

Part I

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

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PhD almost PhD (July 6th defense)

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University of Virginia	Vanderbilt University

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 Candidate in Biostatistics at Vanderbilt: July 6th Defense
 - Dissertation: ‘On second-generation *p*-values for equivalence testing and study planning, and flexible false discovery rate computation for classical *p*-values’
 - After graduation: Research Scientist at Eli Lilly Pharmaceuticals

Course Layout

- Slides Part I
 - Introduction and applications
- Coding Part I
- Slides Part II
 - Equivalence tests, statistical properties, and false discovery rates
- Coding Part II
- 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 a 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
- Introductory examples
- Code Part 1a
- High-dimensional example, 7128 Genes
 - $\alpha=0.05$ vs $\alpha=0.05/7128$ vs SG *p*-value
- High-dimensional example
 - Prostate Cancer SNP data (~247,000)
- Outrageous claim
- Code Part 1b



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Evidential metrics

Example:
Diagnostic Test

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

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

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Second-generation *p*-value

- StatisticalEvidence.com
- Examine statistical properties in module 2
- 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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2nd-generation

The \hat{p} -value (what we want it is)

Version 2.0

- ✓ Number between 0 and 1 → $\begin{cases} \text{near 0 supports alt} \\ \text{near 1 supports null} \\ \text{near } \frac{1}{2} \text{ inconclusive} \end{cases}$
- ✓ Smaller ⇒ support for an alternative hypothesis
 - Larger ⇒ data are ~~inconclusive~~ support null
 - Clinical significance is ~~ignored~~ incorporated
- ✗ ~~Sample size confounds comparisons~~
 - Interpretation → 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

The diagram illustrates the relationship between different types of null hypotheses and the resulting confidence intervals.

Point Null Hypothesis: A single vertical line labeled H_0 on a horizontal axis. Above the axis, a light blue bracket indicates a confidence interval centered around H_0 , with its width labeled \hat{H} . The entire interval is labeled "confidence interval".

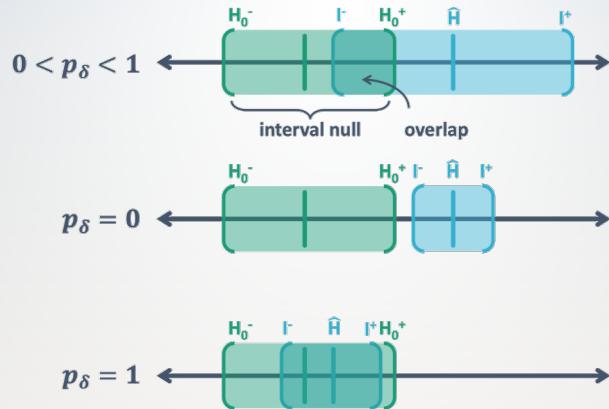
Interval Null Hypothesis: A double-headed arrow labeled H_0^- at the left end and H_0^+ at the right end. This represents an interval of values. Below this interval, a blue bracket labeled δ indicates the width of the "interval null". To the right of the interval null, a light blue bracket labeled CI^- and CI^+ indicates the "overlap" with the confidence interval from the Point Null Hypothesis.

Text below the diagram:

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
 - $p_\delta = 0 \Rightarrow$ null **incompatible** with data
 - $p_\delta = 1 \Rightarrow$ null **compatible** with data
 - $0 < p_\delta < 1 \Rightarrow$ 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)**

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

Proportion of data-supported hypotheses that are also null hypotheses

Small-sample correction factor
shrinks proportion to $\frac{1}{2}$ when $|I|$ wide

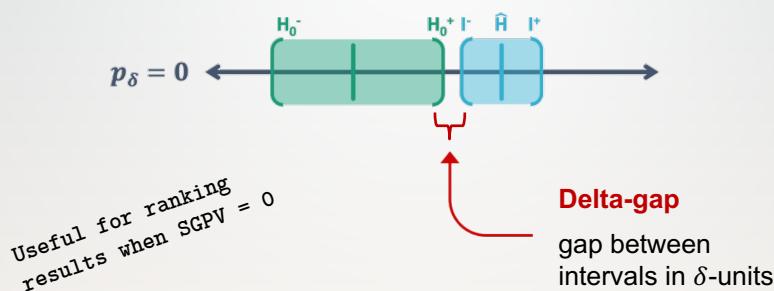
when $|I| > 2|H_0|$

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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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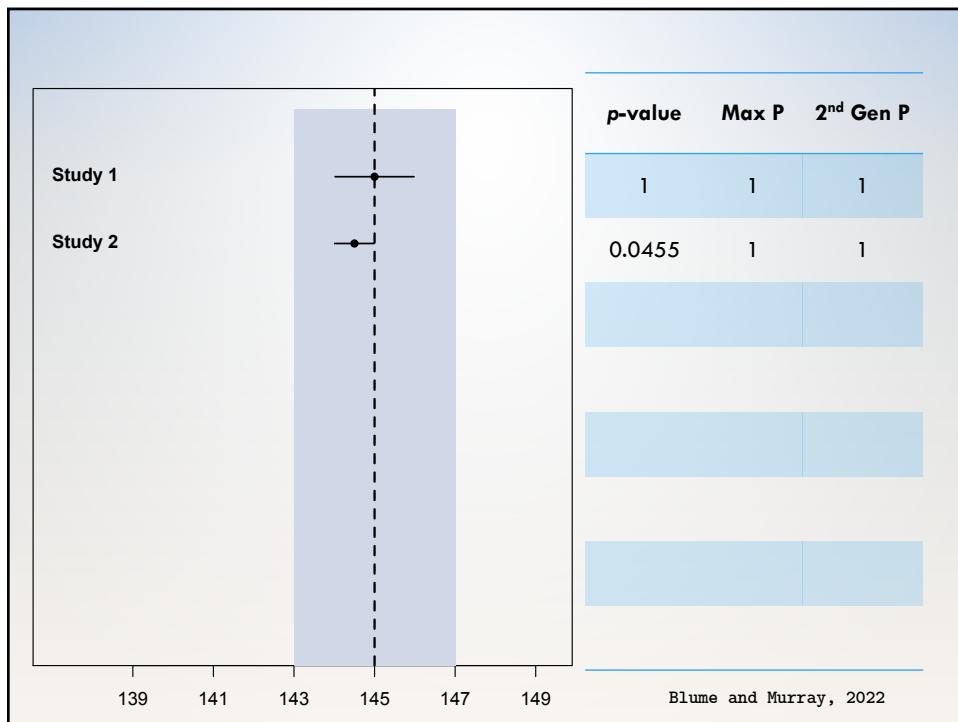
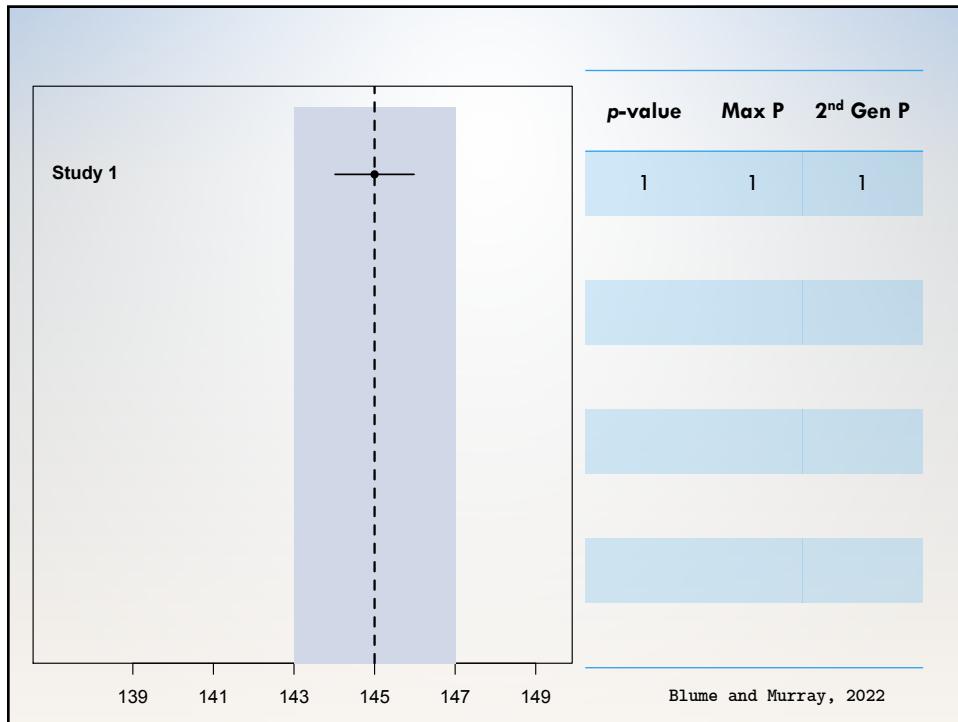
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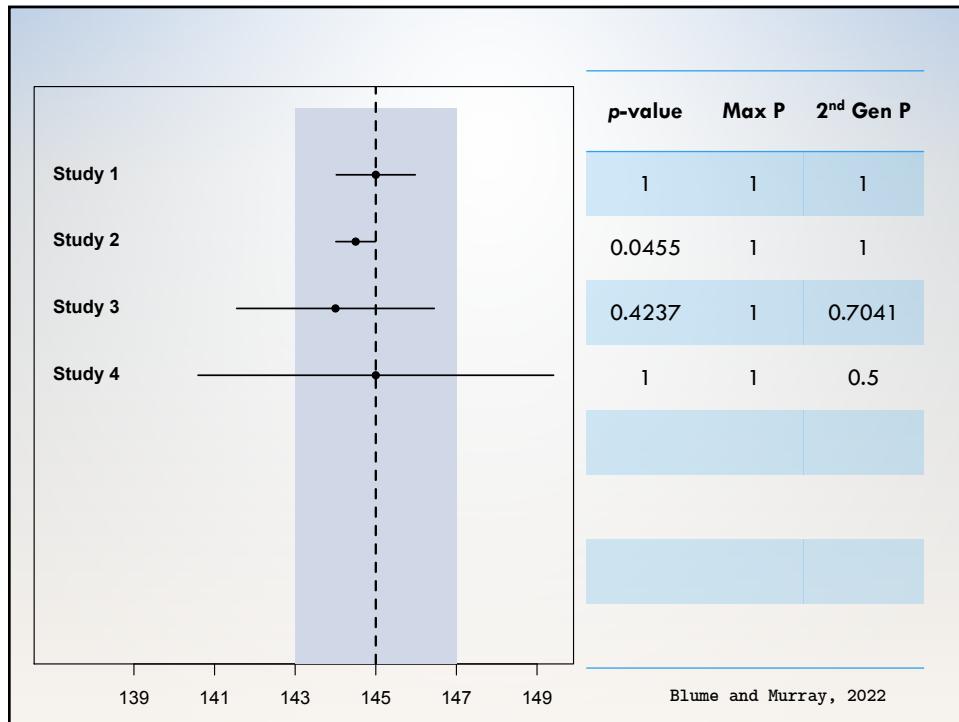
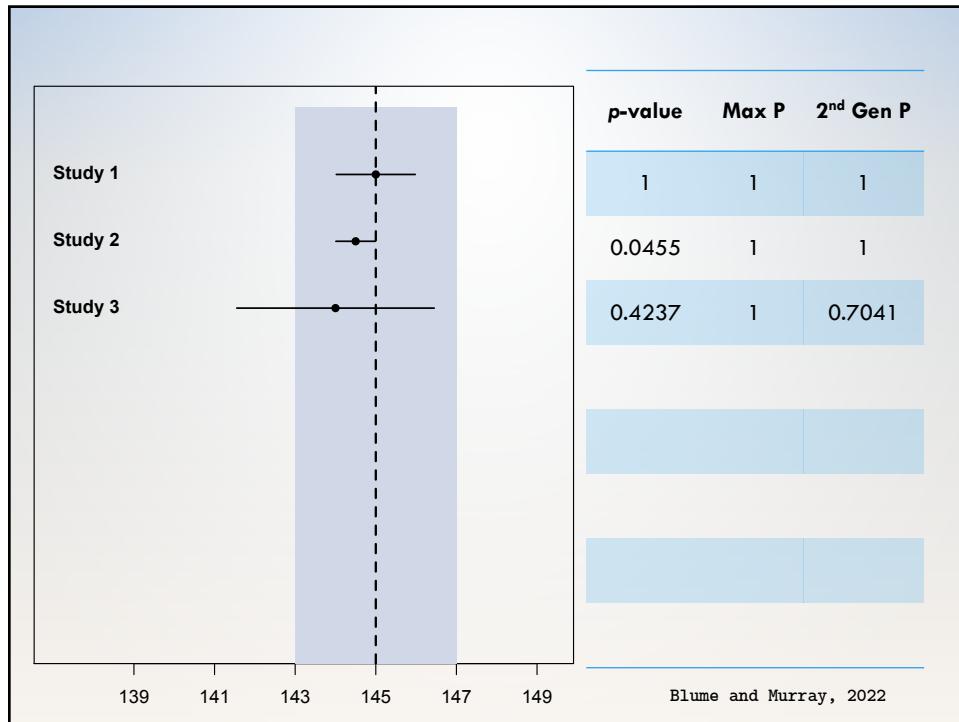
Systolic Blood Pressure

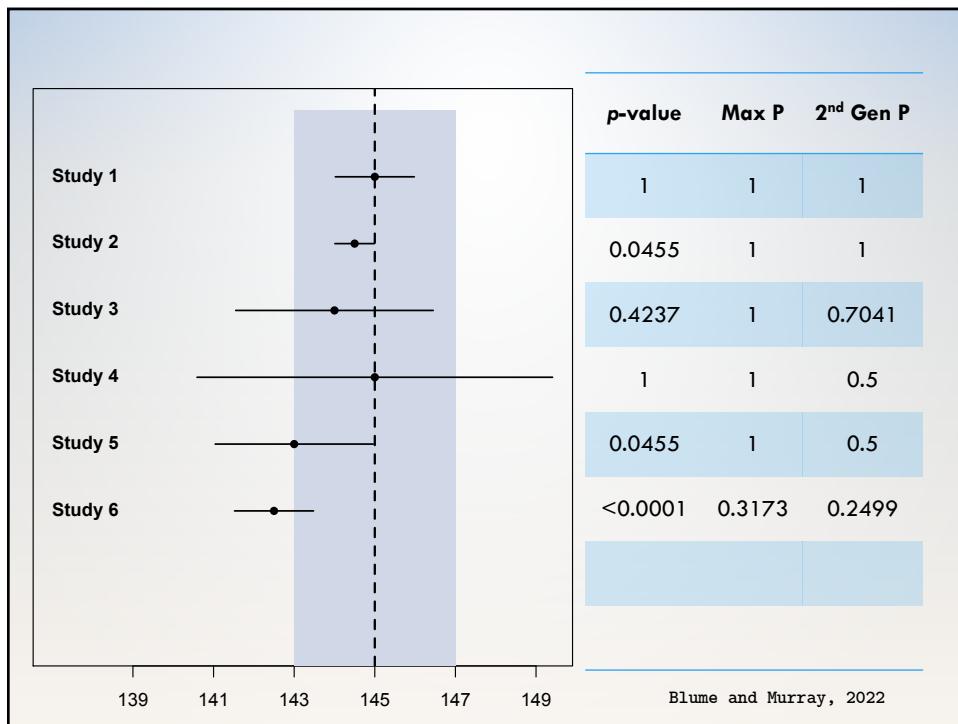
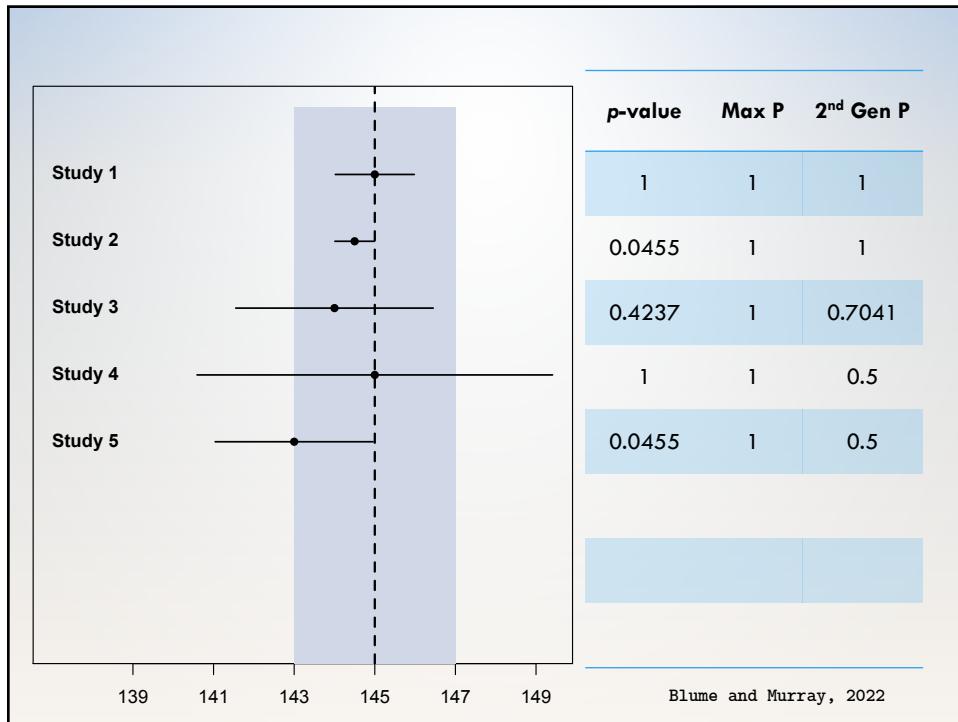
- SBP is reported to the nearest 2 mmHg
- Null Hypothesis: mean SPB is 145 mmHg
- Interval Null hypothesis: mean is 143 to 147 mmHg
- Results from 8 mock studies

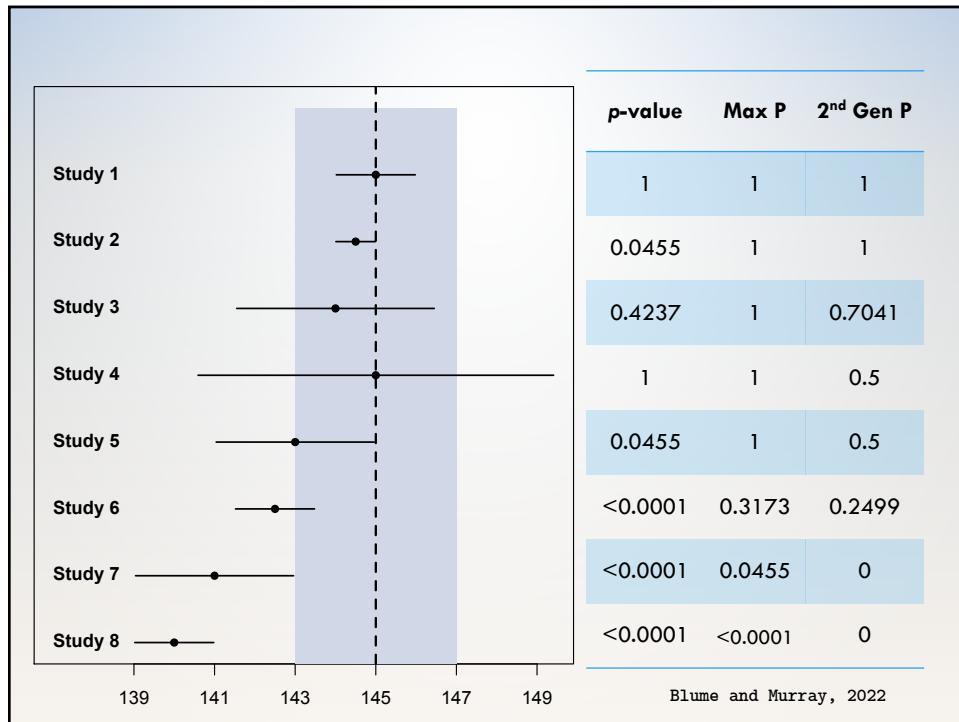
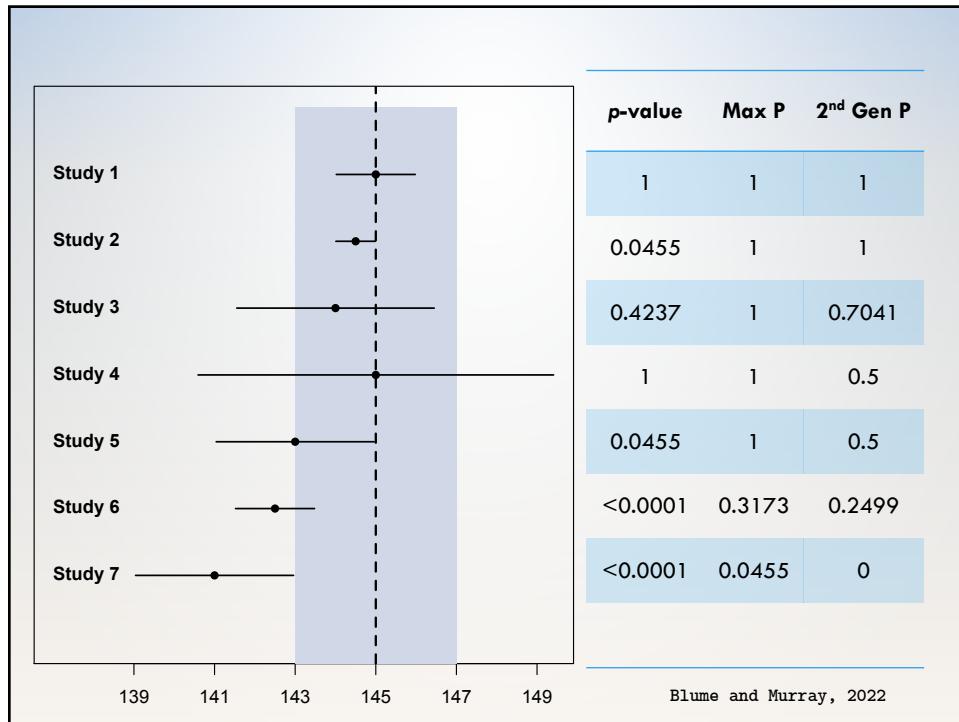
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2x2 Tables & Odds Ratios

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(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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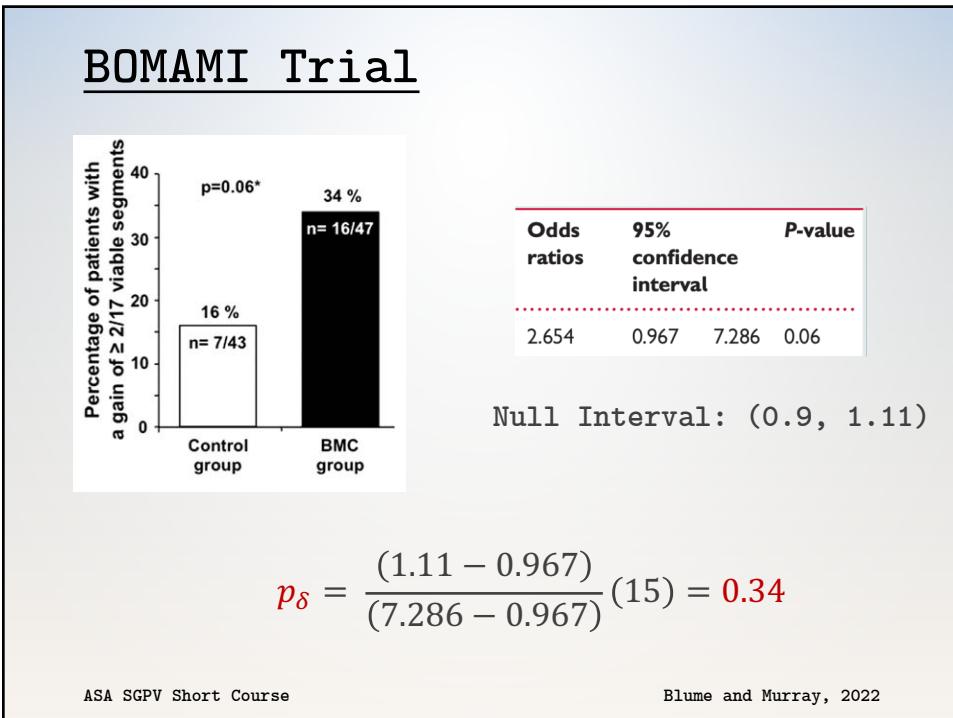
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Bone Marrow in Acute Myocardial Infarction (BOMAMI)

- 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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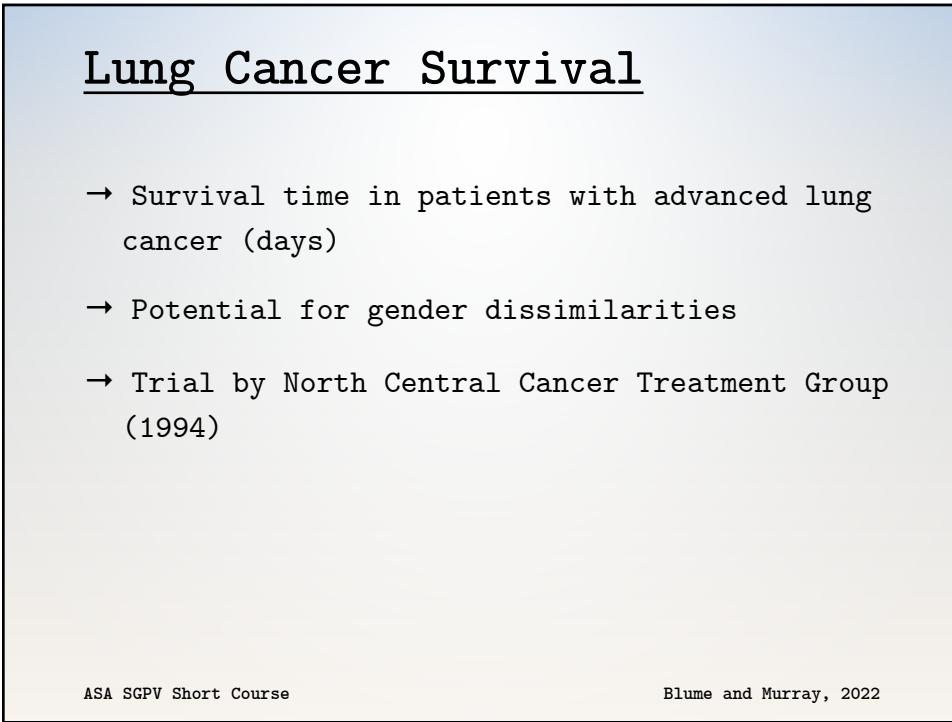
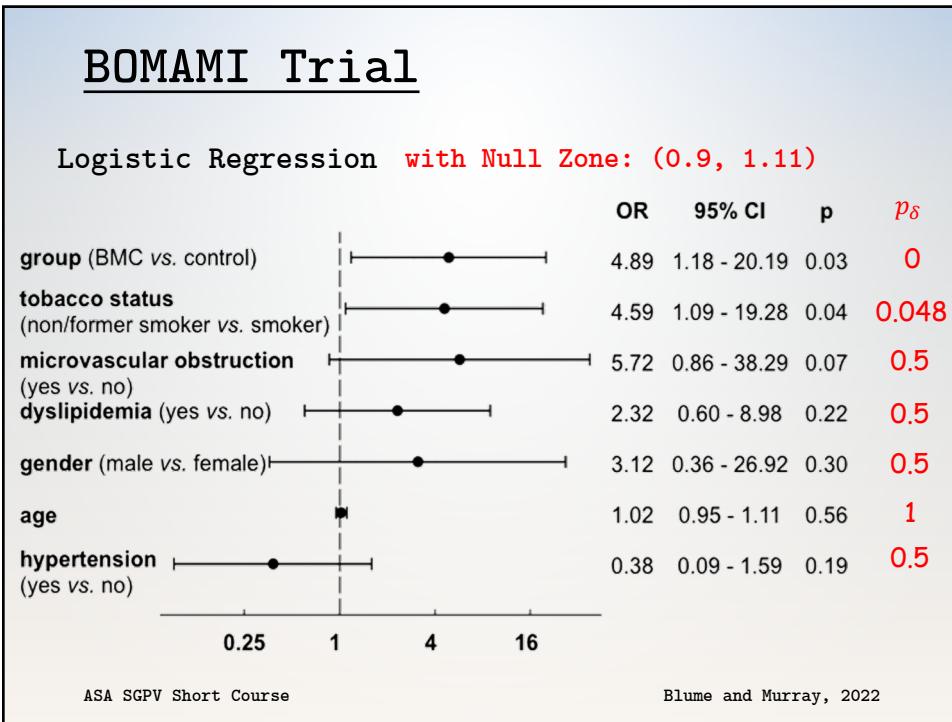


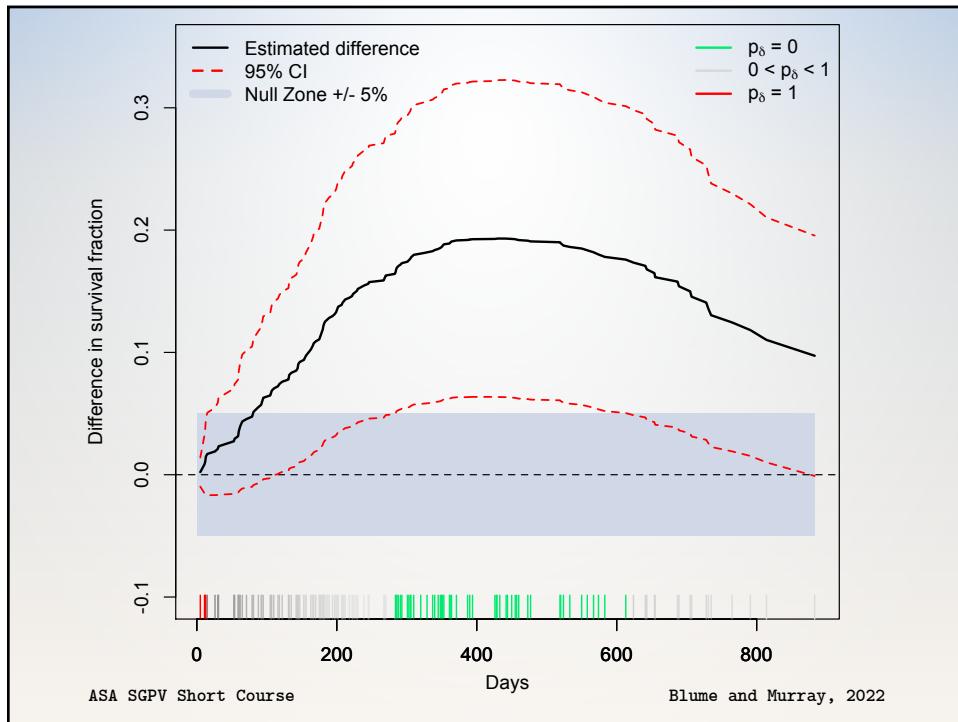
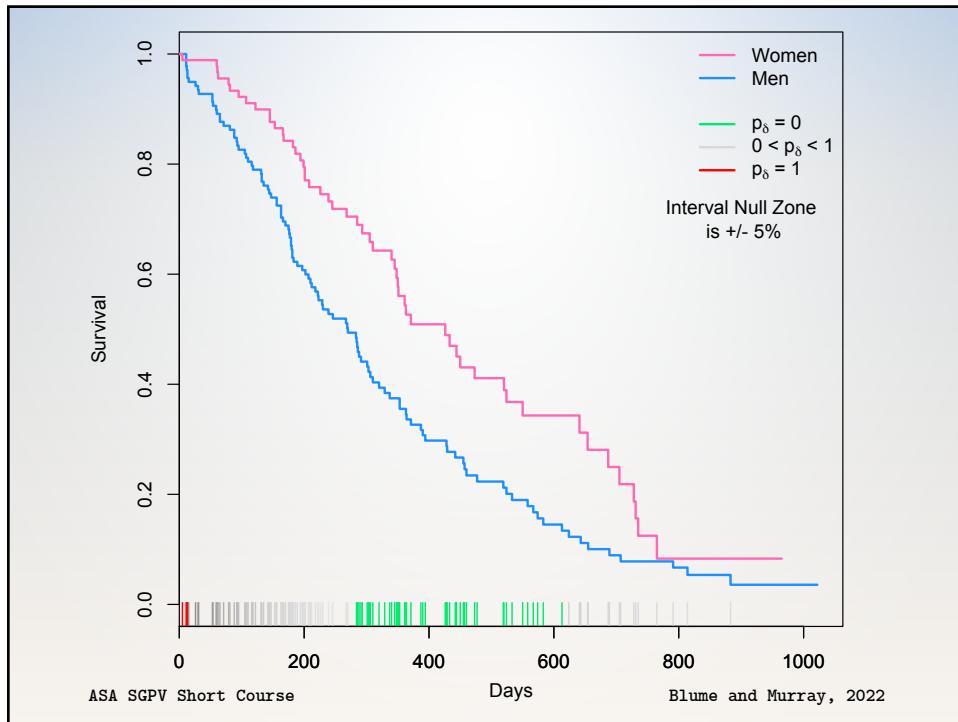
Effect Measures for BOMAMI

	BMC	Control	Total	Null Hypotheses
Gain	16	7	23	OR/RR: (0.9, 1.11)
No Gain	31	36	67	RD: (-0.05, 0.05)
Total	47	43	90	
Risk	0.34	0.16		

	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

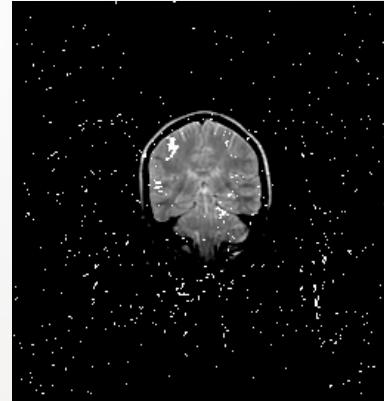
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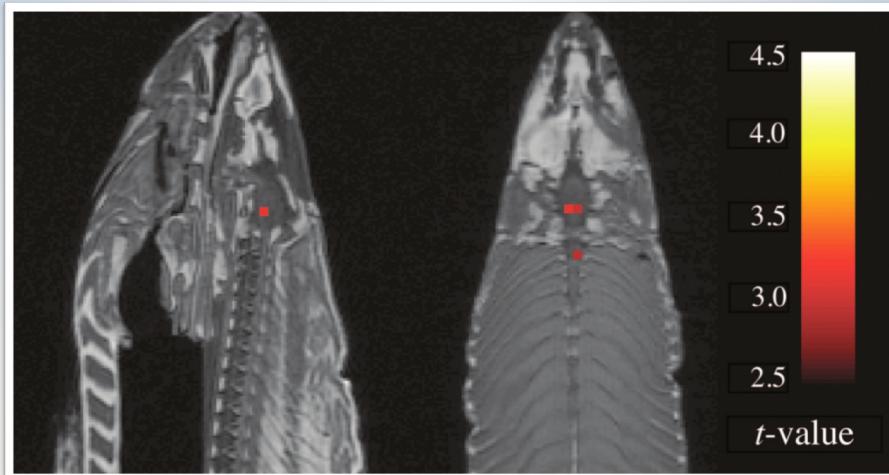
Setting interval null

- 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 saga*



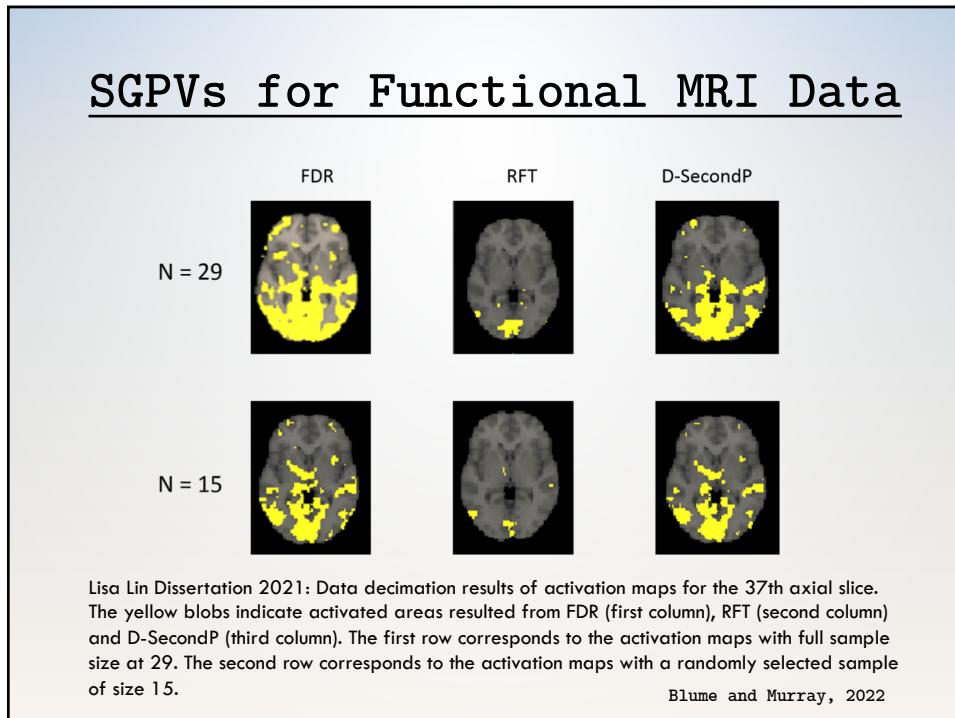
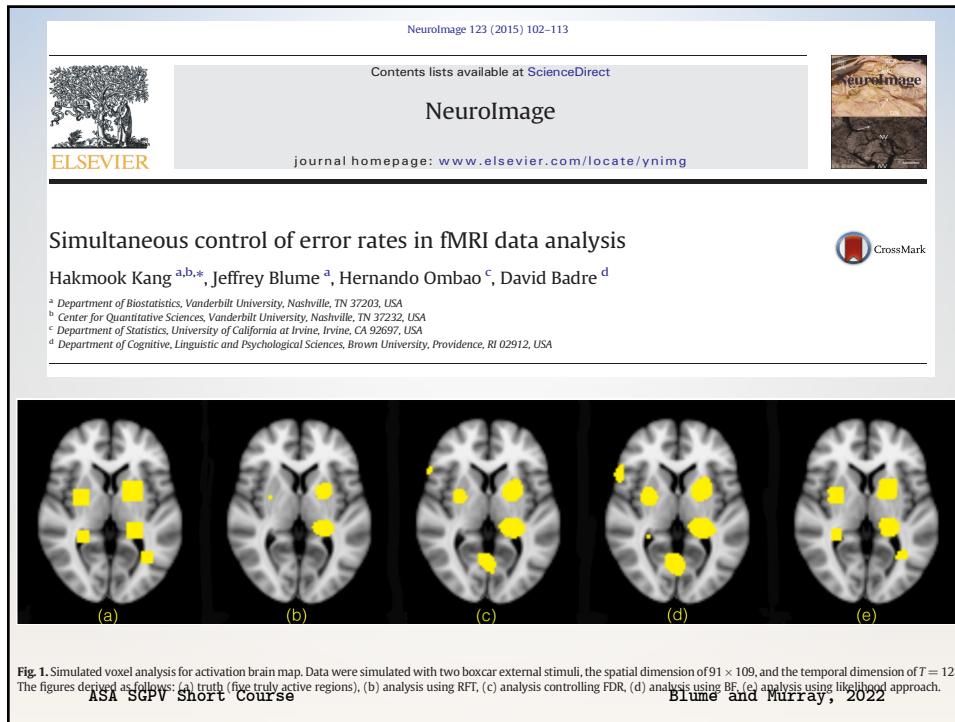
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"Sagittal and axial images; $t(131) > 3.15$, $p(\text{uncorrected}) < 0.001$, 3 voxel extent threshold. Two clusters were observed in the salmon central nervous system. One cluster...in the medial brain cavity and another...in the upper spinal column."

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



COVID Clinical Trial

medRxiv THE PREPRINT SERVER FOR HEALTH SCIENCES CSH Cold Spring Harbor Laboratory BMJ Yale

Preprint

Ivermectin for Treatment of Mild-to-Moderate COVID-19 in the Outpatient Setting: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group, Susanna Naglie
doi: <https://doi.org/10.1101/2022.06.10.22276252>

This article is a preprint and has not been certified by peer review [what does this mean?]. It reports new medical research that has yet to be evaluated and so should not be used to guide clinical practice.

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COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv

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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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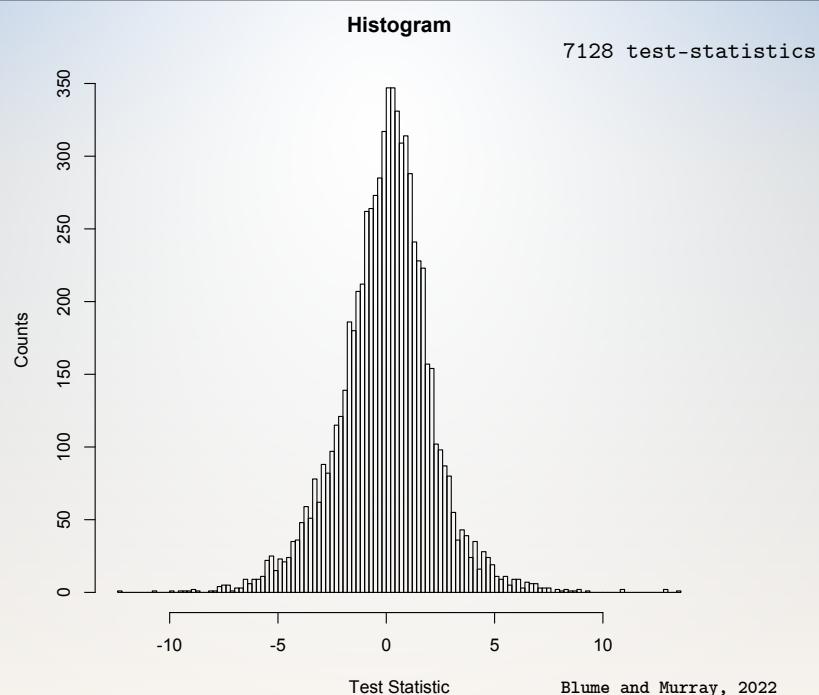
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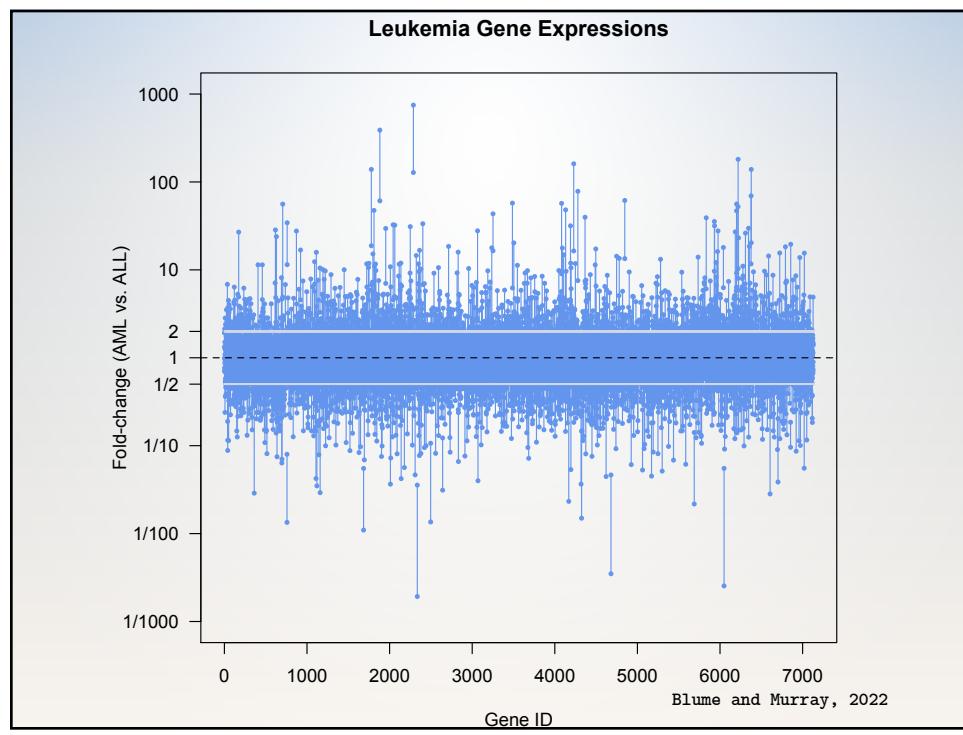
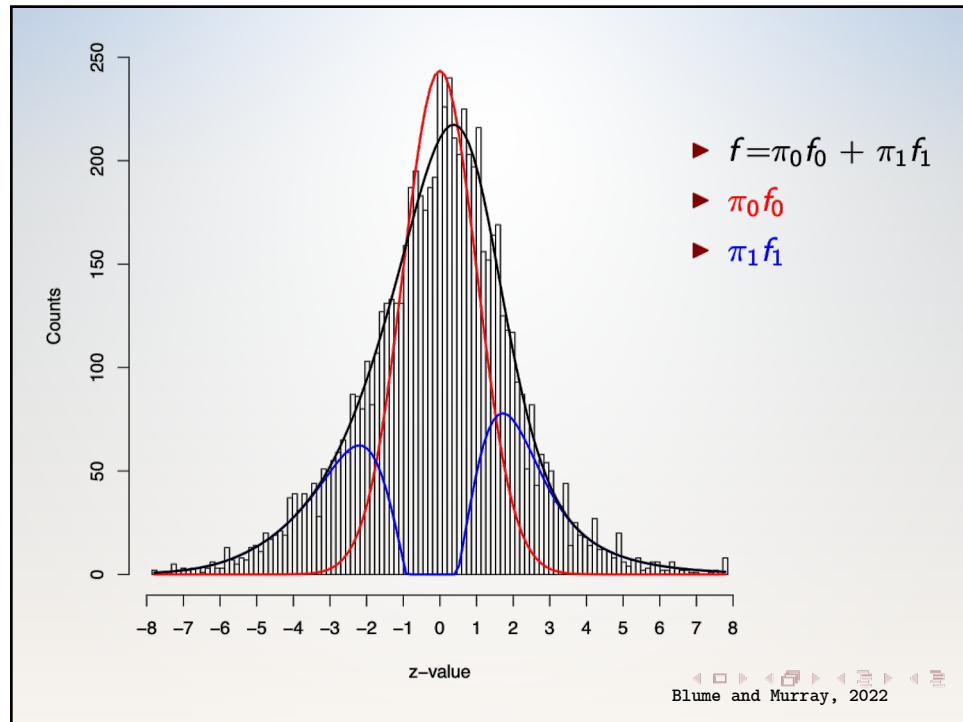
High-Dimensional Data: Leukemia gene expression

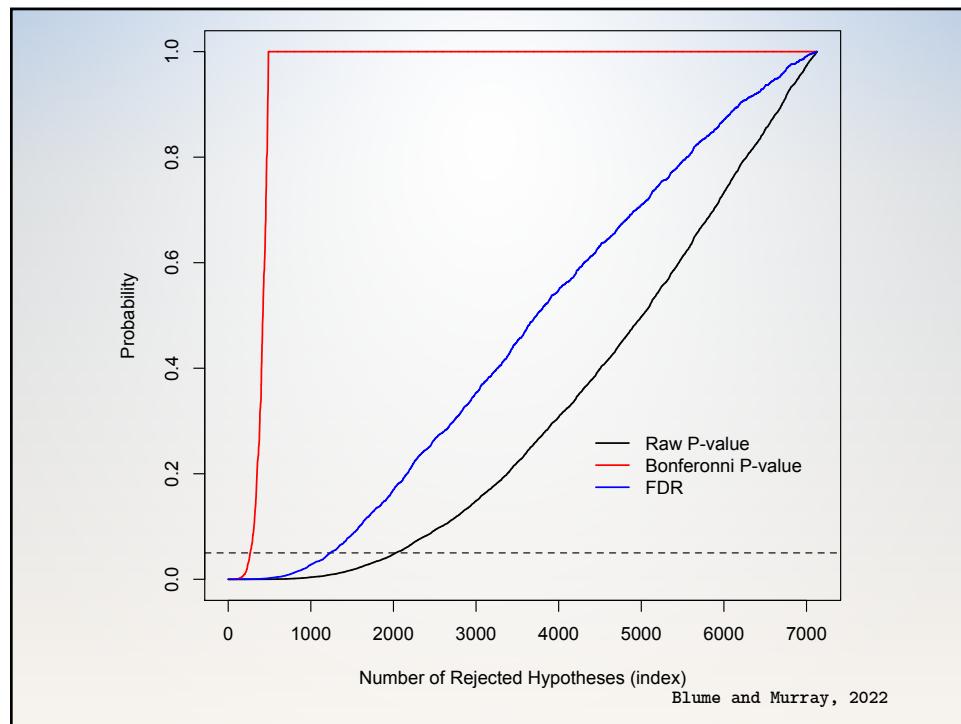
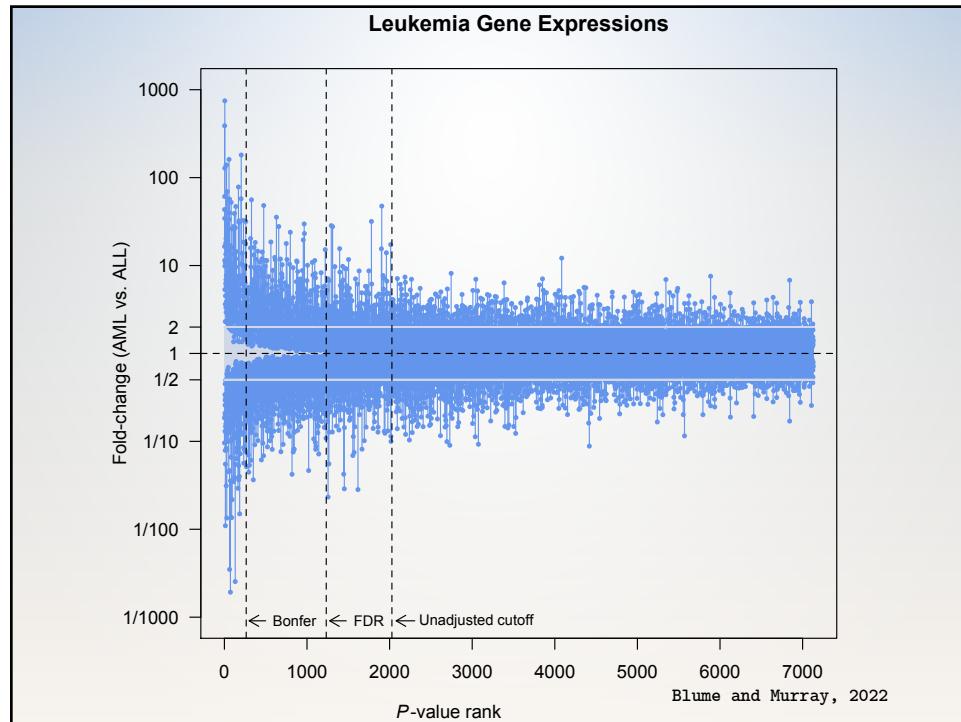
- Classifying acute leukemia by precursors
(Golub 1999, *Science*)
- 7128 genes ; 72 patients (47 ALL and 25 AML)
- Affymetrix chip collected expression levels
- Goal: Identify 'interesting' genes whose expression levels differ between All and AML subjects.
- Looking for fold changes of 2 or more

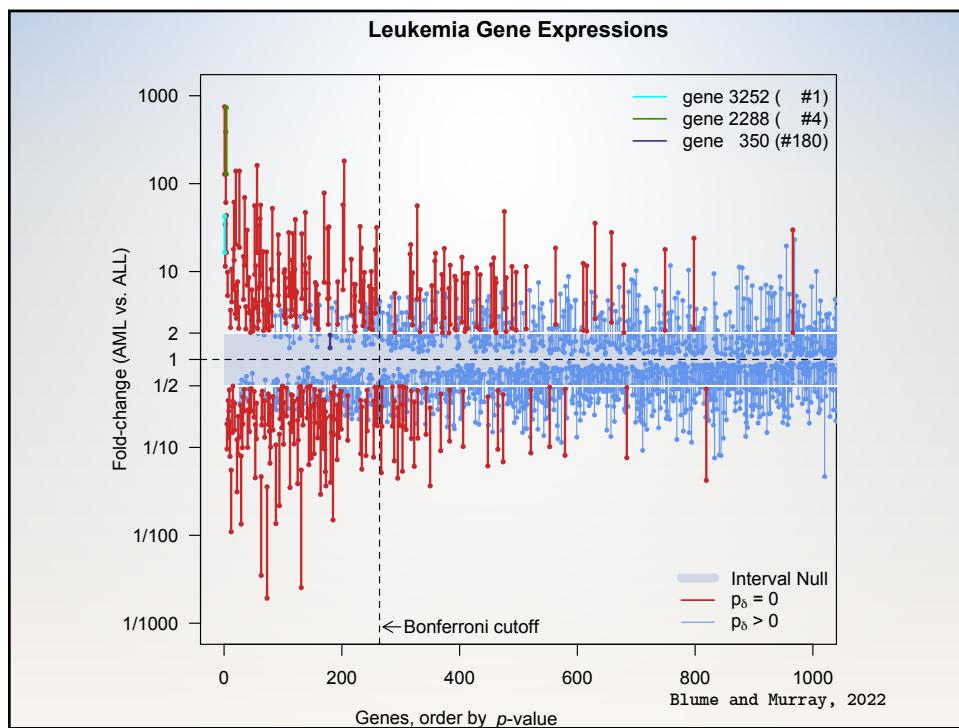
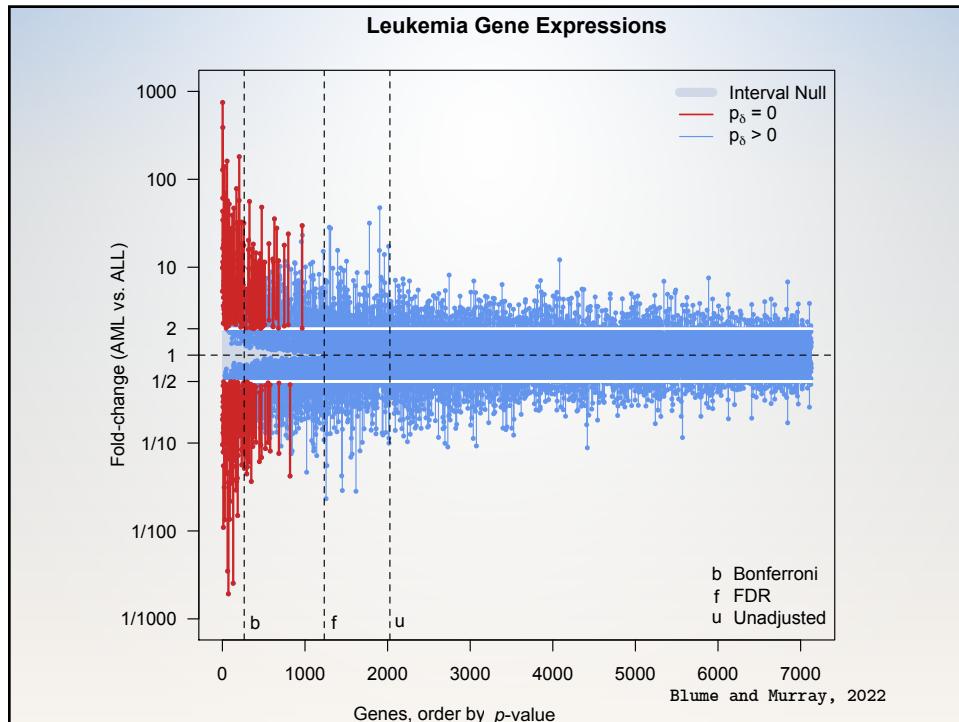
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Cross-Tabulation of Leukemia Results

- 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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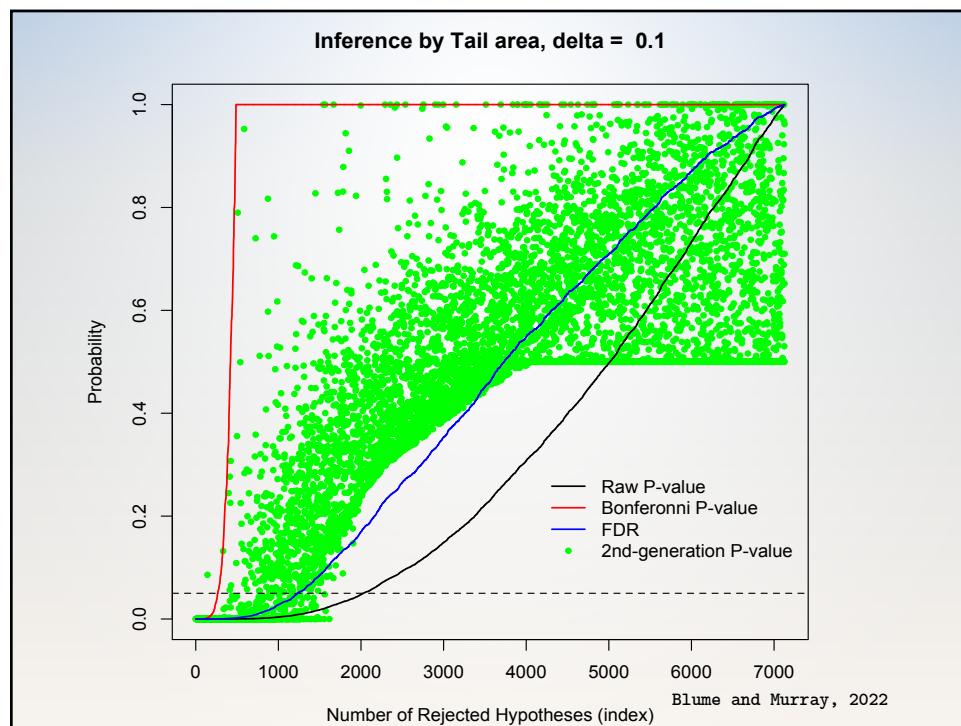
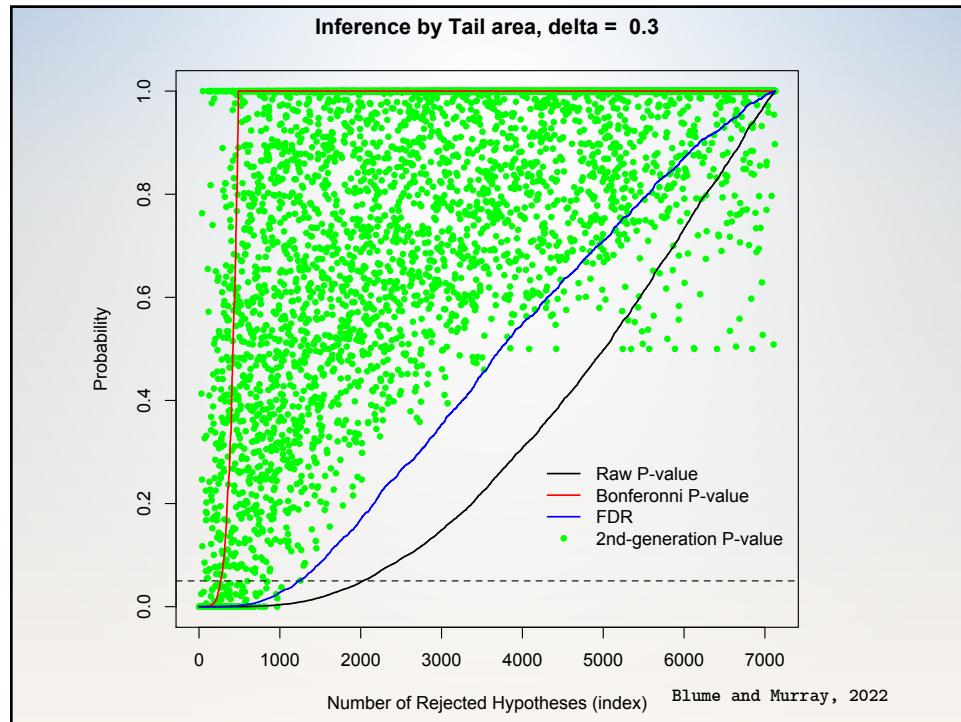
Leukemia study findings

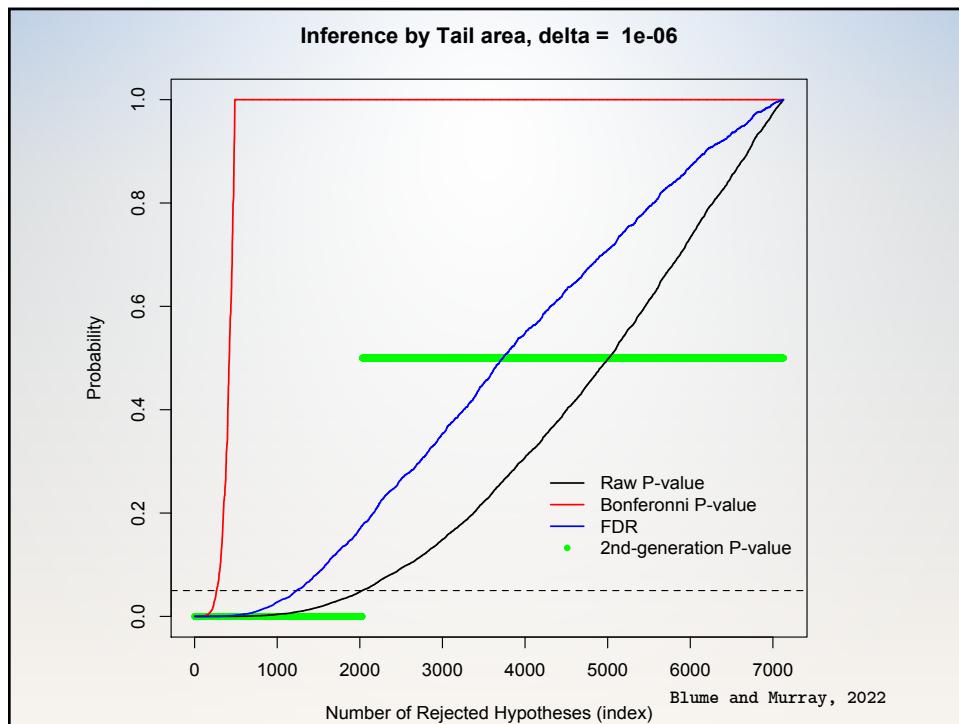
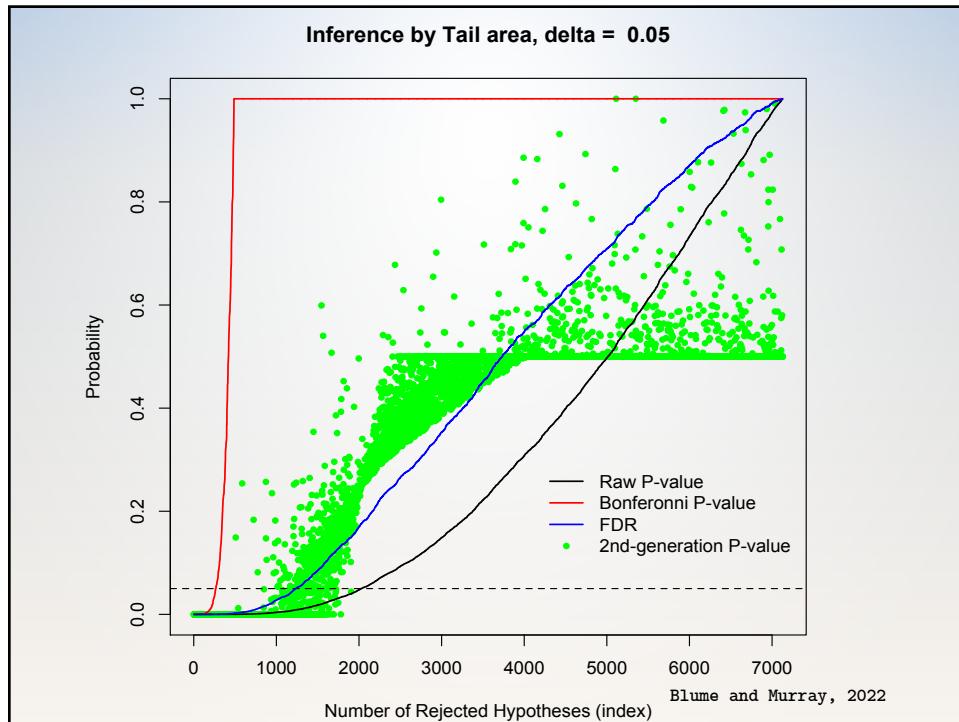
- Findings: Bonferroni 264, SGPV 229
 - Agree on 164 findings
 - Bonferroni +100, SGPV +65
- Effective Type I error rate: 0.037 vs. 0.032
- FDR of 2.45% captures all $p_\delta = 0$, 737 others
- Moving cutoff trades Type I for Type II errors
- SGPV changes the *ranking* of findings
 - Three categories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

Some SGPV findings
have a priori
published validation

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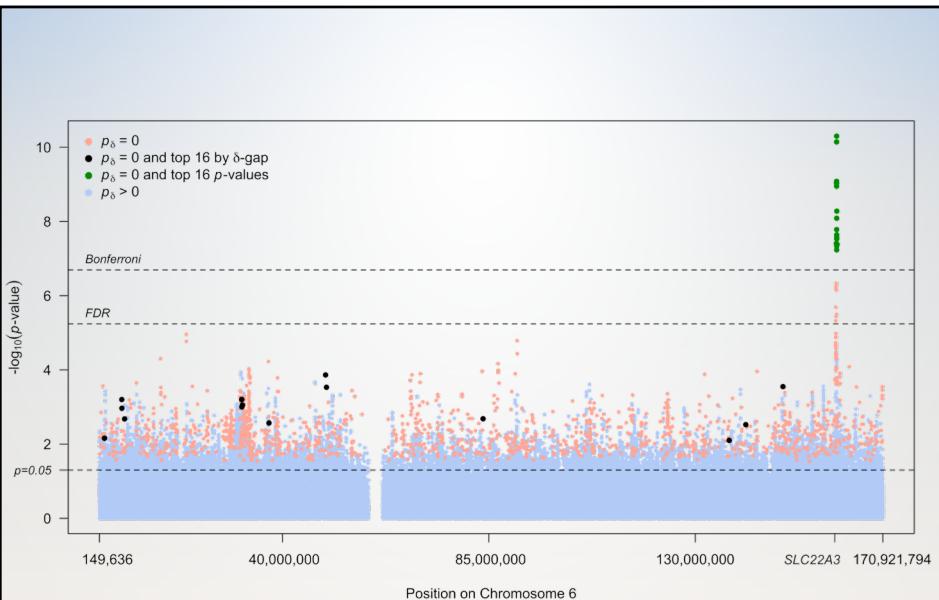


Prostate Cancer SNPs

- 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

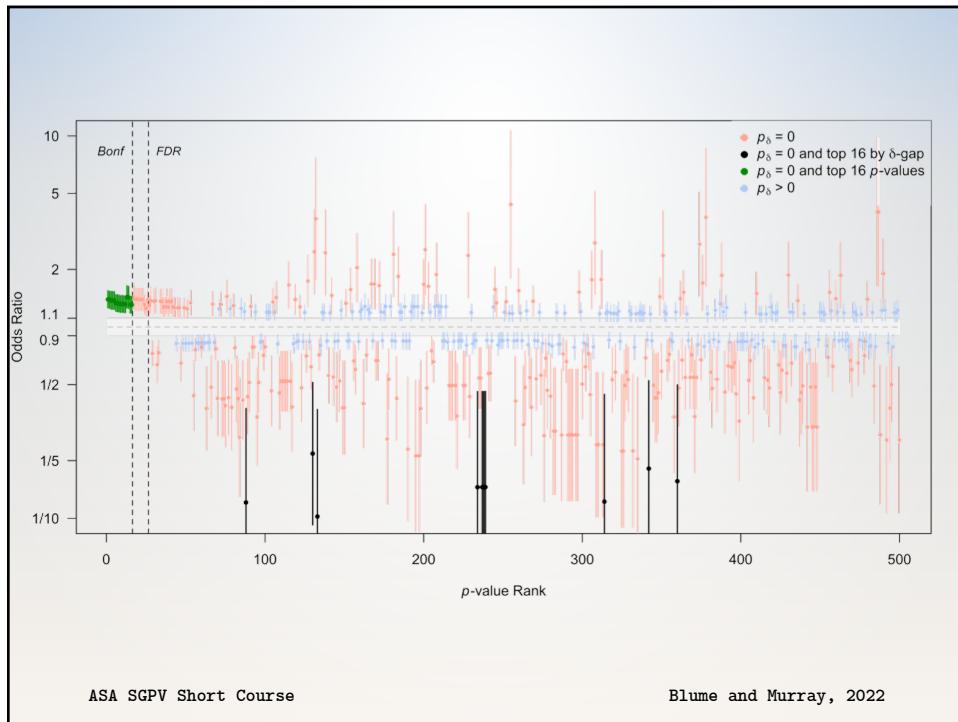
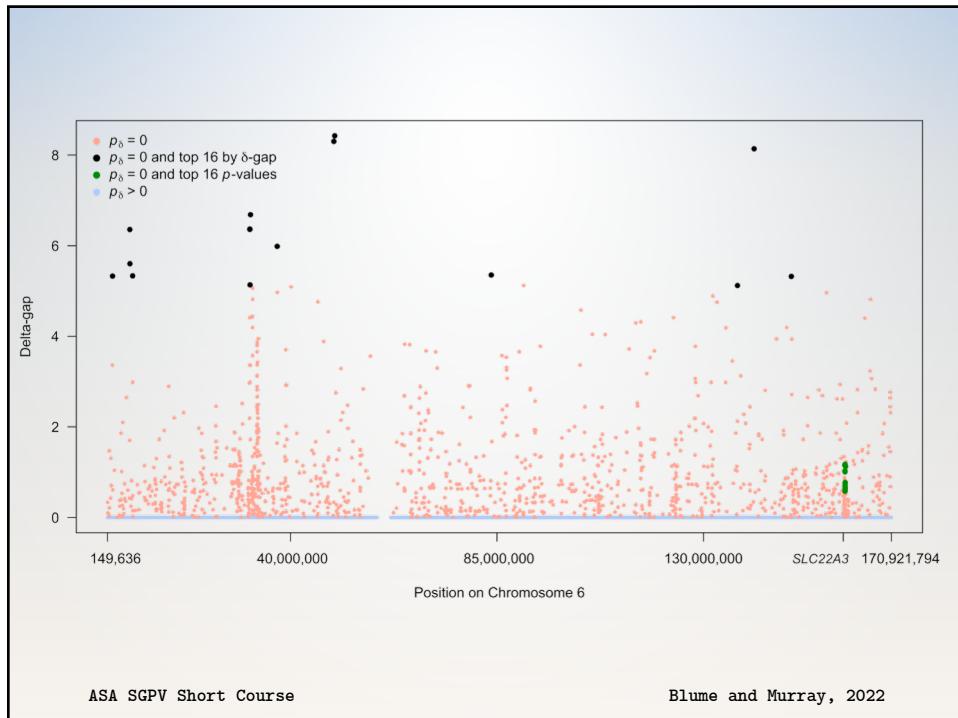
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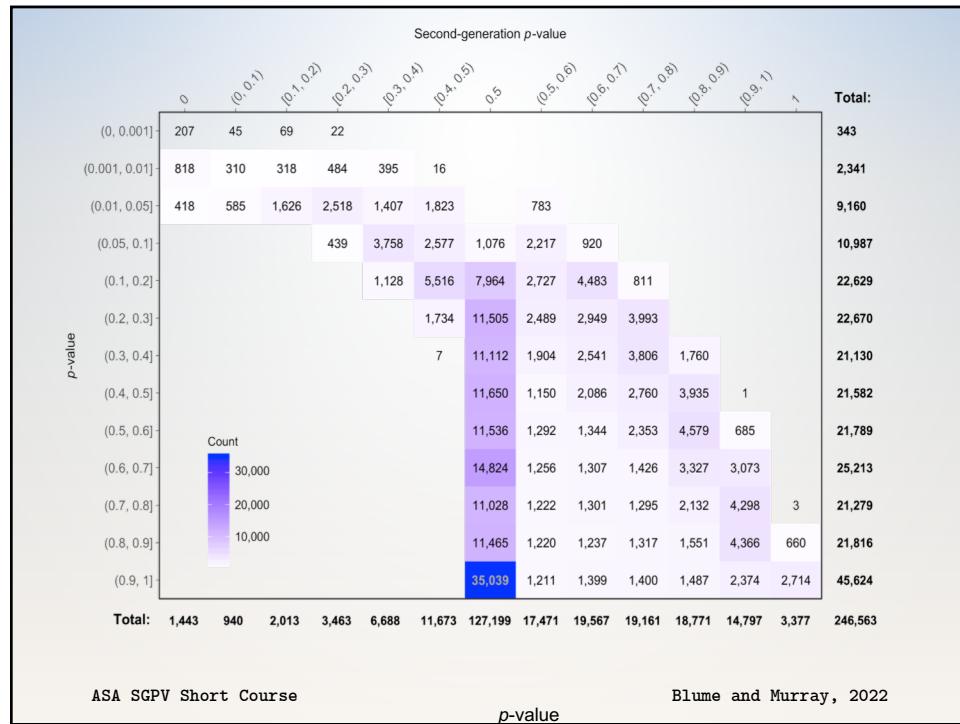
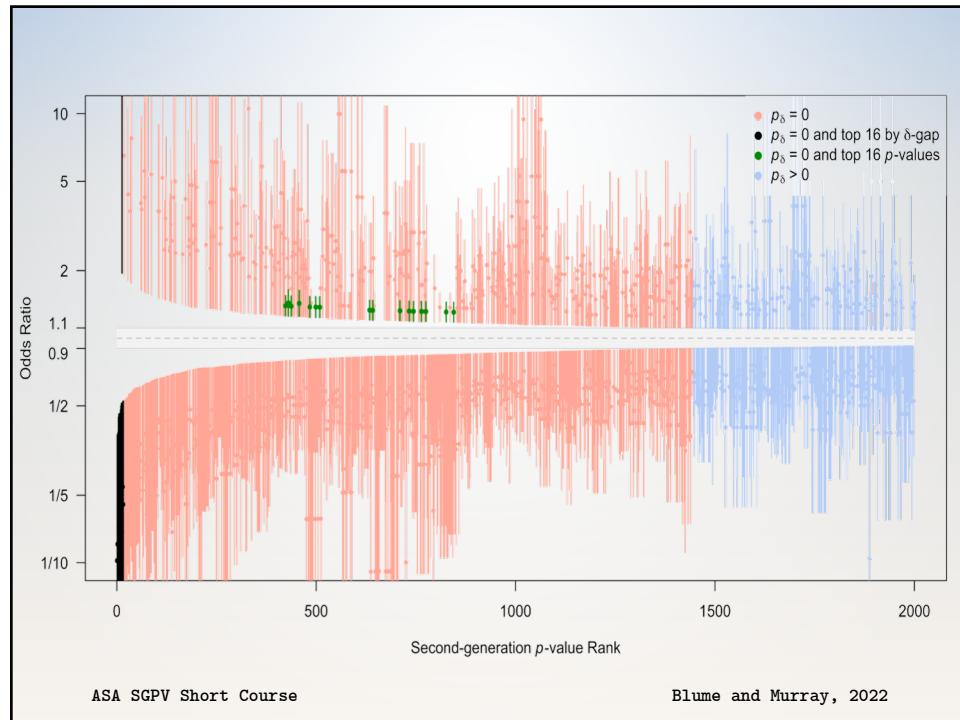
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Outrageous Claim

SGPVs achieve the inferential properties that many scientists hope, or believe, are attributes of the classic *p*-value.

Discussion?

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Time for Code Part 1b!

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