

## Part II

# Second-generation *p*-values: equivalence tests, statistical properties, and false discovery rates

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Jeffrey D. Blume, and Megan H. Murray,

PhD

PhD

School of Data Science

Department of Biostatistics

University of Virginia

Vanderbilt University

## Course Layout

- Slides Part I: Introduction and applications
  - Coding Part I
- Lunch (12:00-1:00pm)
- Slides Part II: Statistical Properties, Equivalence tests, false discovery rates, and study planning
  - Coding Part II
- Slides Part III: SGPV Variable Selection
  - Coding Part III
- Questions and Discussion

## Outline

- Statistical Properties
- Equivalence Tests
  - Two One-Sided Tests (TOST)
  - Comparison to SGPs
- False Discovery Rates
- R Packages
  - `sgpv::fdrisk()`
  - `FDRestimation::p.fdr()`
- SGPV Study Planning

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## Connecting SGPV and Properties

- Three Inferential Categories
  1.  $p_\delta = 0 \Rightarrow$  data **incompatible** with null
  2.  $p_\delta = 1 \Rightarrow$  data **compatible** with null
  3.  $0 < p_\delta < 1 \Rightarrow$  data are **inconclusive**
- Three ‘error’ rates
  1.  $P(p_\delta = 0|H_0)$  when  $H$  is null
  2.  $P(p_\delta = 1|H_1)$  when  $H$  is not null
  3.  $P(0 < p_\delta < 1|H)$  when  $H$  is either
- Assume  $H$  makes statements about a parameter  $\theta$
- Large sample setting

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## Second-generation $p$ -value

- Statistical properties in TAS & PLOS One
- Retains strict error control

Evidential Metric	What it measures	SGPV
1	Summary measure	SGPV ( $p_\delta$ )
2	Operating characteristics	$P(p_\delta = 0   H_0)$ $P(p_\delta = 1   H_1)$ $P(0 < p_\delta < 1   H)$
3	False discovery rates	$P(H_0   p_\delta = 0)$ $P(H_1   p_\delta = 1)$

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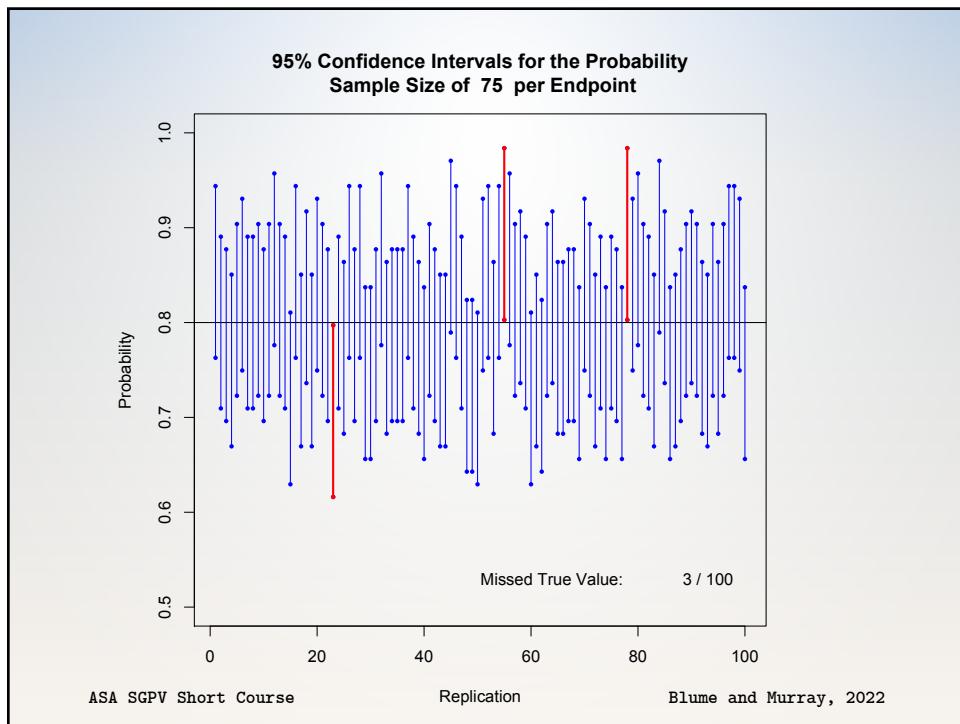
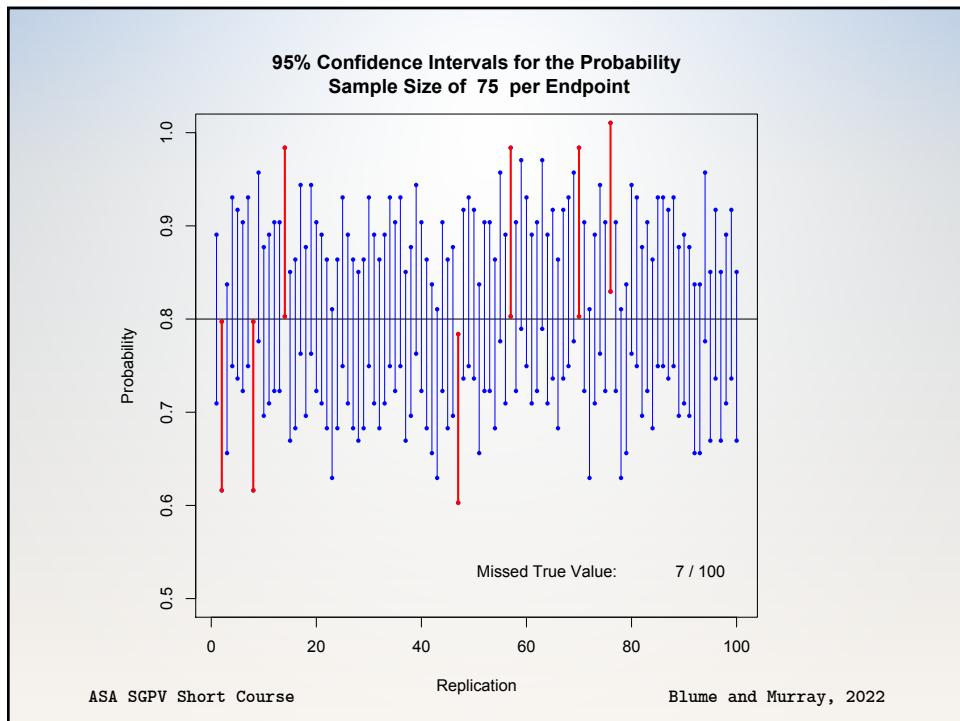
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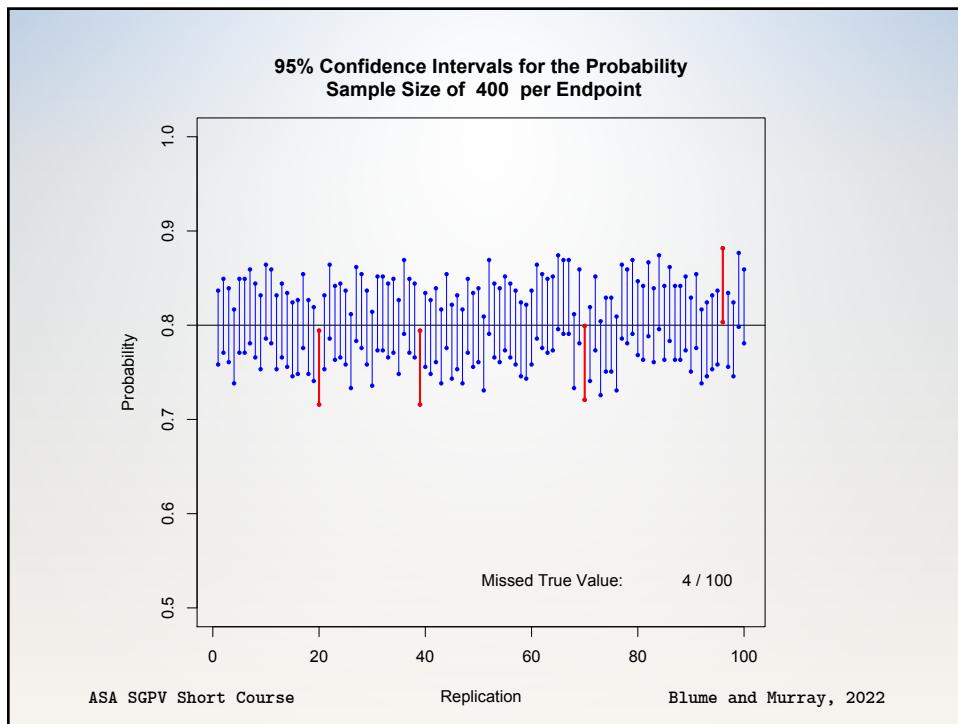
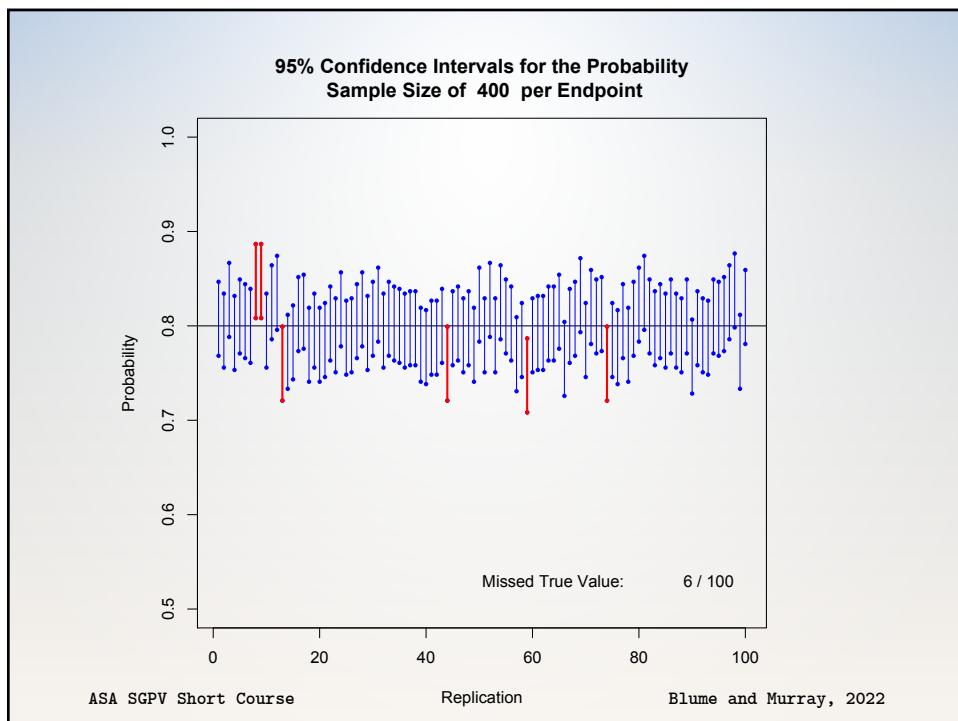
## The Intuition

- 95% CI formulas will exclude the truth 5% of the time
- Increasing the sample size...
  - Does not change the miss rate (!)
  - Reduces the width of the CI
  - Reduces the amount by which the CIs misses the truth (on average)
- The coverage probability (really its compliment) bounds the SGPV error rates

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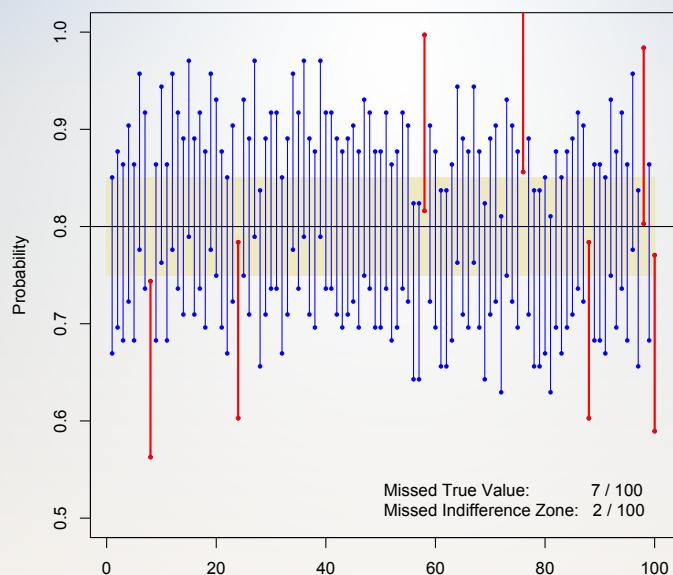
## Impact of using a null 'zone'

- Interval nulls represent scientific significance.
- A CI that does not overlap with the indifference zone implies statistical and clinical significance. ( $SPGV = 0$ )
- A CI that partially overlaps with the indifference zone, but does not include the null value, implies statistical significance but not clinical significance. ( $0 < SGPV < 1$ )
- A CI that is entirely contained in the indifference zone establishes clinical equivalence. ( $SGPV = 1$ )

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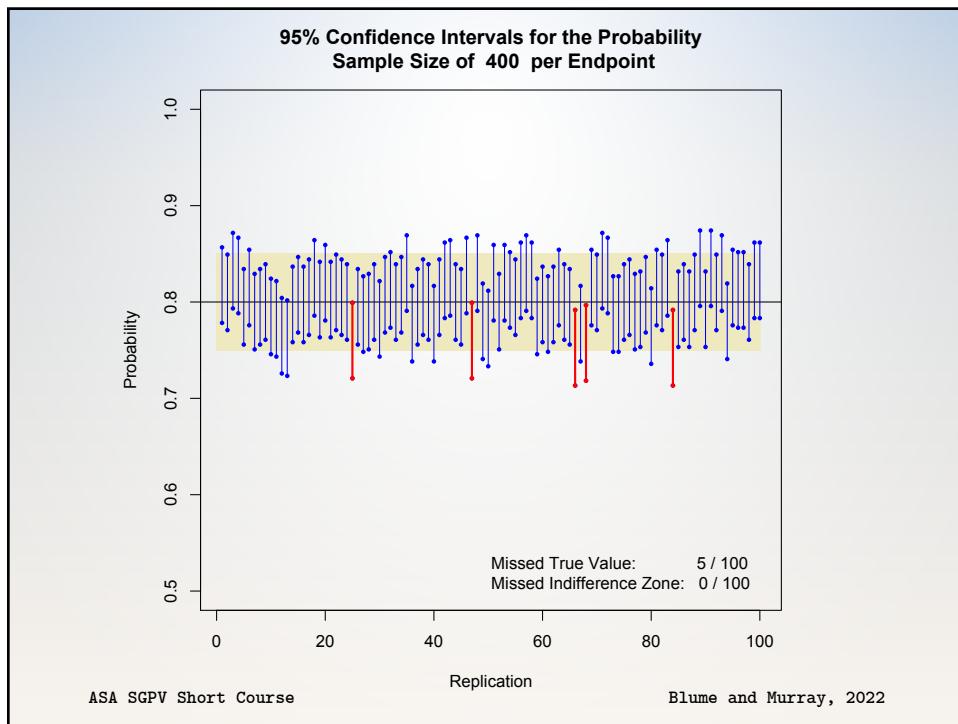
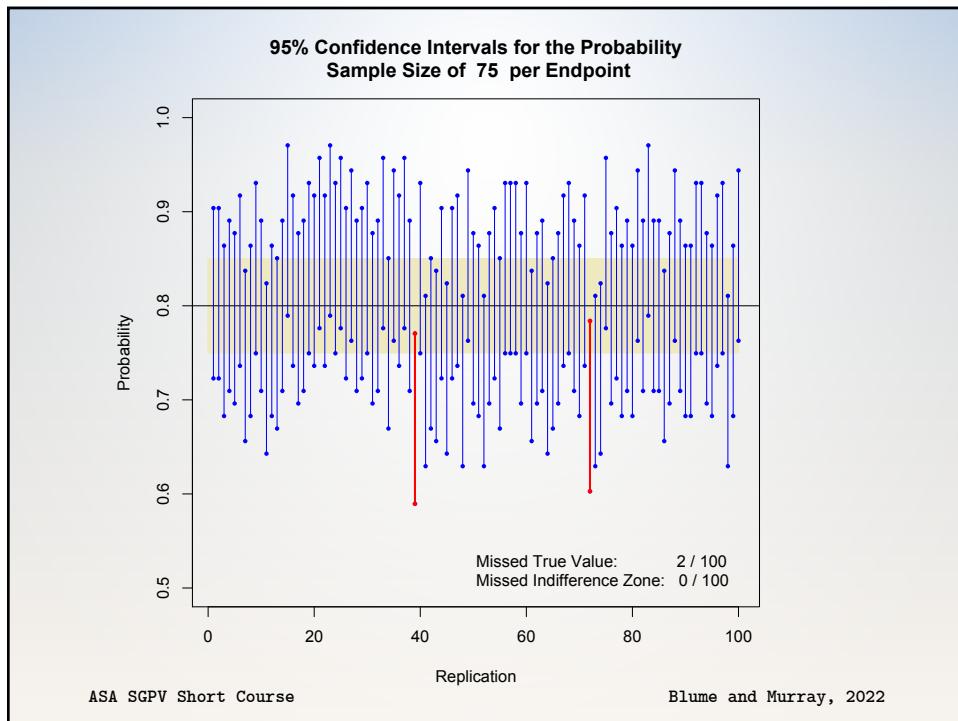
95% Confidence Intervals for the Probability  
Sample Size of 75 per Endpoint

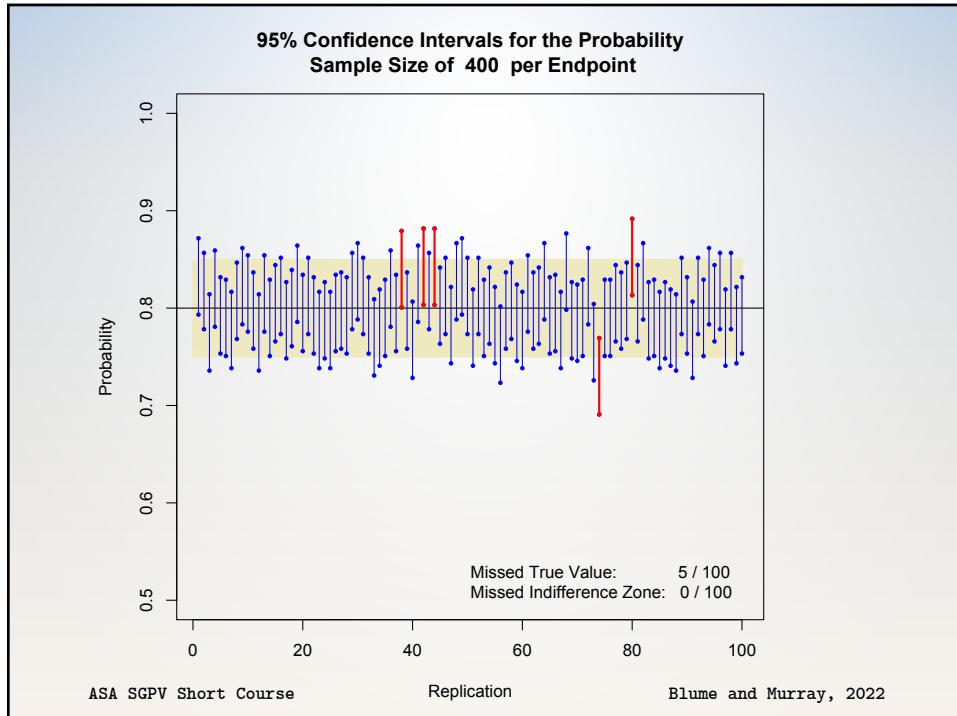


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Replication

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## Statistical Properties

Suppose interval  $I$  has coverage probability  $1-\alpha$ , then

Three ‘Error’ Rates

1.  $P(p_\delta = 0 | H_0) \leq \alpha$  and  $\rightarrow 0$  as  $n \rightarrow \infty$
2.  $P(p_\delta = 1 | H_1) \leq \alpha$  and  $\rightarrow 0$  as  $n \rightarrow \infty$
3.  $P(0 < p_\delta < 1 | H)$  controlled through sample size

*Will examine  
these first*

Two False Discovery Rates

1.  $P(H_0 | p_\delta = 0)$
2.  $P(H_1 | p_\delta = 1)$

*Will graph to  
illustrate*

## Statistical Properties

- How often are the data incompatible with null?
- Examine  $P(p_\delta = 0|\theta)$  as  $\theta$  varies
  - Power function
- This probability
  - converges to one for alternatives not near the edge of interval null
  - converges to zero for null hypotheses not near the edge of the null set
  - converges to alpha for hypotheses approaching or on the edge of the null set

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## ‘Power’ Function

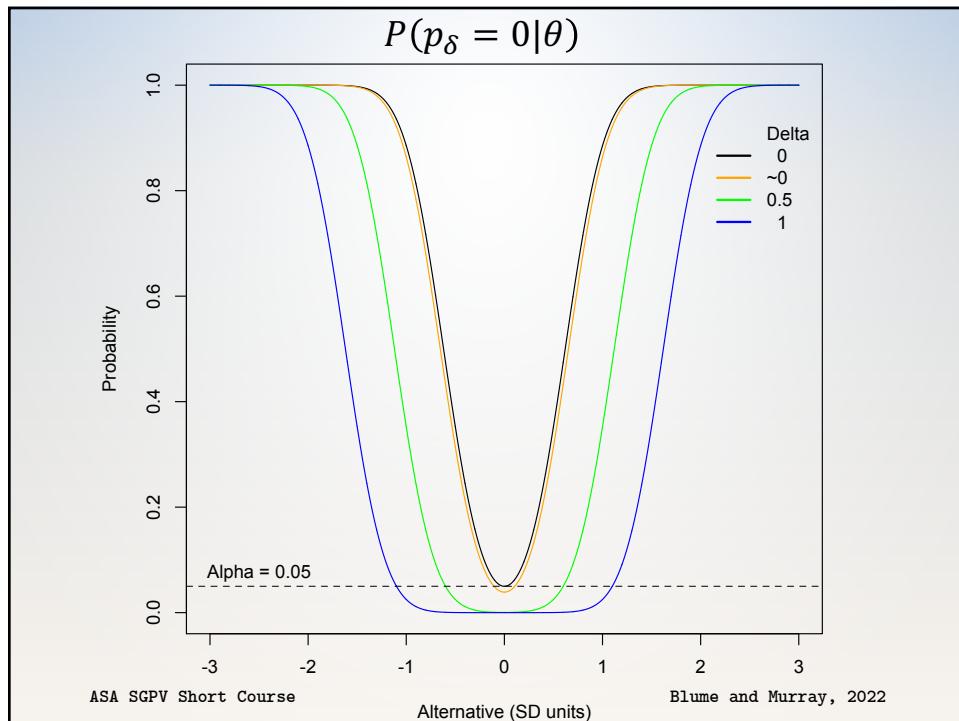
- $\theta_0$ : point null,  $\sigma$ : standard deviation
- $\delta$ : half-width of indifference zone

$$P(p_\delta = 0|\theta) = \Phi \left[ \frac{\sqrt{n}(\theta_0 - \theta)}{\sigma} - \frac{\sqrt{n}\delta}{\sigma} - Z_{\alpha/2} \right] + \Phi \left[ -\frac{\sqrt{n}(\theta_0 - \theta)}{\sigma} - \frac{\sqrt{n}\delta}{\sigma} - Z_{\alpha/2} \right]$$

$$P_{\theta_0}(p_\delta = 0|\theta_0) = 2\Phi \left[ -\frac{\sqrt{n}\delta}{\sigma} - Z_{\alpha/2} \right]$$

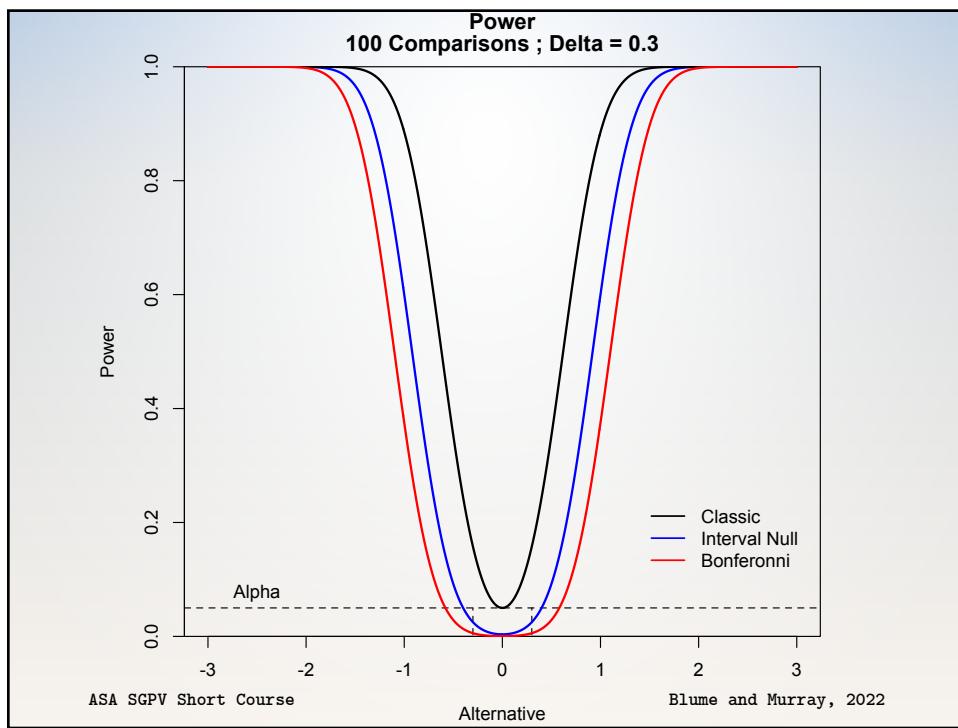
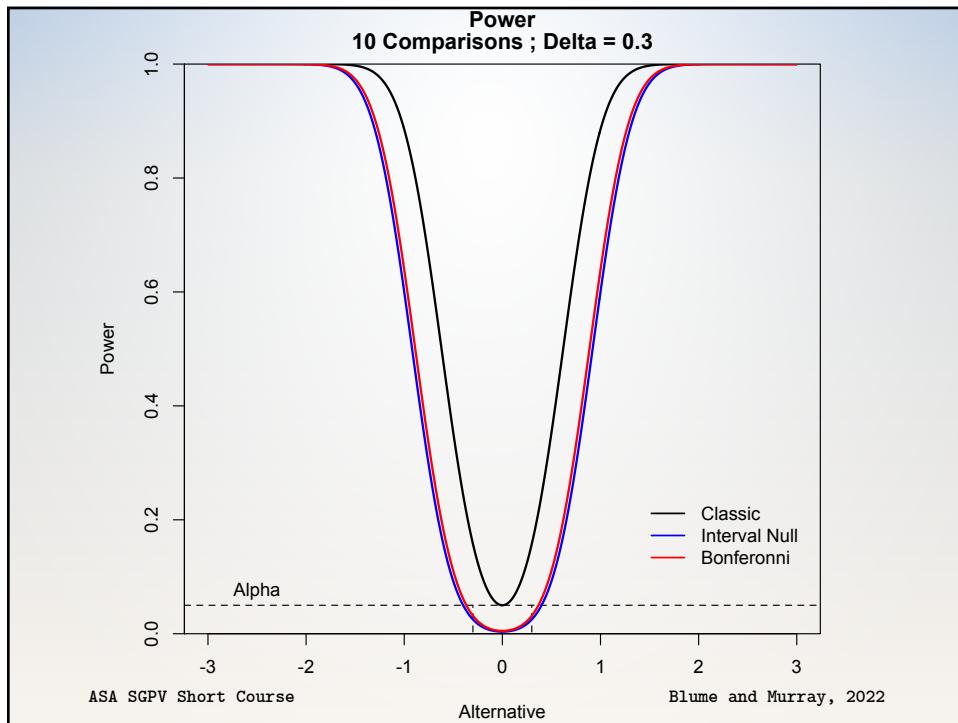
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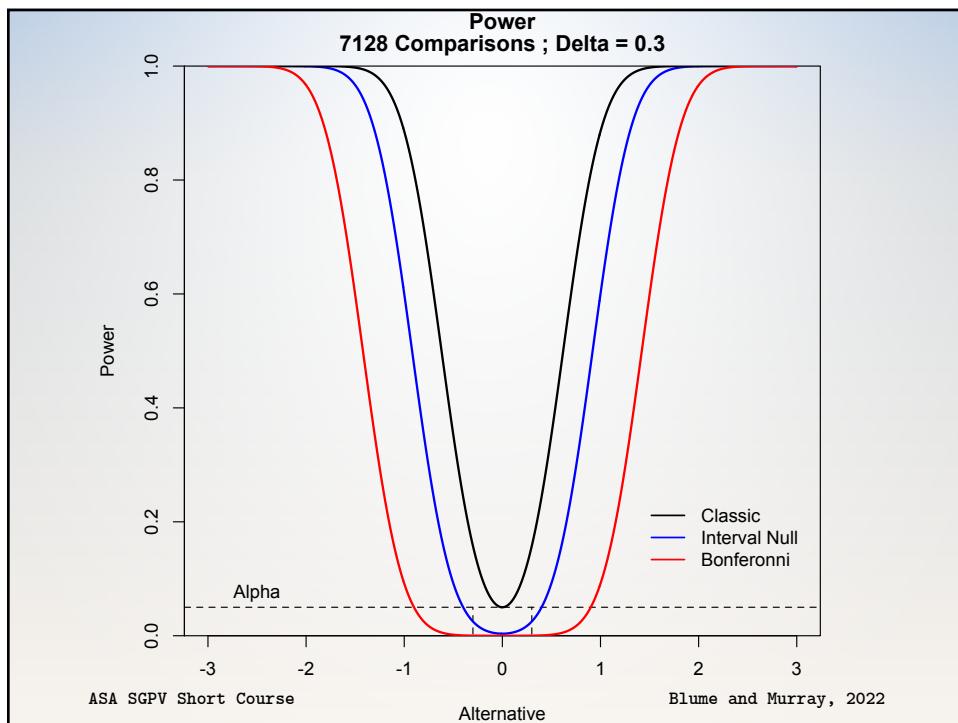
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## Compare with standard methods

- Second-generation  $p$ -value vs. Bonferroni correction
  - Adjusted for  $\{10, 100, 7128\}$  comparisons
  - Leukemia data example
- Remember SGPV are not adjusted for comparisons
- Discuss?





## Compatible with Null

- How often are the data compatible with null?
- Examine  $P(p_\delta = 1|\theta)$  when  $\theta$  is null or practically null
  - Essentially opposite of power function
- Sample size must be large enough to allow the null interval to contain the interval estimate
- This probability
  - converges to zero or one quickly for alternatives not near the edge of interval null

## ‘Null Power’ Function

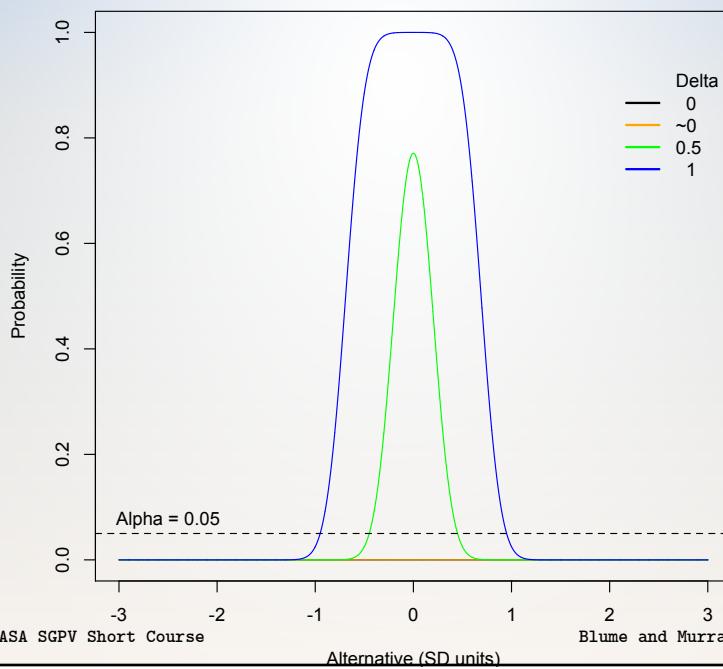
- How often are the data compatible with null?
- Sample size must be large enough to allow null interval to contain the interval estimate, so  $(\delta > Z_{\alpha/2}/\sqrt{n})$  or  $(\sqrt{n} > Z_{\alpha/2}/\delta)$
- This probability converges to 0 or 1 quickly

$$P(p_\delta = 1|\theta) = \Phi \left[ \frac{\sqrt{n}(\theta_0 + \delta)}{\sigma} - \frac{\sqrt{n}\theta}{\sigma} - Z_{\alpha/2} \right] - \Phi \left[ \frac{\sqrt{n}(\theta_0 - \delta)}{\sigma} - \frac{\sqrt{n}\theta}{\sigma} + Z_{\alpha/2} \right]$$

when  $\delta > Z_{\alpha/2}/\sqrt{n}$

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 $P(p_\delta = 1|\theta)$ 

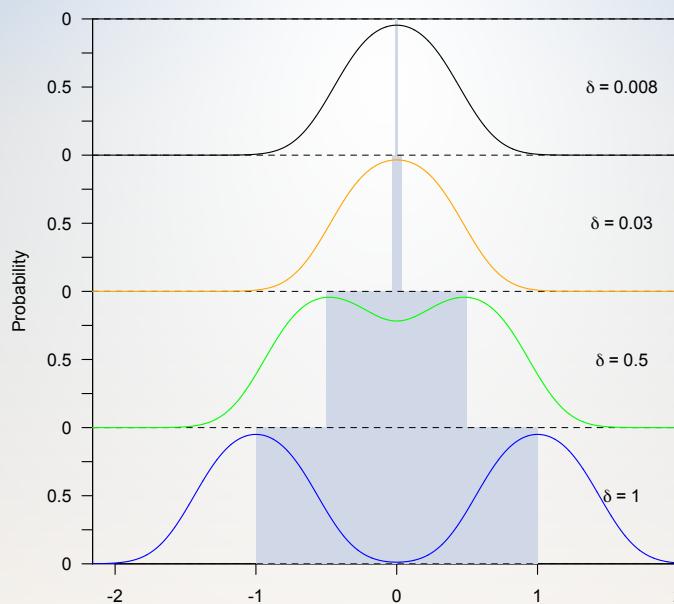
## Probability of Inconclusive Data

- How often are the data inconclusive?
- Examine  $P(0 < p_\delta < 1|\theta)$  for various  $\theta$
- This probability
  - drives sample size projections
  - is maximized when  $H$  is near the interval null edge
  - decreases quickly as  $H$  moves away from edge of null
- $P(0 < p_\delta < 1|\theta) = 1 - P(p_\delta = 0|\theta) - P(p_\delta = 1|\theta)$

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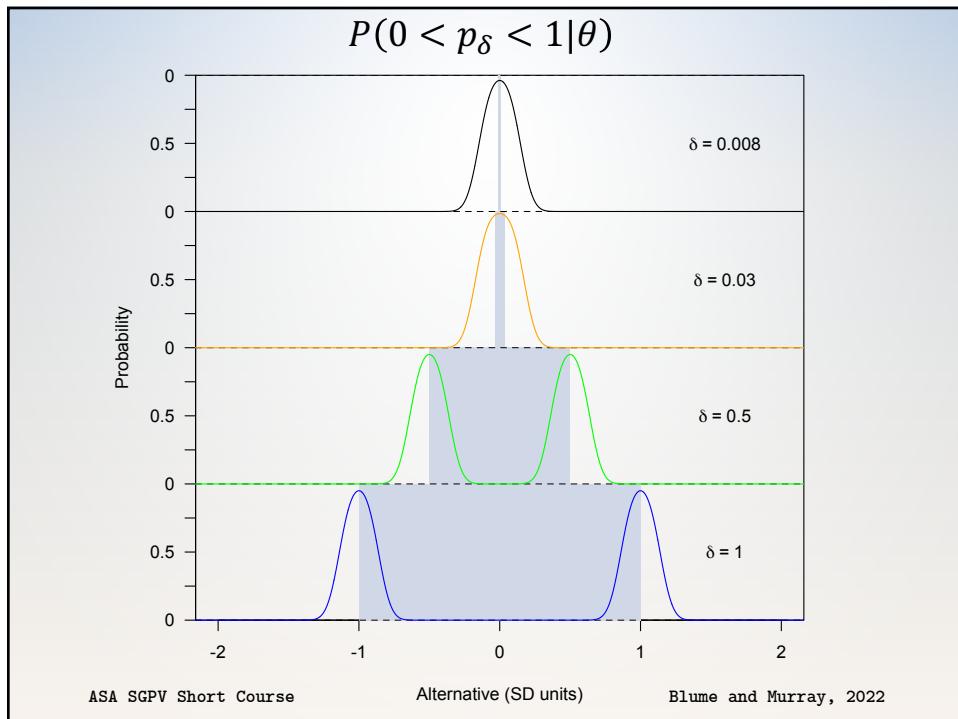
$$P(0 < p_\delta < 1|\theta)$$



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Alternative (SD units)

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## Statistical Properties

Suppose interval  $I$  has coverage probability  $1-\alpha$ , then

Three ‘Error’ Rates

1.  $P(p_\delta = 0 | H_0) \leq \alpha$  and  $\rightarrow 0$  as  $n \rightarrow \infty$
2.  $P(p_\delta = 1 | H_1) \leq \alpha$  and  $\rightarrow 0$  as  $n \rightarrow \infty$
3.  $P(0 < p_\delta < 1 | H)$  controlled through sample size

Two False Discovery Rates (next section!)

1.  $P(H_0 | p_\delta = 0)$
2.  $P(H_1 | p_\delta = 1)$

## Remarks

- Second-generation  $p$ -values...
  - Has three ‘Error’ rates
  - Allows Type I and II rate to converge to zero
  - Control changes of inconclusive results
  - Controls error rate using *science*
  - Reduces the false discovery rate (next section)
- Anchoring the scale of the effect size...
  - Eliminates most Type I Errors
  - Improves scientific translation of statistical model

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Time for Code Part 2a!

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## 10 Minute Break!

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## Equivalence Tests

- Establish bioequivalence between data and an established equivalence range or interval null
- Example: A pharmaceutical company tests for drug approval by comparing new drug's performance to an approved drug's performance
- Uses an interval null or equivalence range
  - $H_0 = [\theta^-, \theta^+]$

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## TOST Test

- Most popular frequentist test is the Two One-Sided t-tests (TOST) (Schuirmann 1987)
  - Flips the null and alternative (be careful)
  - Uses the  $(1-2\alpha)\%$  confidence interval (be careful)
- Tests are ordinary, one-sided,  $\alpha$ -level t-tests
- If *both* one-sided tests reject then conclude the evidence is contained in the equivalence range

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## TOST Test

- **Fail to reject the (original) null:** The confidence interval is outside of the indifference zone  

$$H_0: (\theta < \theta^- \text{ or } \theta > \theta^+)$$
- **Reject the (original) null:** The confidence interval is contained within the indifference zone  

$$H_1: (\theta \geq \theta^- \text{ and } \theta \leq \theta^+)$$
- Reported  $p$ -value is the  $p$ -value of largest magnitude from the two one-sided tests

$$p_T = \max\{p_{T_1}, p_{T_2}\}$$

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## SGPV Definition

**Second-generation  
*p*-value (SGPV)**

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

**Proportion** of data-supported hypotheses that are also null hypotheses

**Small-sample  
correction factor**

shrinks proportion to  $\frac{1}{2}$  when  $|I|$  wide

when  $|I| > 2|H_0|$

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## TOST vs. SGPV comparison

		SGPV Outcomes		
		Consistent with the alternative (SGPV near 0)	Inconclusive (SGPV near $\frac{1}{2}$ )	Consistent with the null (SGPV near 1)
Equivalence Tests Outcomes	Consistent with the alternative ( <i>p</i> -value is unable to indicate this)	Not applicable <b>A</b>	Not applicable <b>B</b>	Not applicable <b>C</b>
	Inconclusive ( <i>p</i> -value is non-significant)	Can occur <b>D</b>	Can occur <b>E</b>	Never occurs <b>F</b>
	Consistent with the null ( <i>p</i> -value is significant)	Never occurs <b>H</b>	Can occur in small samples <b>I</b>	Can occur <b>J</b>

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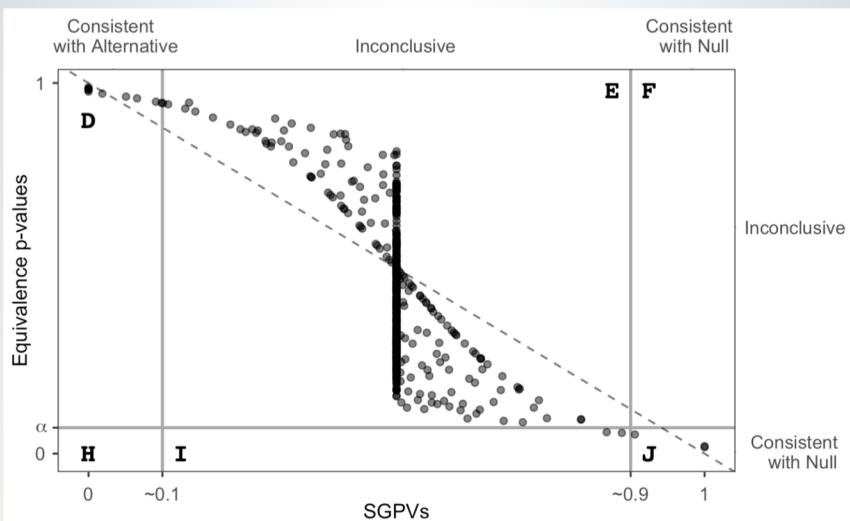
## TOST v SGPV Simulation

- Simulate TOST and SGPV reported  $p$ -values
  - Data generated under the null,  $N(0,1)$
  - Sample size of  $n=6$
  - Yields 70% power for  $\Delta = 1$  with 5% type 1 error
  - Indifference zone is  $[\theta^-, \theta^+] = [-0.375, 0.375]$
  - Uncertainty interval is 95% confidence interval
  - 500 iterations (for illustration)
  - TOSTER R package ([Link](#))

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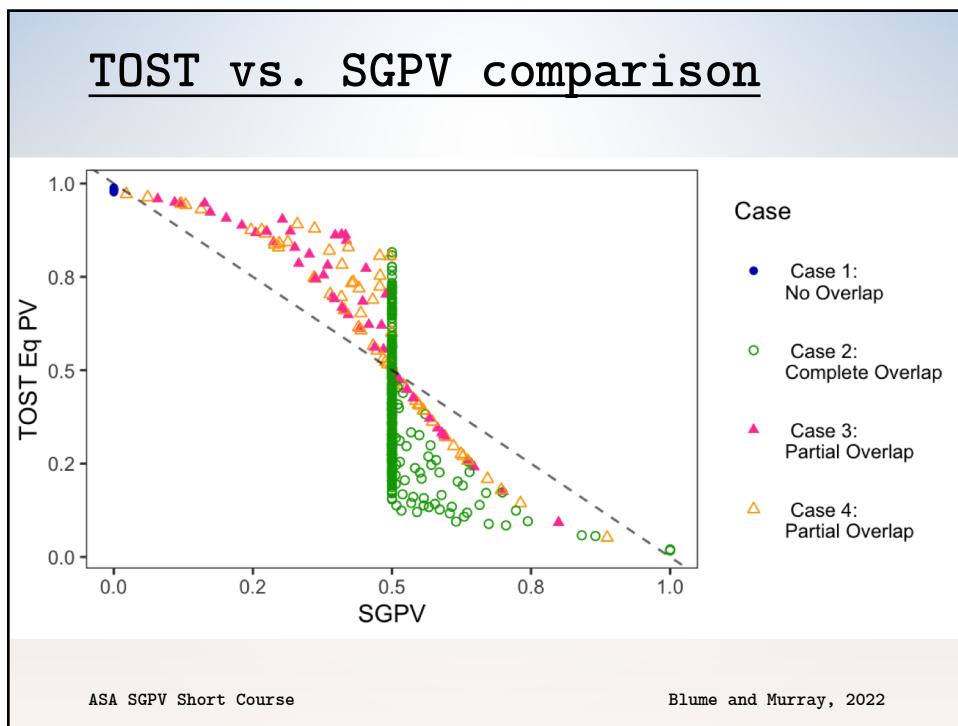
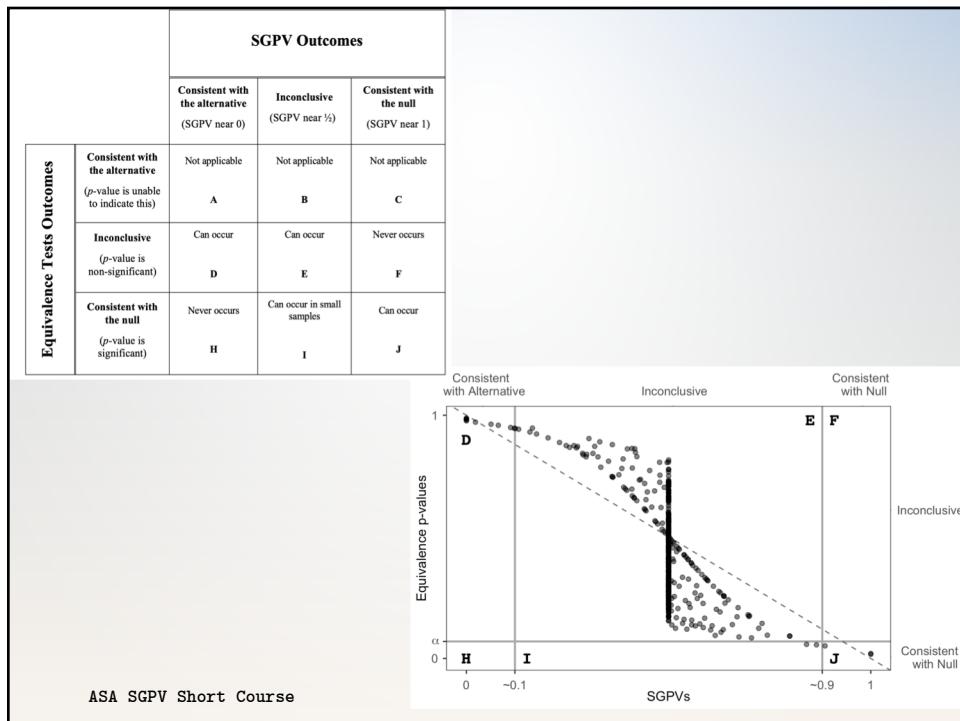
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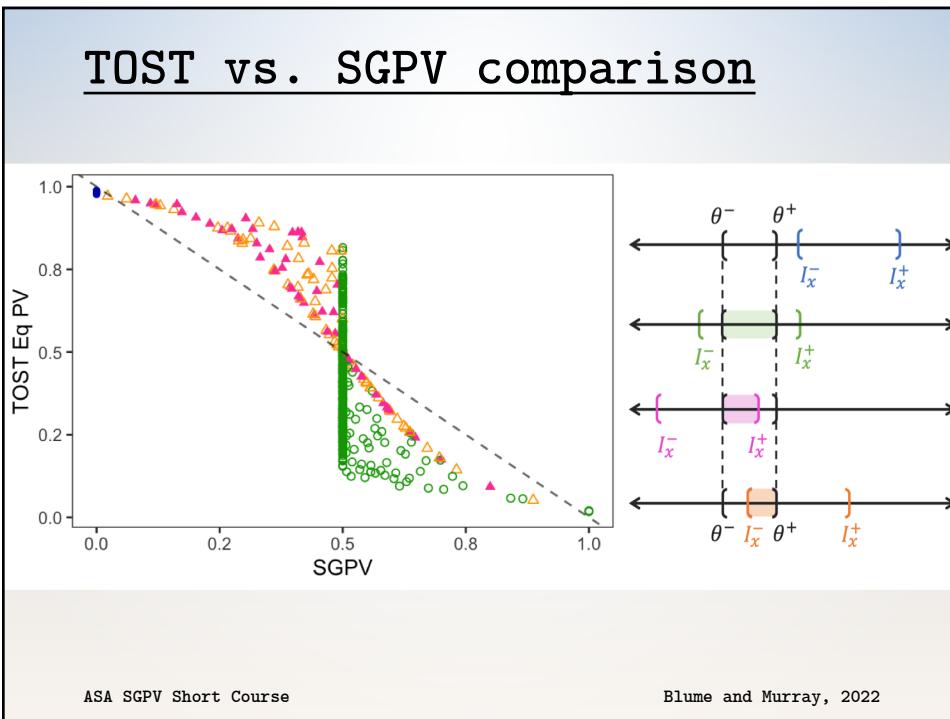
## TOST vs. SGPV comparison



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## Relationship

- Derived the mathematical relationship in all cases of overlap
- Case 3 and 4 of partial overlap:

$$p_\delta = \left[ \left( \frac{1}{2c_\alpha} \right) F_n^{-1}(1 - p_T) + \frac{1}{2} \right] \times \max \left\{ \frac{\frac{c_\alpha S}{\sqrt{n}}}{(\theta^+ - \theta^-)}, 1 \right\}$$

- Limiting behavior under the null

$$P(\text{Case 2}) \rightarrow 1$$

$$\begin{array}{ll} p_\delta \rightarrow 1 & (\text{right}) \\ p_T \rightarrow 0 & (\text{bottom}) \end{array}$$

## TOST vs. SGPV comparison

TOST	SGPV
• 2 inference outcomes	• 3 inference outcomes
• Conclusions only about $(1 - 2\alpha)\%$ confidence interval	• Any uncertainty data interval can be used
• Type I Error is ultra-conservative (distribution of $p_T$ is non-uniform)	• Type I error is accurately assessed (Tied to width of data interval)
• Not uniformly most powerful	• Indicates when data agree with null or alternative without additional testing
• No measure of overlap included in computation	• Includes overlap in reported $p$ -value

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## Comparison

- TOST and SGPV are not one-to-one unless the variance is known
- TOST has significant limitations
- *SGPV is more flexible and easier to interpret*

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**Time for Code Part 2b!**

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**10 Minute Break!**

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## Statistical Properties

Suppose interval  $I$  has coverage probability  $1-\alpha$ , then

Three ‘Error’ Rates

1.  $P(p_\delta = 0 | H_0) \leq \alpha$  and  $\rightarrow 0$  as  $n \rightarrow \infty$
2.  $P(p_\delta = 1 | H_1) \leq \alpha$  and  $\rightarrow 0$  as  $n \rightarrow \infty$
3.  $P(0 < p_\delta < 1 | H)$  controlled through sample size

Two False Discovery Rates

1.  $P(H_0 | p_\delta = 0)$
2.  $P(H_1 | p_\delta = 1)$

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## False Discovery Rates

- FDR for 5 SGPV=0 findings; computed under various null and alternative configurations (w/ flat prior).

SNP ID	SGPV rank	p-value rank	OR	1/8 SI lower limit	1/8 SI upper limit	FDR <sub>1</sub>	FDR <sub>2</sub>	FDR <sub>3</sub>
kgp4568244_C	1	133	0.10	0.03	0.37	2.9%	17.1%	3.3%
kgp8051290_G	13	2002	15.58	1.95	124.68	4.3%	30.3%	4.9%
kgp4497498_A	28	255	4.37	1.80	10.64	2.5%	8.6%	3.1%
rs3123636_G	423	1	1.39	1.26	1.55	0.01%	0.1%	0.4%
kgp7460928_G	1443	3310	1.78	1.11	2.87	2.4%	2.0%	3.0%

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## False discovery rates

- Impact of  $\alpha=0.05$  vs  $\alpha=0.05/7128$  (7128 comparisons)

- False Discovery Rate (**FDR**)

$$P(H_0|p < \alpha) = \left[ 1 + \frac{(1 - \beta)}{\alpha} r \right]^{-1}$$

- False Confirmation Rate (**FCR**)

$$P(H_1|p > \alpha) = \left[ 1 + \frac{(1 - \alpha)}{\beta} \frac{1}{r} \right]^{-1}$$

$$r = P(H_1)/P(H_0)$$

Error rates

Error rates

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## False discovery rates

- Second-generation  $p$ -values

- False Discovery Rate (**FDR**)

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

- False Confirmation Rate (**FCR**)

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

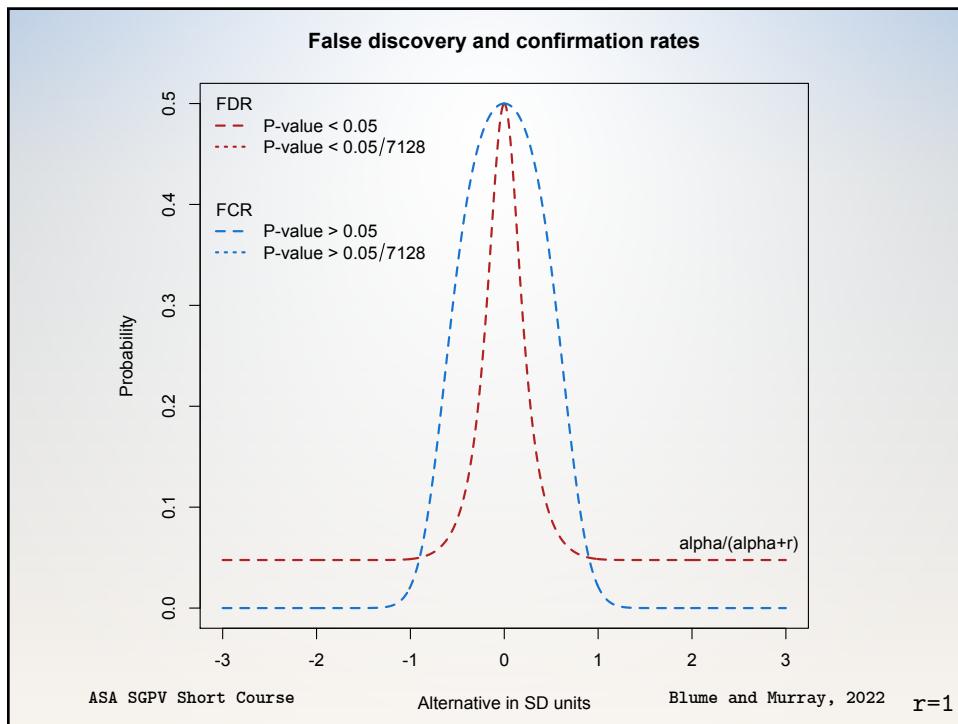
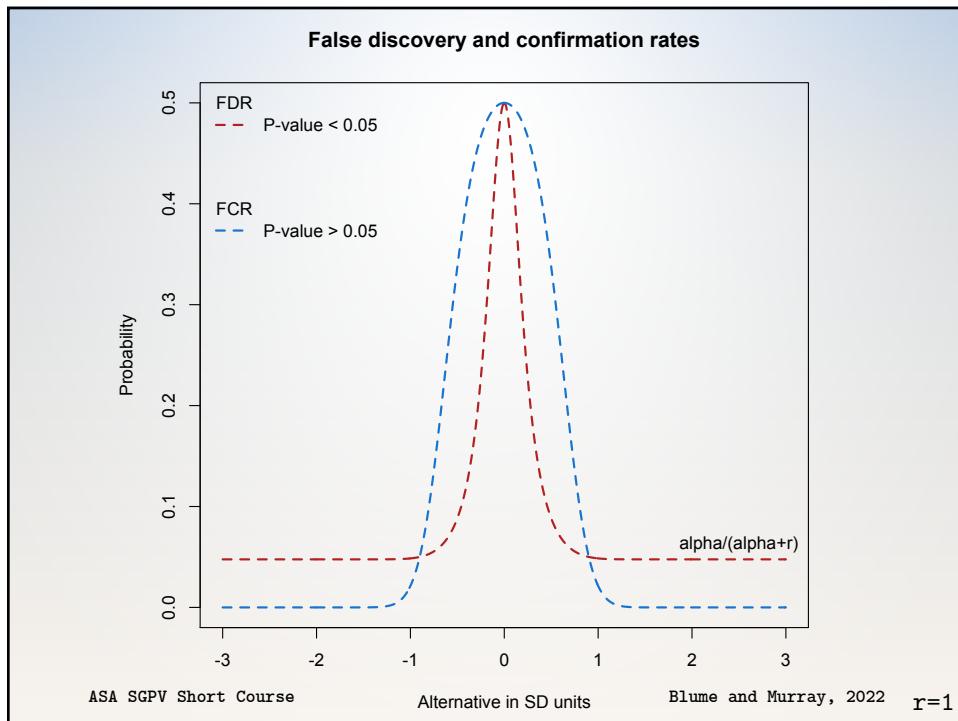
$$r = P(H_1)/P(H_0)$$

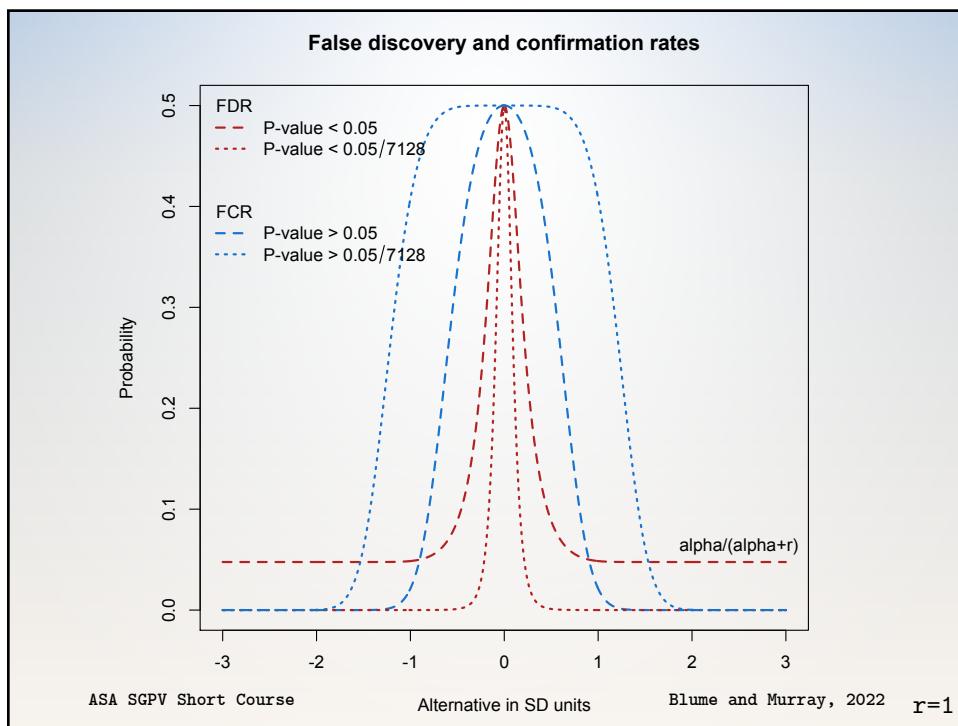
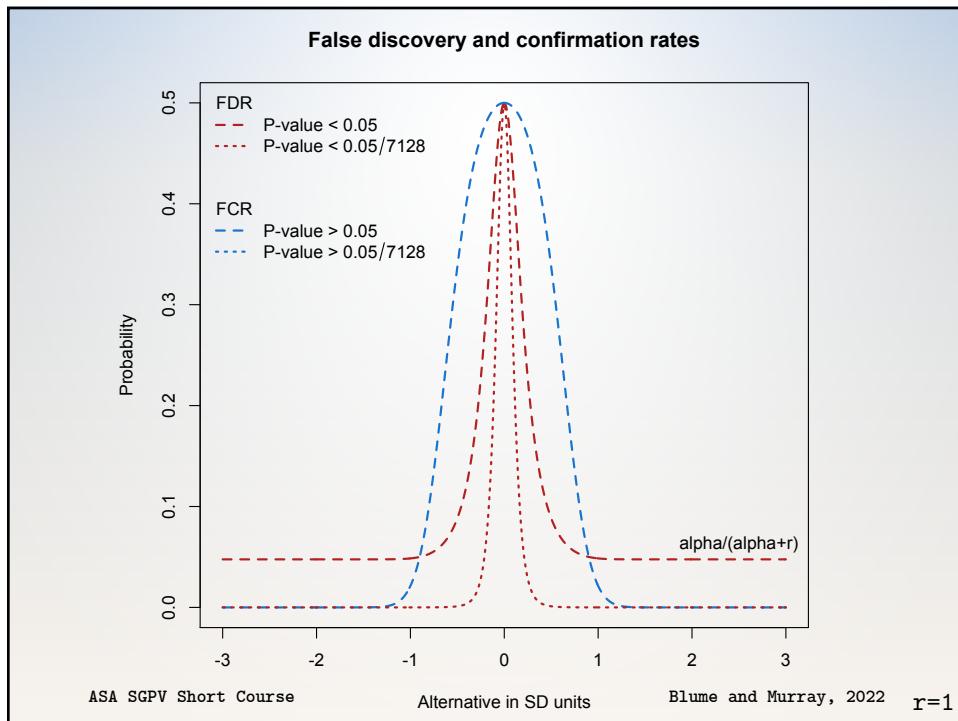
Error Rates

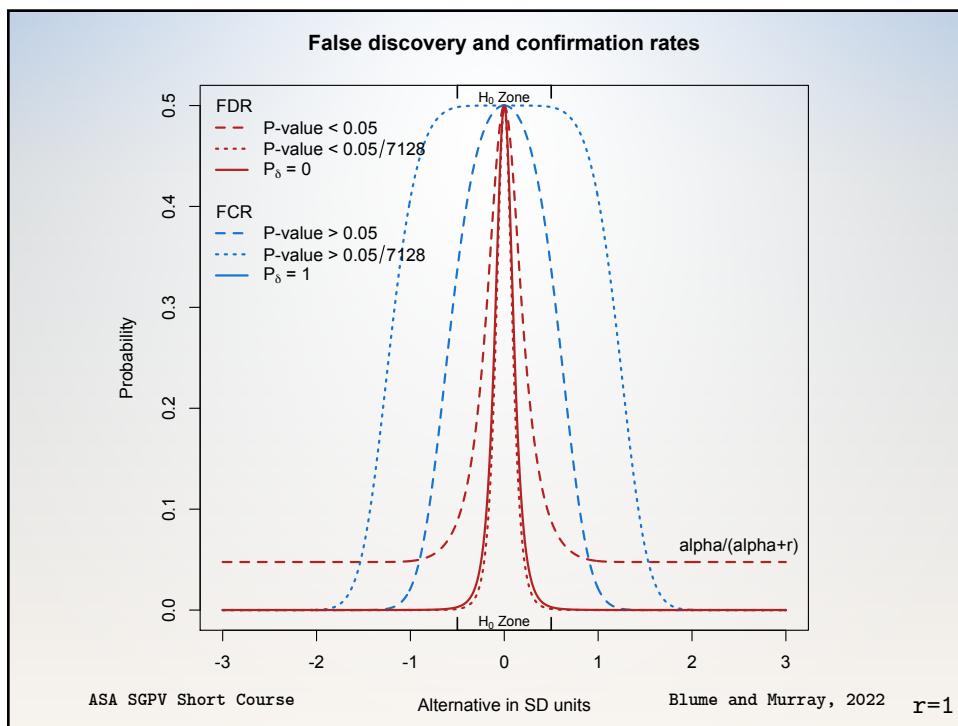
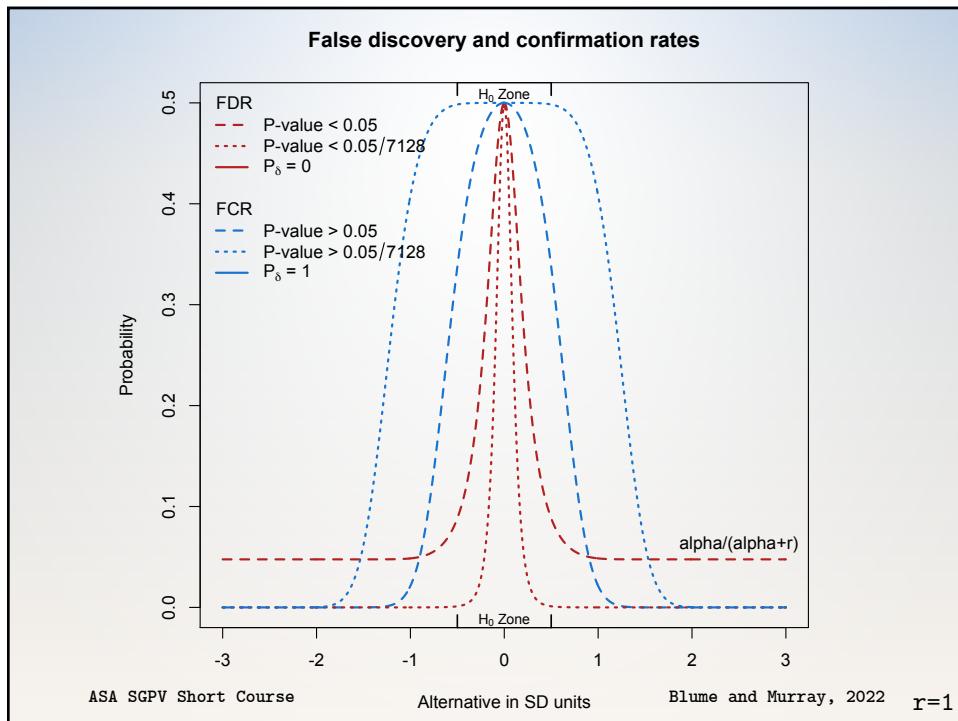
Error Rates

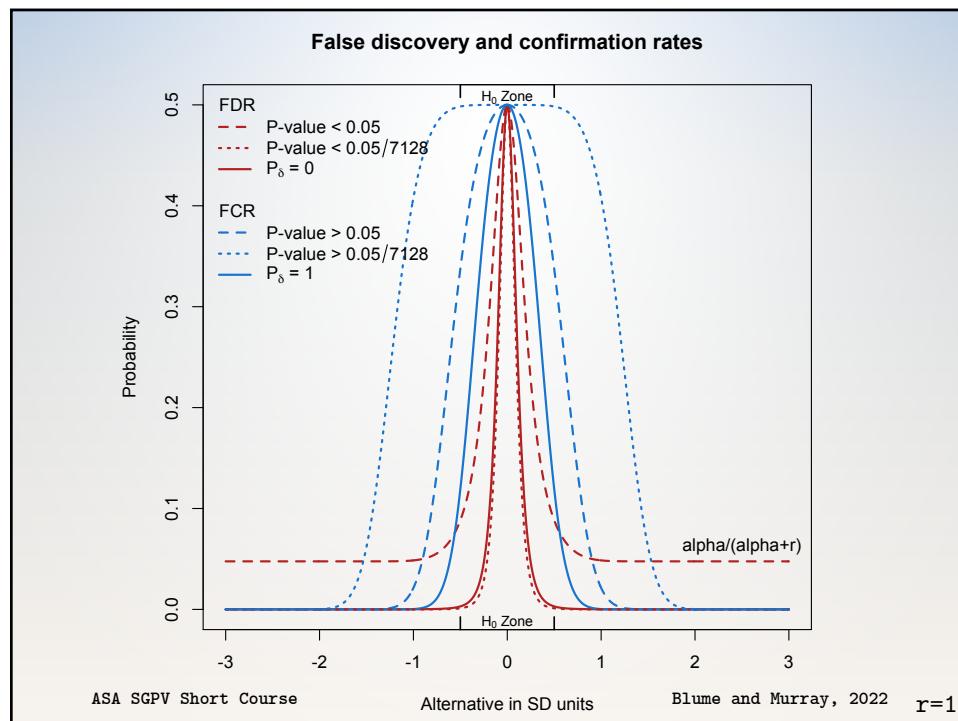
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## FDR R Packages

- SGPVs
  - Valerie Welty
  - `sgpv::fdrisk()`
  - This function computes the false discovery risk (sometimes called the "empirical bayes FDR") for a second-generation  $p$ -value of 0, or the false confirmation risk for a second-generation  $p$ -value of 1.
- Raw p-values
  - `FDRestimation::p.fdr()`
  - This function computes FDRs and Method Adjusted p-values.
  - Methods include: Benjamini-Hochberg, Benjamini-Yekutieli, Bonferroni, Holm, Hochberg, and Sidak.

**Time for Code Part 2c!**  
**(FDRestimation?)**

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**10 Minute Break!**

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## Study Planning for SGPs

- Will edit paper and submit by end of 2022
- Purpose: Evaluate how different techniques of setting the indifference zone effect the SGpv study properties.
- What options does a collaborator have when they are uncertain of the indifference zone?

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## Traditional p-value vs. SGpv

		Null is true		Alternative is true	
		Traditional p-value		Traditional p-value	
Inference	Data are consistent with the alternative	Type I error $P_{\theta_0} (p \leq 0.05)$		Power or (1 - Type II error) $P_{\theta_1} (p \leq 0.05)$	
	Data are inconclusive	1 - Type I error $P_{\theta_0} (p > 0.05)$		Type II error $P_{\theta_1} (p > 0.05)$	
	Data are consistent with the null	NA		NA	

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## Traditional p-value vs. SGPV

		Null is true		Alternative is true	
		SGPV		SGPV	
Inference	Data are consistent with the alternative		$\beta_0$ $P_{\theta_0}(p_\delta = 0)$		$\beta_1$ $P_{\theta_1}(p_\delta = 0)$
	Data are inconclusive		$\gamma_0$ $P_{\theta_0}(0 < p_\delta < 1)$		$\gamma_1$ $P_{\theta_1}(0 < p_\delta < 1)$
	Data are consistent with the null		$\omega_0$ $P_{\theta_0}(p_\delta = 1)$		$\omega_1$ $P_{\theta_1}(p_\delta = 1)$

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## Traditional p-value vs. SGPV

		Null is true		Alternative is true	
		Traditional p-value	SGPV	Traditional p-value	SGPV
Inference	Data are consistent with the alternative	Type I error $P_{\theta_0}(p \leq 0.05)$	$\beta_0$ $P_{\theta_0}(p_\delta = 0)$	Power or (1 - Type II error) $P_{\theta_1}(p \leq 0.05)$	$\beta_1$ $P_{\theta_1}(p_\delta = 0)$
	Data are inconclusive	1 - Type I error $P_{\theta_0}(p > 0.05)$	$\gamma_0$ $P_{\theta_0}(0 < p_\delta < 1)$	Type II error $P_{\theta_1}(p > 0.05)$	$\gamma_1$ $P_{\theta_1}(0 < p_\delta < 1)$
	Data are consistent with the null	NA	$\omega_0$ $P_{\theta_0}(p_\delta = 1)$	NA	$\omega_1$ $P_{\theta_1}(p_\delta = 1)$

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## Traditional p-value vs. SGPV

		Null is true		Alternative is true	
		Traditional p-value	SGPV	Traditional p-value	SGPV
Inference	Data are consistent with the alternative	Type I error $P_{\theta_0}(p \leq 0.05)$	$\beta_0$ $P_{\theta_0}(p_\delta = 0)$	Power or (1 - Type II error) $P_{\theta_1}(p \leq 0.05)$	$\beta_1$ $P_{\theta_1}(p_\delta = 0)$
	Data are inconclusive	1 - Type I error $P_{\theta_0}(p > 0.05)$	$\gamma_0$ $P_{\theta_0}(0 < p_\delta < 1)$	Type II error $P_{\theta_1}(p > 0.05)$	$\gamma_1$ $P_{\theta_1}(0 < p_\delta < 1)$
	Data are consistent with the null	NA	$\omega_0$ $P_{\theta_0}(p_\delta = 1)$	NA	$\omega_1$ $P_{\theta_1}(p_\delta = 1)$

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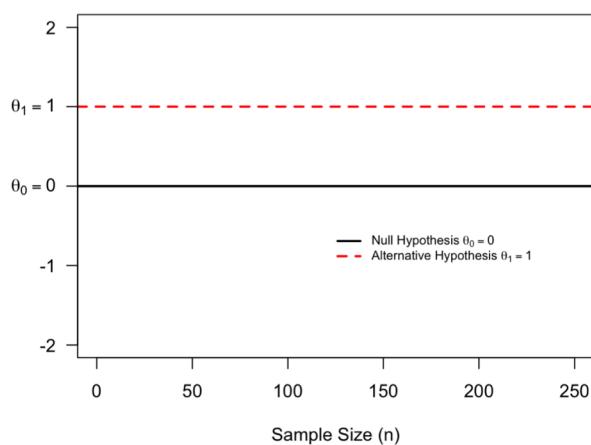
## Traditional p-value vs. SGPV

		Null is true		Alternative is true	
		Traditional p-value	SGPV	Traditional p-value	SGPV
Inference	Data are consistent with the alternative	Type I error $P_{\theta_0}(p \leq 0.05)$	$\beta_0$ $P_{\theta_0}(p_\delta = 0)$	Power or (1 - Type II error) $P_{\theta_1}(p \leq 0.05)$	$\beta_1$ $P_{\theta_1}(p_\delta = 0)$
	Data are inconclusive	1 - Type I error $P_{\theta_0}(p > 0.05)$	$\gamma_0$ $P_{\theta_0}(0 < p_\delta < 1)$	Type II error $P_{\theta_1}(p > 0.05)$	$\gamma_1$ $P_{\theta_1}(0 < p_\delta < 1)$
	Data are consistent with the null	NA	$\omega_0$ $P_{\theta_0}(p_\delta = 1)$	NA	$\omega_1$ $P_{\theta_1}(p_\delta = 1)$

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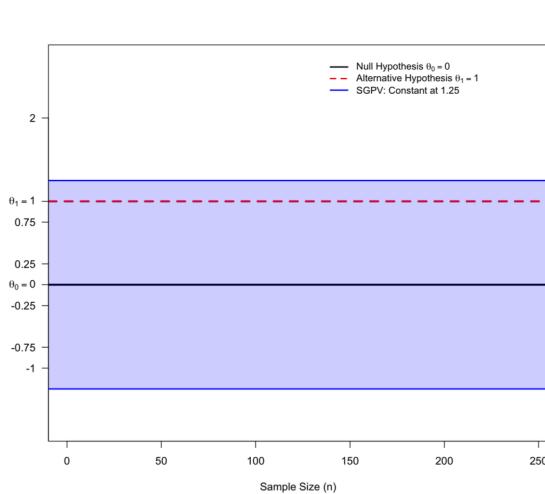
## Standard Assumptions



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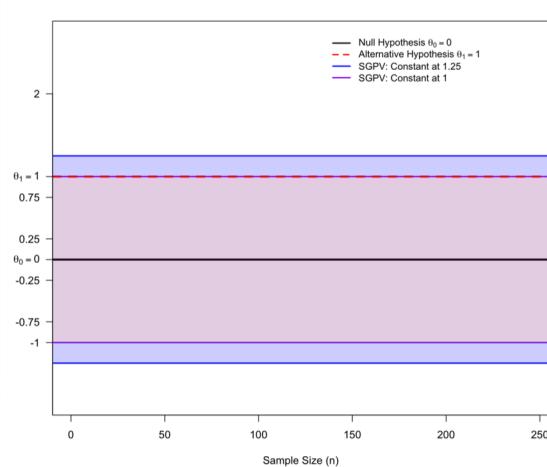
## Example Indifference Zones



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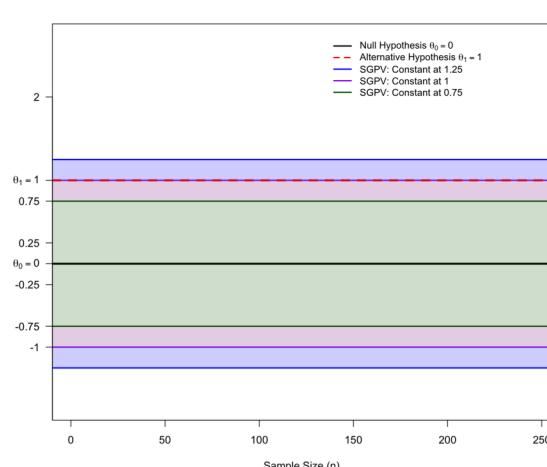
## Example Indifference Zones



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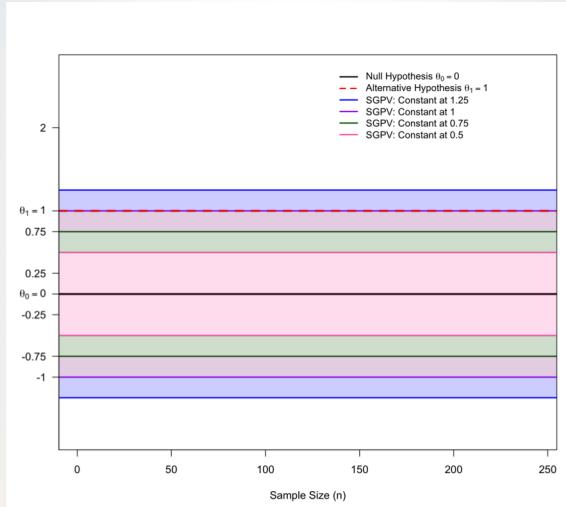
## Example Indifference Zones



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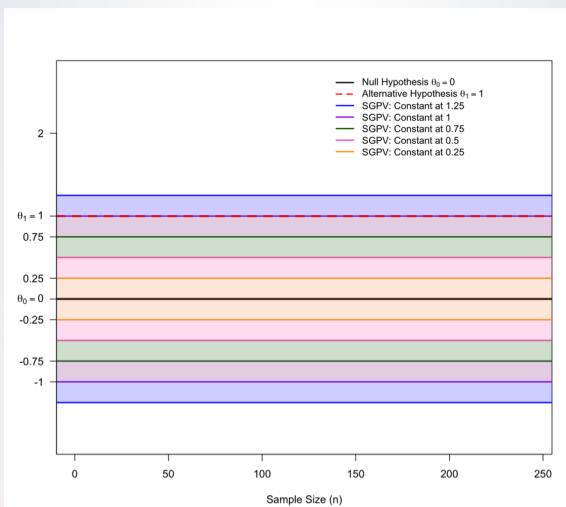
## Example Indifference Zones



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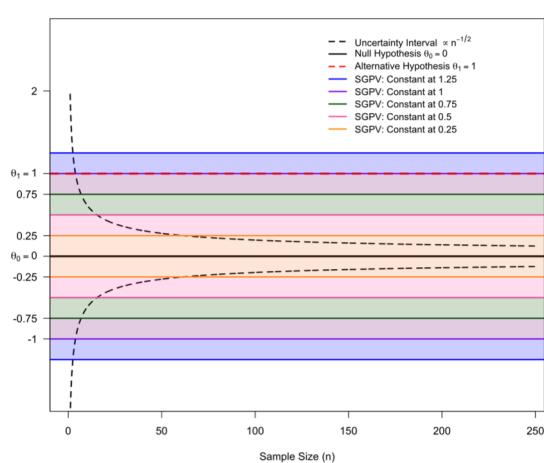
## Example Indifference Zones



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## Now with CI centered at null



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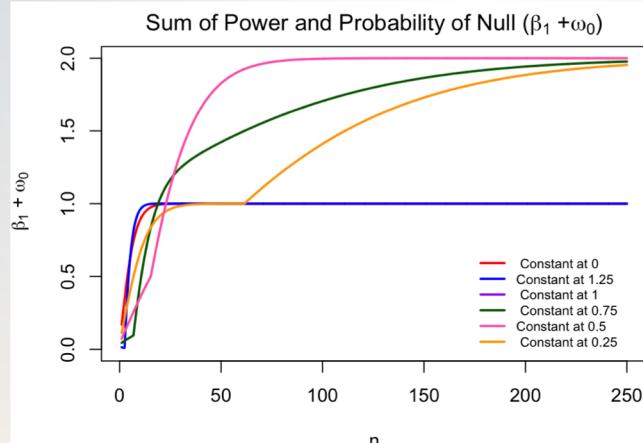
## Traditional p-value vs. SGPV

		Null is true		Alternative is true	
		Traditional p-value	SGPV	Traditional p-value	SGPV
Inference	Data are consistent with the alternative	Type I error $P_{\theta_0}(p \leq 0.05)$	$\beta_0$ $P_{\theta_0}(p_\delta = 0)$	Power or (1 - Type II error) $P_{\theta_1}(p \leq 0.05)$	$\beta_1$ $P_{\theta_1}(p_\delta = 0)$
	Data are inconclusive	1 - Type I error $P_{\theta_0}(p > 0.05)$	$\gamma_0$ $P_{\theta_0}(0 < p_\delta < 1)$	Type II error $P_{\theta_1}(p > 0.05)$	$\gamma_1$ $P_{\theta_1}(0 < p_\delta < 1)$
	Data are consistent with the null	NA	$\omega_0$ $P_{\theta_0}(p_\delta = 1)$	NA	$\omega_1$ $P_{\theta_1}(p_\delta = 1)$

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## Indifference Zone Properties

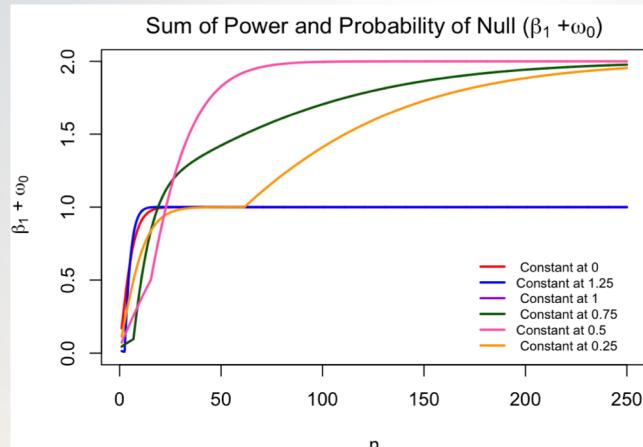


- Maximize power and probability of true nulls
- Plot  $\beta_1 + \omega_0$  over sample size

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## Indifference Zone Properties



- Maximize power and probability of true nulls
- Plot  $\beta_1 + \omega_0$  over sample size
- The half a standard deviation between  $\theta_1$  and  $\theta_0$  gives the highest sum for reasonable sample sizes

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## Shrinking Indifference Zones

- Collaborator is uncertain but comfortable with a wider interval to begin

For example:  $[-0.9, 0.9]$

- Limit shrinking to half distance between  $(\theta^-$  or  $\theta^+)$  and  $\theta_0$   $[-0.45, 0.45]$
- We can let the indifference zone shrink over sample size at different rates:

$$\delta_1(n) \propto \frac{\sqrt{V}}{n^{1/4}}$$

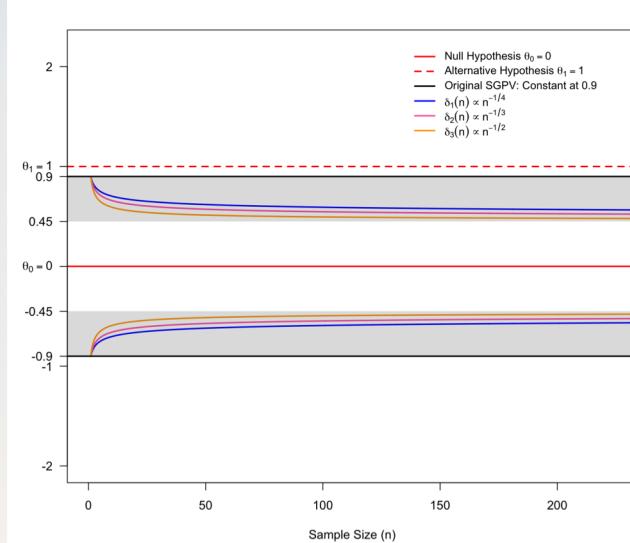
$$\delta_2(n) \propto \frac{\sqrt{V}}{n^{1/3}}$$

$$\delta_3(n) \propto \frac{\sqrt{V}}{n^{1/2}}$$

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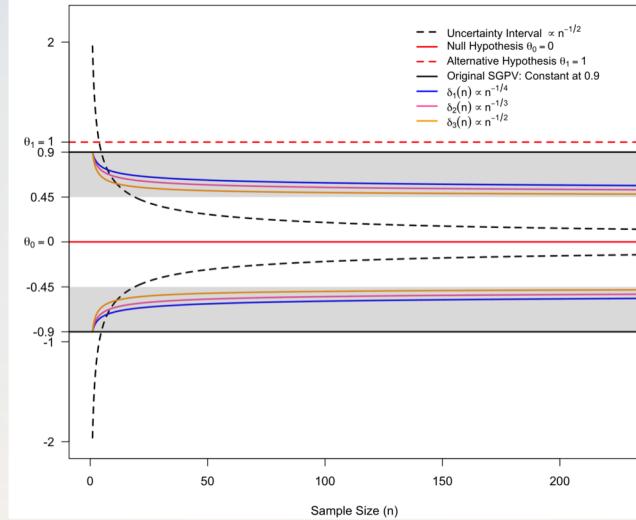
## Shrinking Indifference Zones



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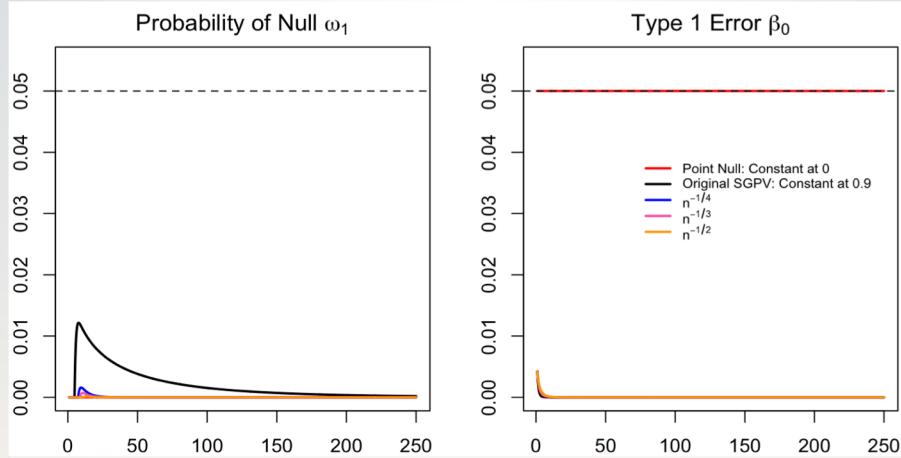
## Now with CI centered at null



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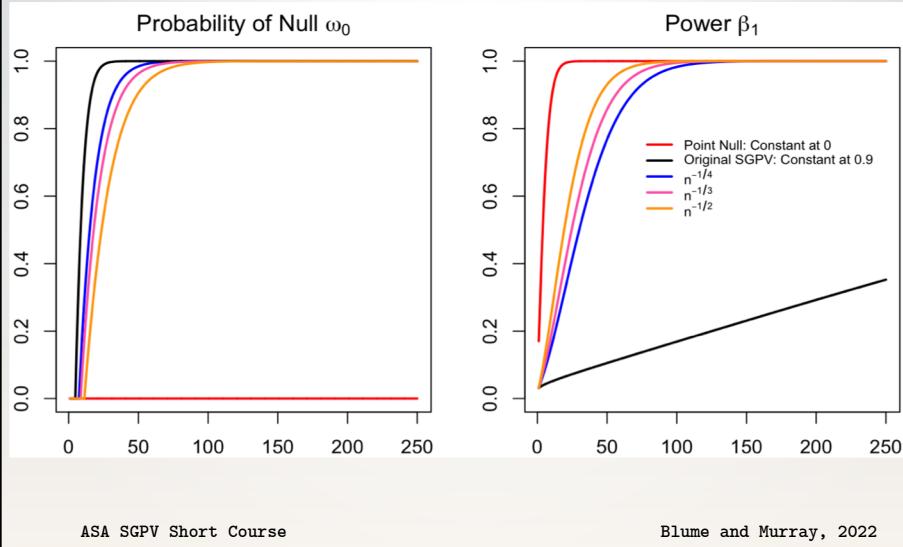
## Incorrect probabilities (Error)



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## Correct probabilities (Power)



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## Recommendations for Collaborator Uncertainty

Collaborator Hypothesis	Suggested SGPV Analysis	Outcome
Confident in a null zone.	Use it!	Ideal
Confident in the alternative point closest to null.	Use the halfway point as the null zone.	Great
Uncertain of null zone.	Use the null zone that shrinks.	Good
Uncertain of alternative point.	Use the null zone that shrinks.	Ok
Cannot identify.	Do NOT use SGPV! (but can't ever measure evidence for null)	Poor

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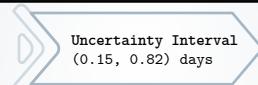
## COVID Clinical Trial Example

- Randomized 1,591 patients to ivermectin treatment or placebo
- Mean time spent unwell was estimated using a longitudinal ordinal regression model; range was 0 to 14 days
- Results: “The difference in the amount of time spent feeling unwell with COVID was estimated to be 0.49 days in favor of ivermectin with a 95% credible interval of (0.15, 0.82).”

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## COVID Clinical Trial Example



Collaborator Hypothesis	SGPV results	Outcome
Confident in a null zone, $[\theta^-, \theta^+] = [-1, 1]$ .	$p_\delta = 1$	Data are consistent with the null.
Confident in an alternative point, $\theta_1 = 1$ , use half standard deviation $[-0.5, 0.5]$ .	$p_\delta = 0.522$	Inconclusive
Uncertain of wide small sample null zone, $[\theta^-, \theta^+] = [-1.5, 1.5]$ , shrunk to <b><math>[-0.753, 0.753]</math></b> .	$p_\delta = 0.900$	Data are almost fully consistent with the null.
Uncertain of small sample alternative point, $\theta_1 = 0.75$ , shrunk to <b><math>[-0.377, 0.377]</math></b> .	$p_\delta = 0.338$	Inconclusive
Cannot identify.	NA	NA

## SGPV Study Planning Conclusions

- Goal is to balance statistical properties
- Results and inference will vary depending on the chosen indifference zone
- Promotes conversation between collaborator and statistician
  - Point null
  - Indifference zone or closest alternative point of interest
  - Sample size
  - If shrinking is necessary

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**Time for Code Part 2d!**

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## 10 Minute Break!

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