15	0	1.125	0.0476	0.0044



Take home messages

- Report the propensity for the observed results to be misleading (FDR/pFDR) along with the measure of evidence
  - In addition to the interval estimate

- The second-generation p-value incorporates clinical relevance, reduces type I error and false discovery rate

- Behavior of the pFDR for second-generation p-values highly dependent upon estimation methods/assumptions

R package sgpv

- https://github.com/weltybiostat/sgpv

  - sgpvalue

```
sgpvalue(est.lo=dat$lb, est.hi=dat$ub, null.lo=-1, null.hi=1)$p.delta
```

  - plotsgpv

```
plotsgpv(est.lo=dat$lb, est.hi=dat$ub, null.lo=-1, null.hi=1,
         set.order=order(dat$p), legend.on=TRUE)
```

  - fdrisk

```
fdrisk(sgpval=0, null.lo=-1, null.hi=1, std.err=dat$se, pi0=0.5,
       null.weights='Point', null.space=0,
       alt.weights='Point', alt.space=dat$est)
```

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
- Yi Zuo

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

Blume JD, D'Agostino McGowan L, Dupont WD, Greevy RA Jr (2018) Second-generation *p*-values: Improved rigor, reproducibility, & transparency in statistical analyses. PLoS ONE 13(3): e0188299. https://doi.org/10.1371/journal.pone.0188299

References continued

Benjamini, Y. & Hochberg, Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J Royal Statistical Soc Ser B Methodol* **57,** 289–300 (1995).

Storey, J. D. The positive false discovery rate: a Bayesian interpretation and the q-value. *Ann Statistics* **31,** 2013–2035 (2003).