

Part I

Second-generation *p*-values: Introduction and Applications

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PhD almost PhD (July 6th defense)

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About Us

- Jeffrey
 - Associate Dean and Professor in Data Science (UVA)
 - Areas of research include statistical inference, likelihood methods, second-generation *p*-values, prediction modeling, ROC curves, mediation modeling, missing data in prediction problems, and false discovery rates.
 - Website: www.statisticalevidence.com
 - UVA Profile: www.datascience.virginia.edu/people/jeffrey-blume
- Megan
 - PhD in Biostatistics at Vanderbilt: July 6th 2022
 - Dissertation: "On second-generation *p*-values for equivalence testing and study planning, and flexible false discovery rate computation for classical *p*-values"
 - Fall 2022: Research Scientist at Eli Lilly Pharmaceuticals

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Course Layout

- Slides Part I: Introduction, applications, and statistical properties
 - Coding Part I
- Lunch (11:30-12:30)
- Slides Part II: Equivalence tests and false discovery rates
 - Coding Part II
- Slides Part III: SGPV Variable Selection
 - Coding Part III
- Questions and Discussion

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Resources

- GitHub with Slides and Code
 - www.github.com/murraymegan/SGPV-ASA-Short-Course
 - RStudio Desktop
 - www.rstudio.com/products/rstudio/download
 - Interrupt or use Zoom chat for questions!
 - For technical difficulties email Megan
 - megan.c.hollister@vanderbilt.edu

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Synopsis

- Classical *p*-values are
 - Ubiquitous, Sacrosanct, Imperfect, Misused
 - Misunderstood (Significance vs. Hypothesis testing roles)
 - Openly debated in practice and theory
 - Trend toward estimation in reporting of results
 - Report an estimation interval (e.g. confidence interval)
 - Does interval contain only clinically significant values?
 - Second-generation *p*-values (SGPVs)
 - Embody and formalize this trend
 - Maintain and improve error rate control
 - Define clinically significant before looking at the data

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Outline

- Evidential Metrics
 - Second-generation *p*-value
 - Live coding using R
 - Introductory examples
 - High-dimensional examples
 - Outrageous claim
 - Statistical properties



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Evidential metrics

Example:
Diagnostic Test

1. Measure of the strength evidence	Positive Test
→ Axiomatic and intuitive justification	Negative Test
→ Summary statistic, yardstick	
2. Propensity to collect data that will yield a misleading #1	Sensitivity
→ Error rates	Specificity
→ Properties of the study design (!)	
3. Probability that an observed #1 is misleading	
→ False Discovery rate, False Confirmation rate	PPV
→ Chance that an observed result is mistaken	NPV
→ Properties of the observed data (!)	

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Testing

Evidential Metric	What it measures	Hypothesis Testing	Significance Testing
1	strength of the evidence	Absent	Tail-area probability (<i>p</i> -value)
2	propensity for study to yield misleading evidence	Tail-area probability (error rates)	Absent
3	propensity for observed results to be misleading	misinterpret	misinterpret

- The tail-area probability is used to measure three distinct metrics

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Second-generation *p*-value

- StatisticalEvidence.com
- Examine statistical properties later
- Retains strict error control

Evidential Metric	What it measures	SGPV
1	Summary measure	p_δ
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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The p -value (what it is)

- Number between 0 and 1
- Smaller \Rightarrow support for an alternative hypothesis
- Larger \Rightarrow data are inconclusive
- Clinical significance is ignored
- Sample size confounds comparisons
- Interpretation
 - awkward
 - assumes null hypothesis true
 - rooted in inductive reasoning
- Not clear if/when ‘adjustments’ are necessary

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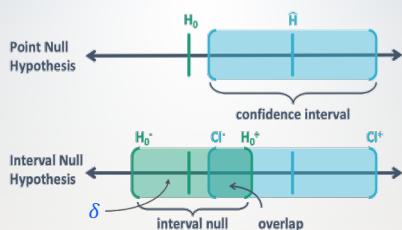
The p -value (what it is)

- Version 2.0* ✓ *2nd-generation we want*
- ✓ Number between 0 and 1 \rightarrow [near 0 supports alt
near 1 supports null
near $\frac{1}{2}$ inconclusive]
 - ✓ Smaller \Rightarrow support for an alternative hypothesis
 - Larger \Rightarrow data are inconclusive ~~support null~~
 - Clinical significance is ~~ignored~~ incorporated
 - ✗ Sample size confounds comparisons
 - Interpretation \rightarrow Fraction of data-supported hypotheses that are null
 - ~~awkward~~ straightforward
 - ~~assumes null hypothesis true~~ conditions on observed data
 - ~~rooted in inductive reasoning~~ descriptive, summarizes
 - Not clear if/when ‘adjustments’ are necessary *Ideally, never*

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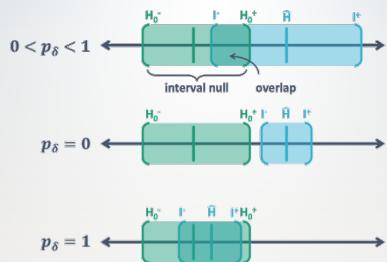
Illustration

Point null hypothesis H_0 and interval null hypothesis $[H_0^-, H_0^+]$ Data-supported hypothesis \hat{H} and confidence interval $[CI^-, CI^+]$

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Illustration



Works with confidence, credible, and support intervals

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Second-generation p -value

- SGPV is in $[0,1]$ and denoted by p_{δ}
 - δ for scientific significance
 1. $p_{\delta} = 0 \Rightarrow$ null **incompatible** with data
 2. $p_{\delta} = 1 \Rightarrow$ null **compatible** with data
 3. $0 < p_{\delta} < 1 \Rightarrow$ data are **inconclusive**
 - Fraction of data-supported hypotheses that are null
 - Retains strict error control, all rates $\rightarrow 0$



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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

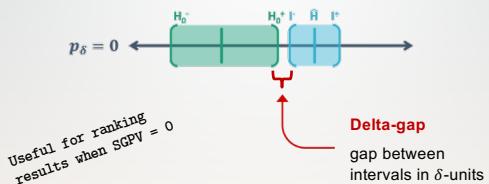
when $|I| > 2|H_0|$

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The Delta-gap

When $SGPV=0$, there is a gap between the intervals. The length of that gap, in δ -units is the **delta-gap**.



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Steps

- SGPV ~ the fraction of data-supported hypotheses that are null or practically null
 1. Specify an the interval null hypothesis or a point null with indifference zone
 2. Find confidence, support or credible interval
 3. Measure the fraction of interval (#2) that is in the null interval
 4. Apply small-sample correction factor, as necessary

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COVID Clinical Trial



COVID Clinical Trial

- 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
- Patients reported each day their symptoms and severity, health care visits, and medications.

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

Uncertainty Data Interval: (0.15, 0.82) days			
Difference in mean time unwell between ivermectin treatment and placebo.			
Hypothesis	Indifference or Null Zone	SGPV (p_δ)	Inference Outcome
3 hours difference	[-0.125, 0.125] days	$p_\delta = 0$	Consistent with alternative zone effects
12 hours difference	[-0.5, 0.5] days	$p_\delta = 0.522$	Inconclusive
18 hours difference	[-0.75, 0.75] days	$p_\delta = 0.896$	Inconclusive
1 day difference	[-1, 1] days	$p_\delta = 1$	Consistent with null zone effects
2 days difference	[-2, 2] days	$p_\delta = 1$	Consistent with null zone effects

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Time for Code Part 1a!

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10 Minute Break!

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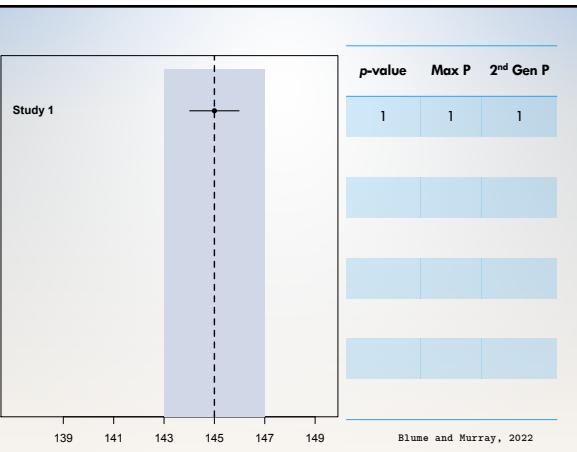
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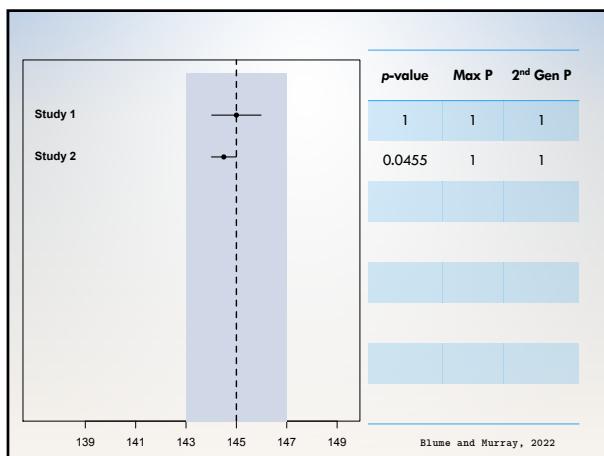
Systolic Blood Pressure

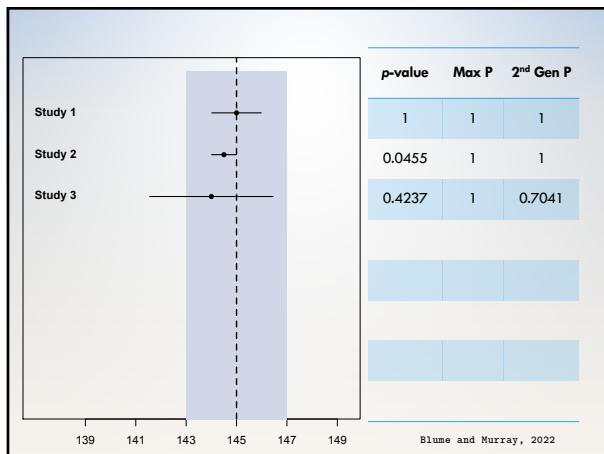
- SBP is reported to the nearest 2 mmHg
- Null Hypothesis: mean SPB is 145 mmHg
- Interval Null hypothesis: mean is 143 to 147 mmHg
- Results from 8 mock studies

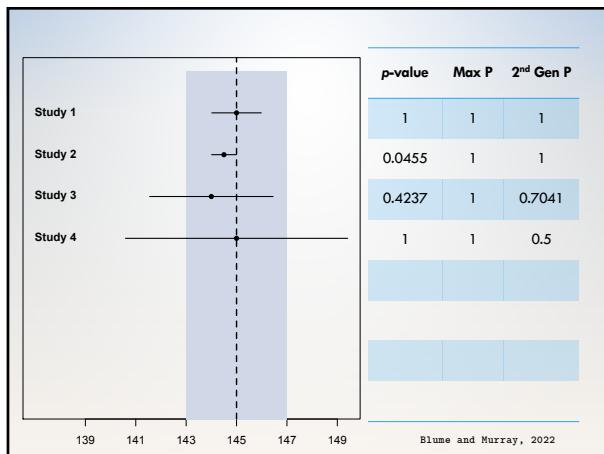
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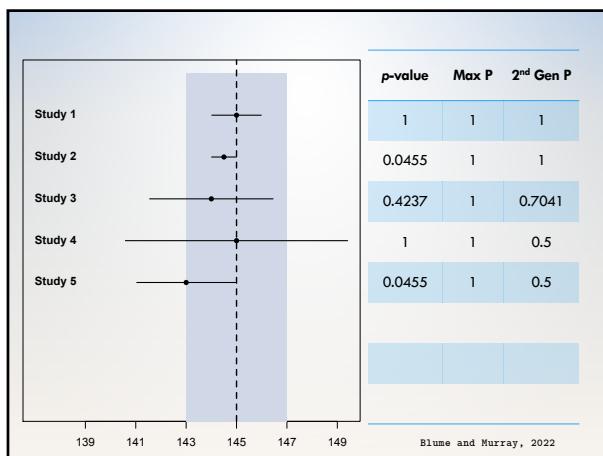
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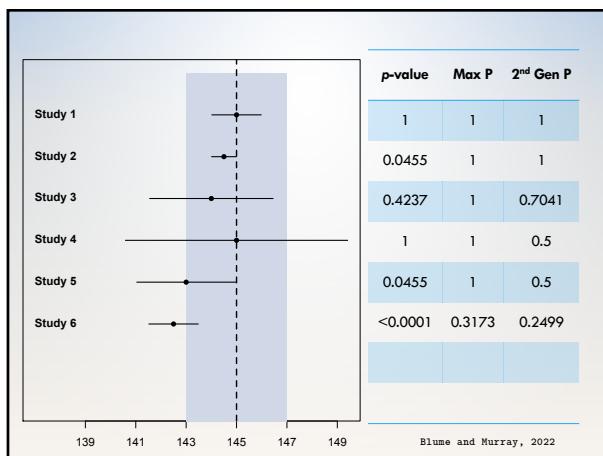


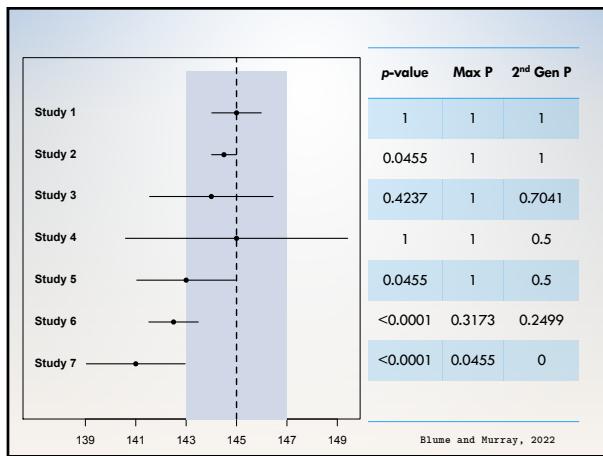


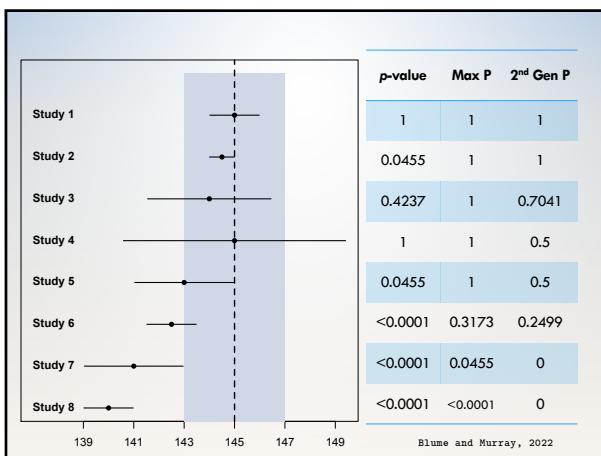












2x2 Tables & Odds Ratios

Exposure	Outcome	
	No	Yes
Exposed	35	65
Unexposed	50	50

OR = 1.86
95% CI: (1.05, 3.29)

Null: (0.9, 1.11)

$p_\delta = \frac{(1.11 - 1.05)}{(3.29 - 1.05)}(1) = 0.024$

$\log(\text{or}) = 0.62$
95% CI: (0.05, 1.19)

Null: (-0.1, 0.1)

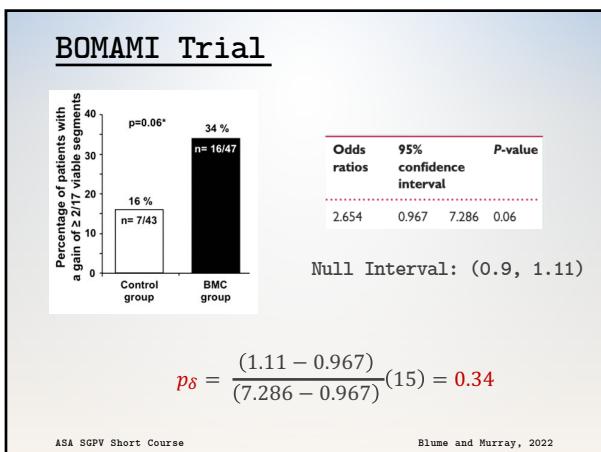
$p_\delta = \frac{(0.1 - 0.05)}{(1.19 - 0.05)}(1) = 0.044$

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Bone Marrow in Acute Myocardial Infarction (BOMAMI)

- European Heart Journal (2011)
- Randomized multicenter study
- Intracoronary administration of autologous bone marrow cells (BMCs) can lead to a modest improvement in cardiac function
- Aim: Evaluate the effect of BMC therapy on myocardial viability in patients with decreased left ventricular ejection fraction (LVEF) after acute myocardial infarction (AMI)

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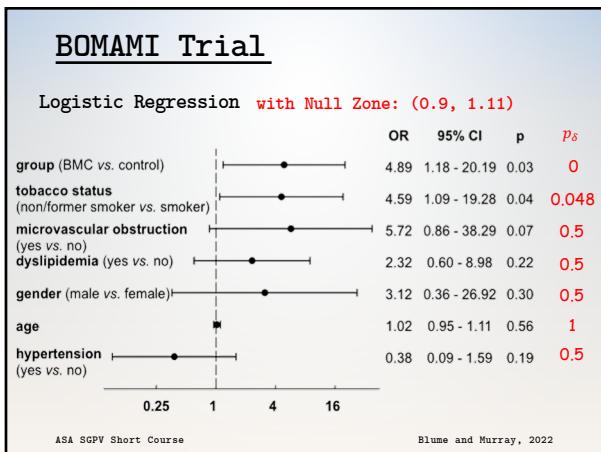
Effect Measures for BOMAMI

	BMC	Control	Total
Gain	16	7	23
No Gain	31	36	67
Total	47	43	90
Risk	0.34	0.16	

Null Hypotheses
OR/RR: (0.9, 1.11)
RD: (-0.05, 0.05)

	Estimate	CI Lower	CI Upper	SGPV
Odds Ratio	2.65	0.967	7.286	0.34
Risk Ratio	2.09	0.953	4.589	0.37
Risk Difference	0.18	0.003	0.352	0.24

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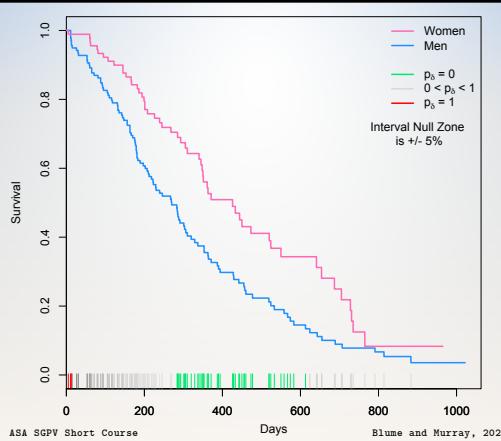


Lung Cancer Survival

- Survival time in patients with advanced lung cancer (days)
 - Potential for gender dissimilarities
 - Trial by North Central Cancer Treatment Group (1994)

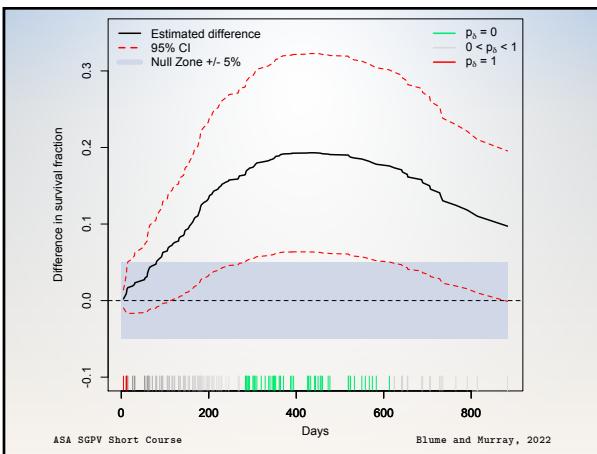
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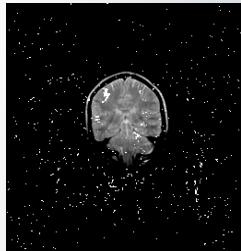


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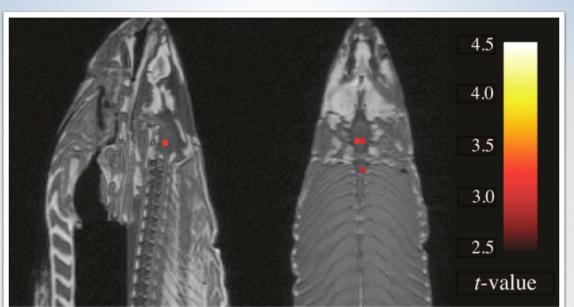
Setting interval null

- Before analyzing data (!)
 - Measurement error
 - Subject matter knowledge
 - Impact of findings
 - Community standard
 - Get creative (fMR example)
 - Width not critical, buffer
 - *The Atlantic salmon imaging*



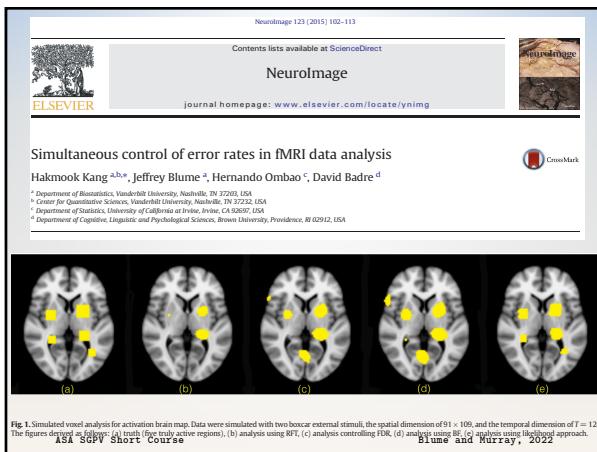
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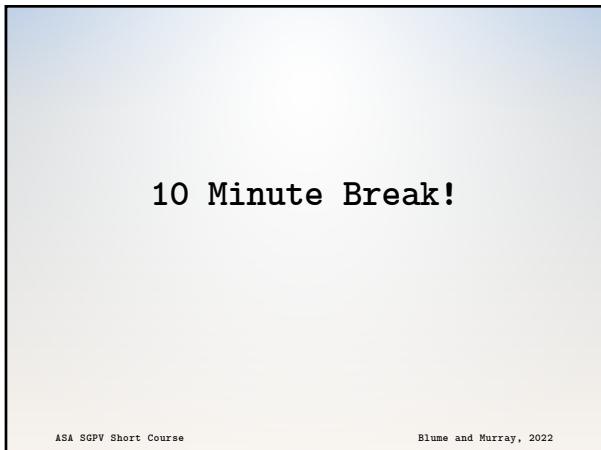
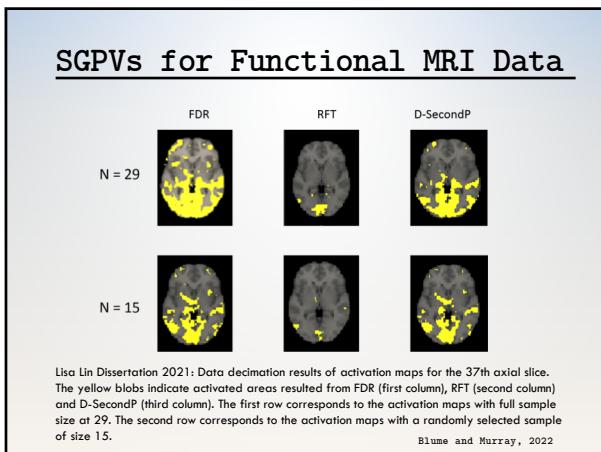
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"Sagittal and axial images; $t(131) > 3.15$, $p(\text{uncorrected}) < 0.001$, 3 voxel extent threshold. Two clusters were observed in the salmon central nervous system. One cluster...in the medial brain cavity and another...in the upper spinal column."

From Bennett et. al., 2010, JSUR 1:1 1-5. **8064 total voxels; 16 identified.**



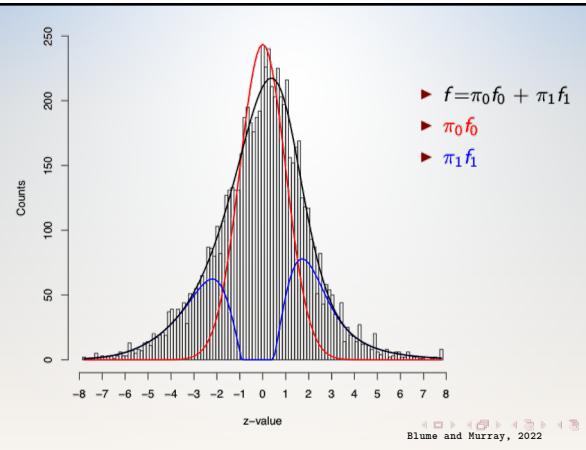
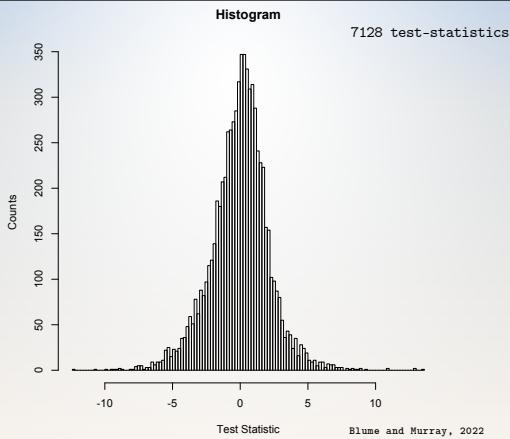


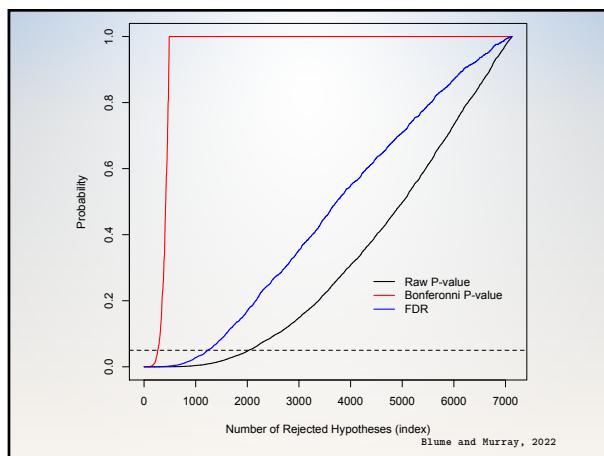
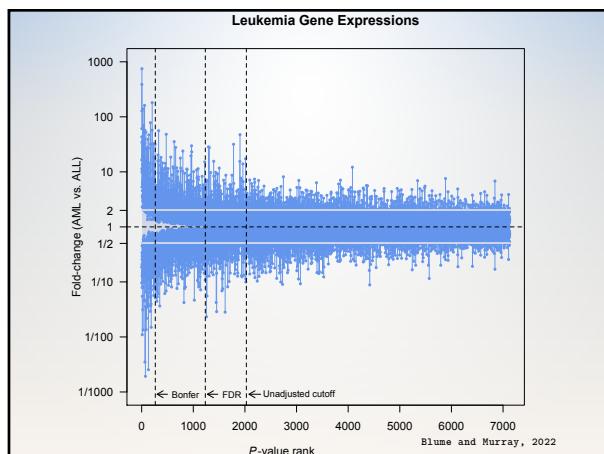
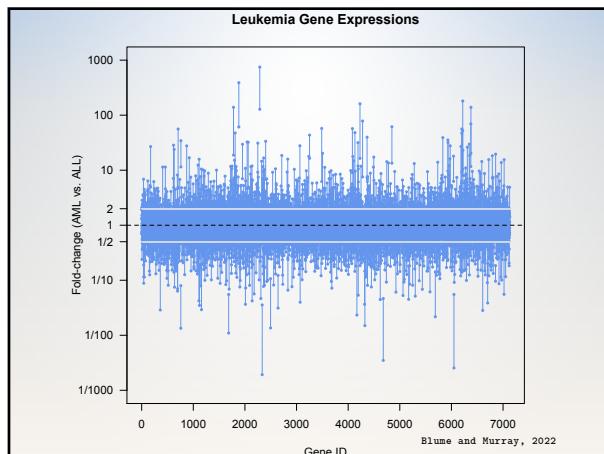
High-Dimensional Data: Leukemia gene expression

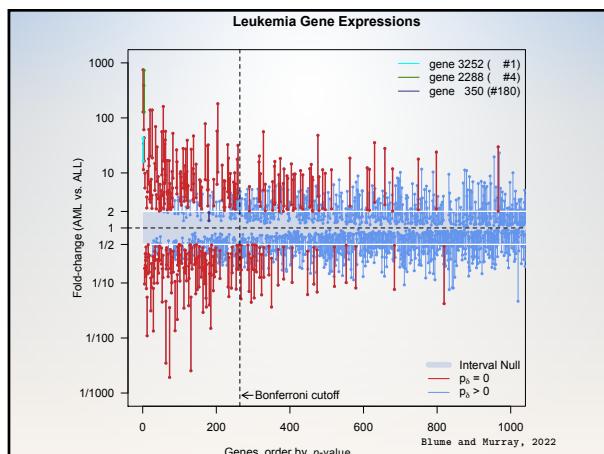
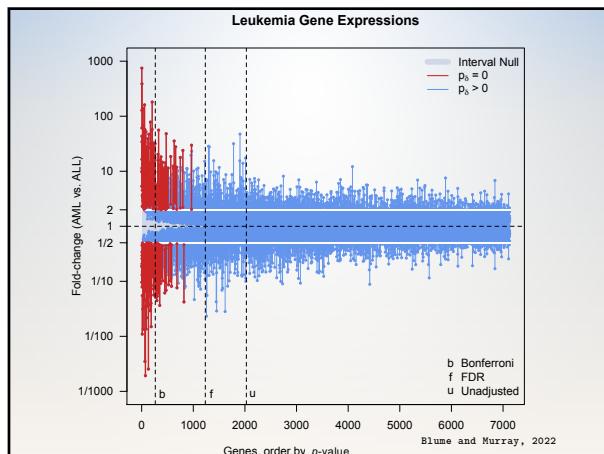
- Classifying acute leukemia by precursors
(Golub 1999, *Science*)
 - 7128 genes ; 72 patients (47 ALL and 25 AML)
 - Affymetrix chip collected expression levels
 - Goal: Identify 'interesting' genes whose expression levels differ between All and AML subjects.
 - Looking for fold changes of 2 or more

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Cross-Tabulation of Leukemia Results

- Bonferroni vs ASA SGPV Short Course

	$1/2 < \text{Fold Change} < 2$ ($\delta = 0.3$)		$1/1.915 < \text{Fold Change} < 1.915$ ($\delta = 0.282$)	
	$p_{\delta} = 0$	$p_{\delta} > 0$	$p_{\delta} = 0$	$p_{\delta} > 0$
$p_{bon} < 0.05$	164	100	182	82
$p_{bon} > 0.05$	65	6799	82	6782
Total	229	6899	264	6864

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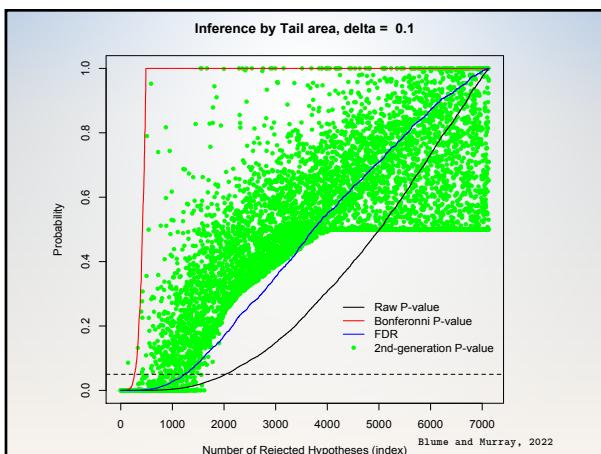
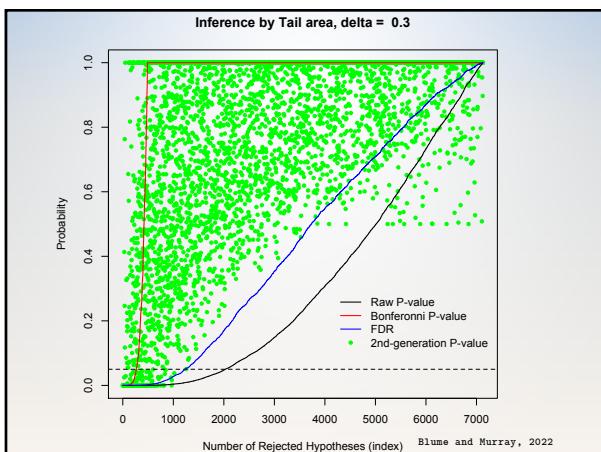
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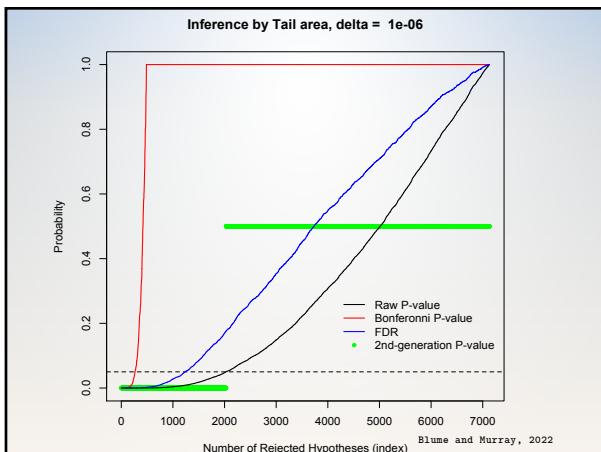
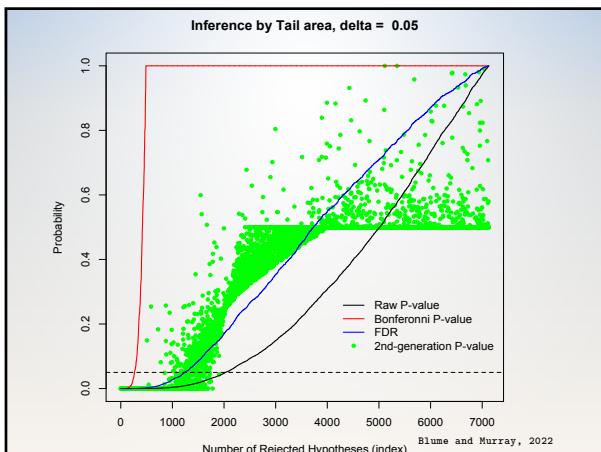
Leukemia study findings

- Findings: Bonferroni 264, SGPV 229
 - Agree on 164 findings
 - Bonferroni +100, SGPV +65
- Effective Type I error rate: 0.037 vs. 0.032
- FDR of 2.45% captures all $p_\delta = 0$, 737 others
- Moving cutoff trades Type I for Type II errors
- SGPV changes the *ranking* of findings
 - Three categories now: null, alt, inconclusive
 - Null findings not illustrated here

Some SGPV findings have a priori published validation

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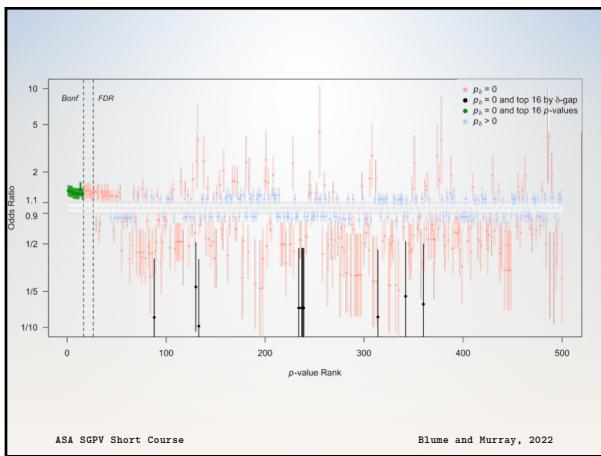
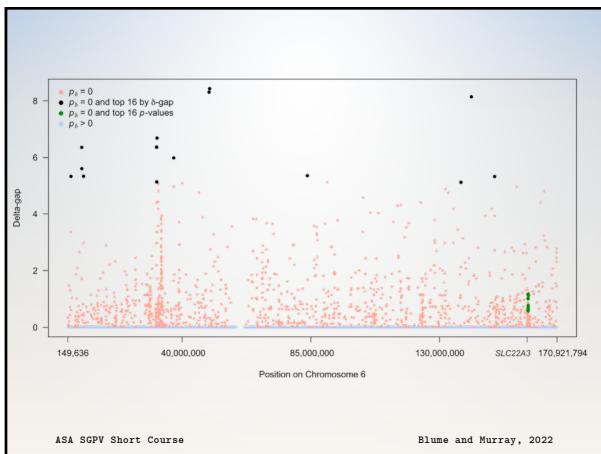
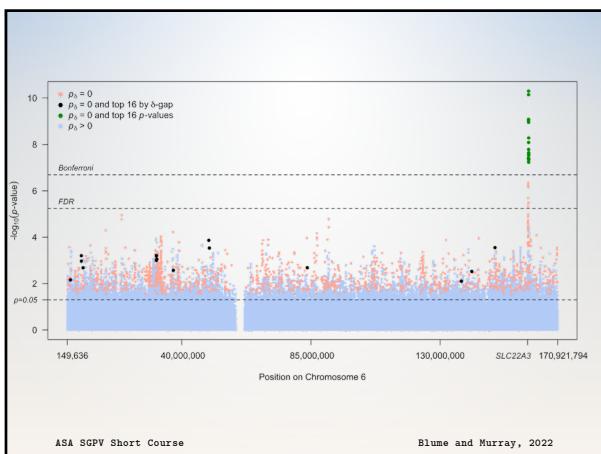


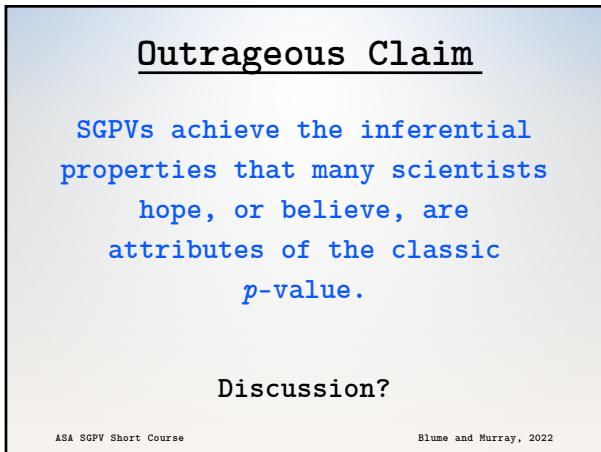
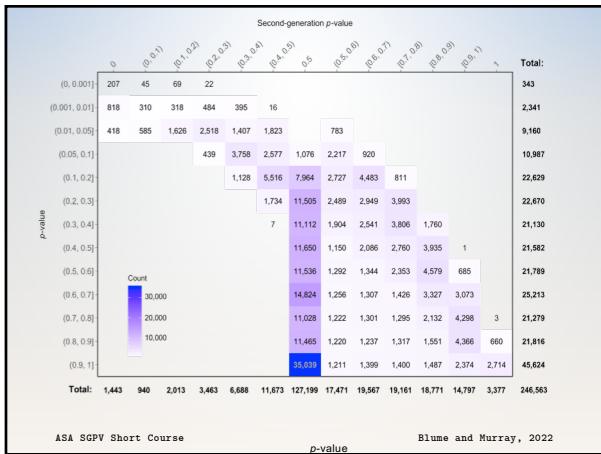
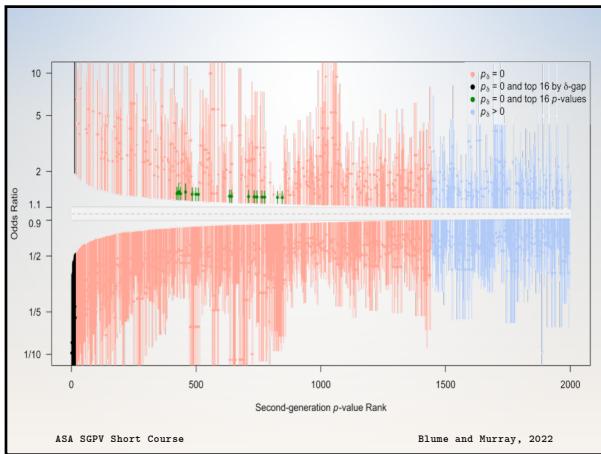
Prostate Cancer SNPs

- International Consortium for Prostate Cancer Genetics (Schaid and Chang 2055; ICPCG 2018)
- 3,894 subjects: 2,511 cases & 1,383 controls
- 247,000 single-nucleotide polymorphisms (SNPs) from Chromosome 6
- Goal: Identify ‘interesting’ SNPs potentially associated with prostate cancer
- Looking for odds ratios of <0.9 or >1.11

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Time for Code Part 1c!

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10 Minute Break!

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Second-generation p -value

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

Evidential Metric	What it measures	SPGV
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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Statistical Properties

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

Three ‘Error’ Rates

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

Will examine
these first

Two False Discovery Rates

- $$1. \quad P(H_0 | p_\delta = 0)$$

Will graph to illustrate

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Statistical 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. $P(p_\delta = 0|H)$ when H is null
 2. $P(p_\delta = 1|H)$ when H is not null
 3. $P(0 < p_\delta < 1|H)$ when H is either
 - Assume H makes statements about a parameter θ
 - Large sample setting

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Statistical Properties

- How often are the data incompatible with null?
 - Examine $P(p_\delta = 0|\theta)$ as θ 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

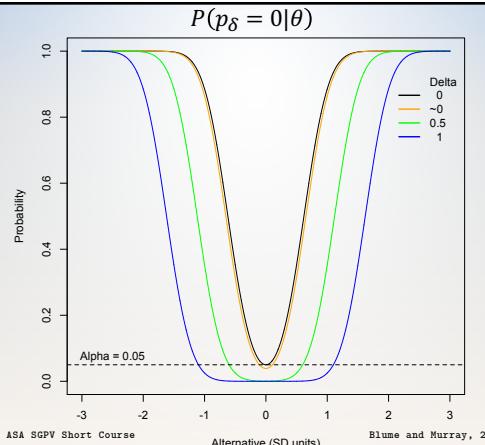
- θ_0 : point null, σ : standard deviation
- δ : half-width of indifference zone

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

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

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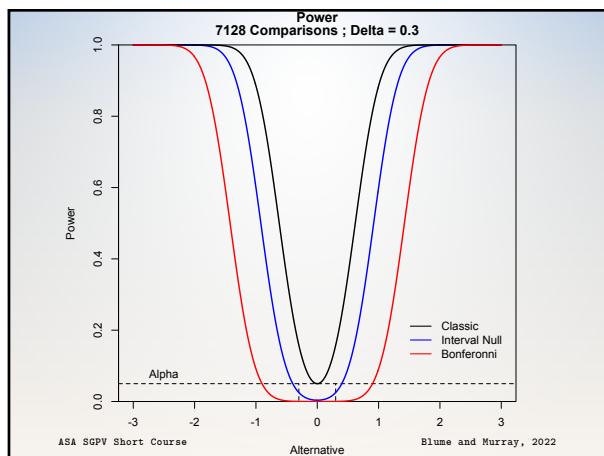
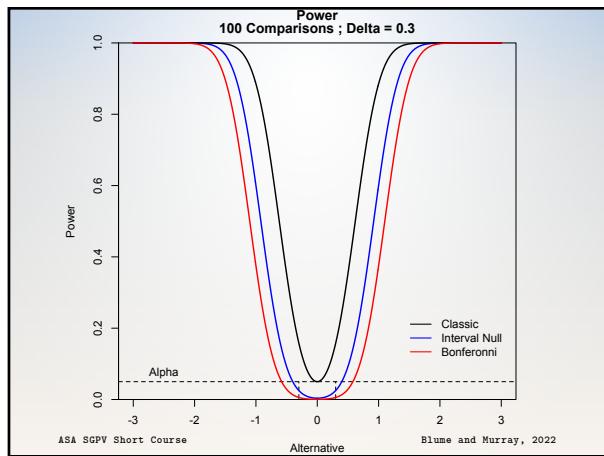
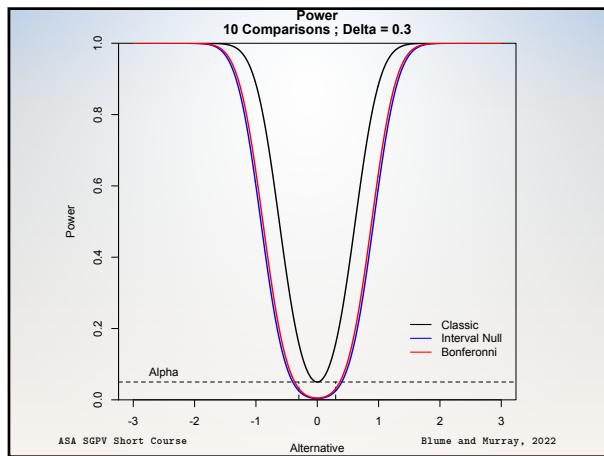
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Compare with standard methods

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

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Compatible with Null

- How often are the data compatible with null?
- Examine $P(p_\delta = 1|\theta)$ when θ 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

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'Null Power' Function

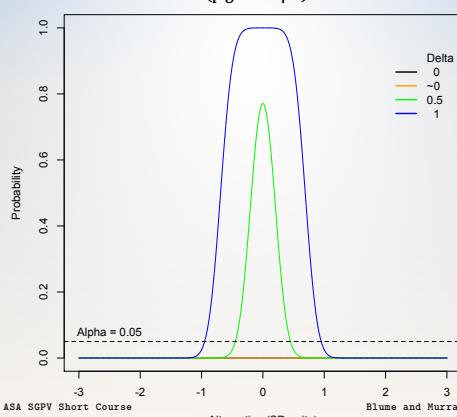
- How often are the data compatible with null?
- Sample size must be large enough to allow null interval to contain the interval estimate, so $(\delta > Z_{\alpha/2}/\sqrt{n})$ or $(\sqrt{n}\delta > Z_{\alpha/2}/\delta)$
- This probability converges to 0 or 1 quickly

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

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

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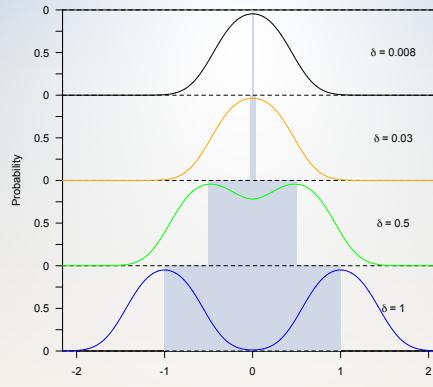
 $P(p_\delta = 1|\theta)$ 

Probability of Inconclusive Data

- How often are the data inconclusive?
- Examine $P(0 < p_\delta < 1|\theta)$ for various θ
- This probability
 - drives sample size projections
 - is maximized when H_0 is near the interval null edge
 - decreases quickly as H_0 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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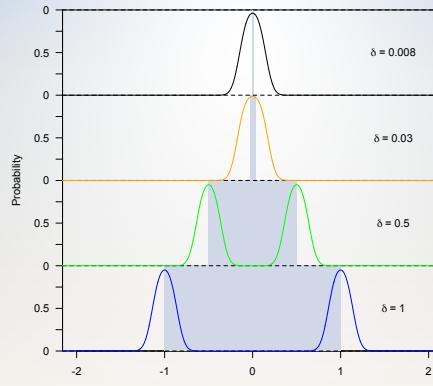
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 $P(0 < p_\delta < 1|\theta)$ 

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Alternative (SD units)

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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

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

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Time for Code Part 1d!

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