

Part I

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

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PhD

PhD

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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 in Biostatistics at Vanderbilt: August 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 at a pharmaceutical company

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

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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
 - 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

- Axiomatic and intuitive justification
- Summary statistic, yardstick

Positive Test
Negative Test

2. Propensity to collect data that will yield a misleading #1

- Error rates
- Properties of the study design (!)

Sensitivity
Specificity

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 (!)

PPV
NPV

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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 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 ^{2nd-generation}[^]p-value (what ^{we want}it is)

Version 2.0

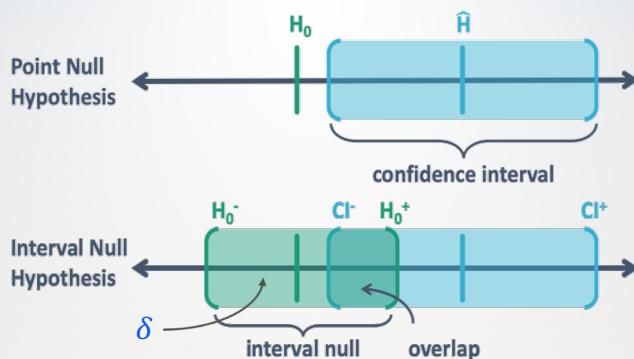
- ✓ Number between 0 and 1 →
 - near 0 supports alt
 - near 1 supports null
 - near $\frac{1}{2}$ inconclusive
- ✓ Smaller ⇒ support for an alternative hypothesis
 - Larger ⇒ data ~~are inconclusive~~ support null
 - Clinical significance is ~~ignored~~ incorporated
- ✗ Sample size confounds comparisons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



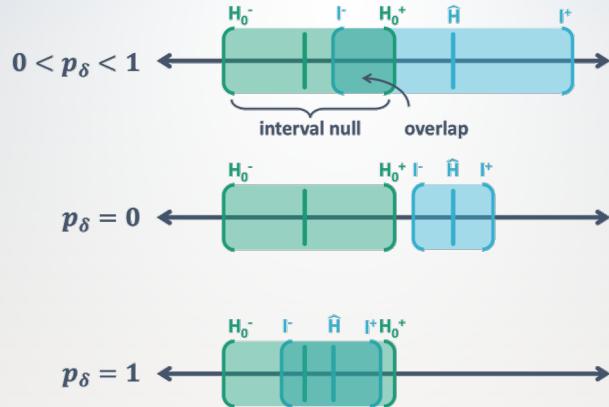
Point null hypothesis H_0 and interval null hypothesis $[H_0^-, H_0^+]$

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

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Illustration



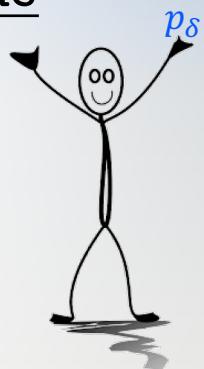
Works with confidence, credible, and support intervals

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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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Funny?

<u>P-VALUE</u>	<u>INTERPRETATION</u>
0.001	HIGHLY SIGNIFICANT
0.01	HIGHLY SIGNIFICANT
0.02	HIGHLY SIGNIFICANT
0.03	HIGHLY SIGNIFICANT
0.04	SIGNIFICANT
0.049	SIGNIFICANT
0.050	OH CRAP. REDO CALCULATIONS.
0.051	ON THE EDGE OF SIGNIFICANCE
0.06	ON THE EDGE OF SIGNIFICANCE
0.07	HIGHLY SUGGESTIVE,
0.08	SIGNIFICANT AT THE P<0.10 LEVEL
0.09	SIGNIFICANT AT THE P<0.10 LEVEL
0.099	HEY, LOOK AT THIS INTERESTING SUBGROUP ANALYSIS
≥0.1	HEY, LOOK AT THIS INTERESTING SUBGROUP ANALYSIS

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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

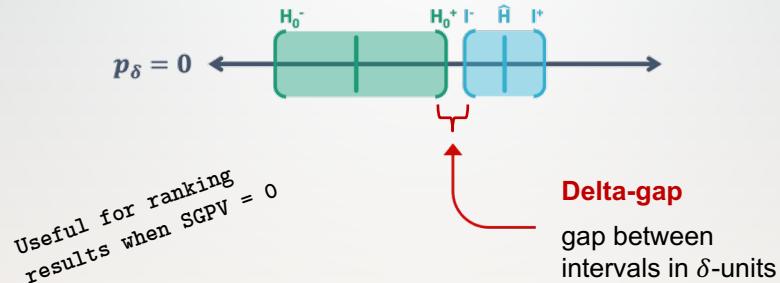
when $|I| > 2|H_0|$

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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 \sim the fraction of data-supported hypotheses that are null or practically null
1. Specify an 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

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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COVID Clinical Trial

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Time for Code Part 1a!

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10 Minute Break!

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Systolic Blood Pressure

- SBP is reported to the nearest 2 mmHg
- Null Hypothesis: mean SPB is 146 mmHg
- Interval Null hypothesis: mean is 144 to 148 mmHg
- Results from 8 mock studies

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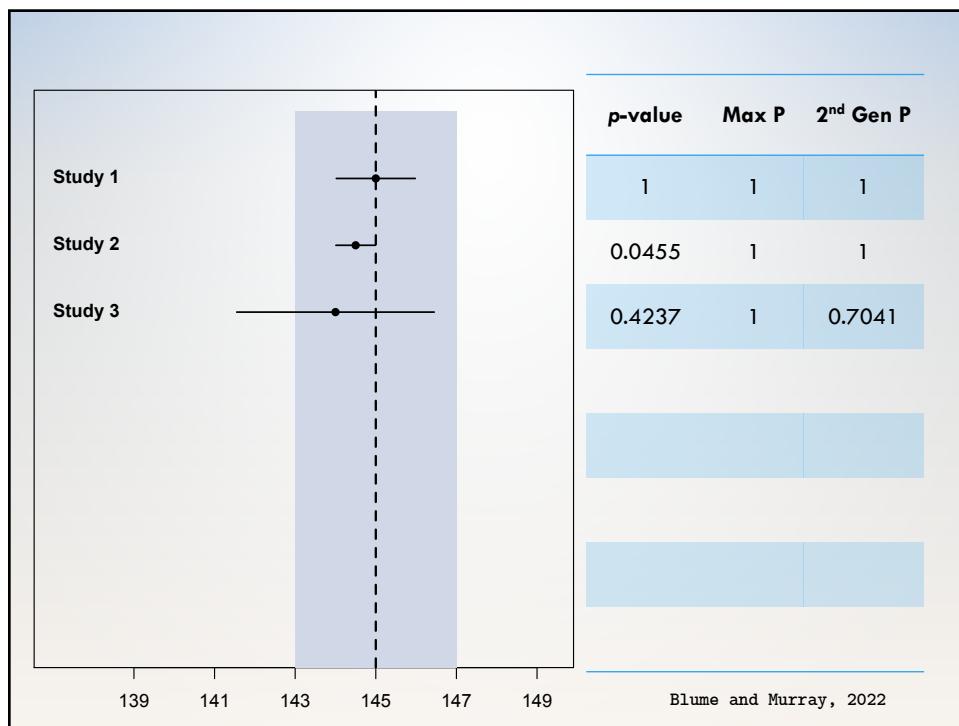
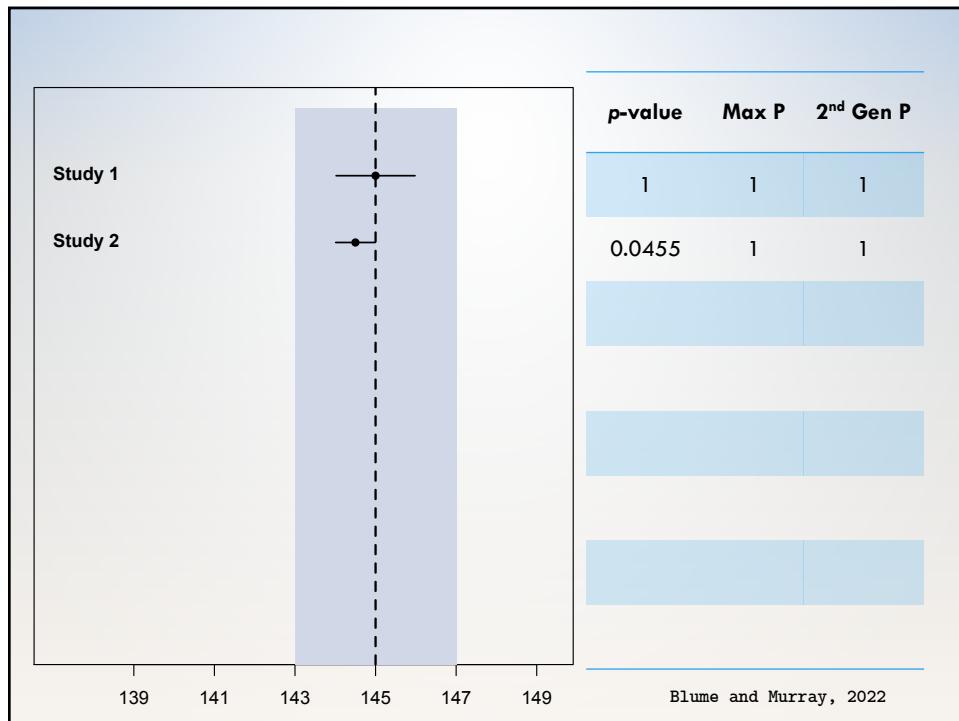
Study 1

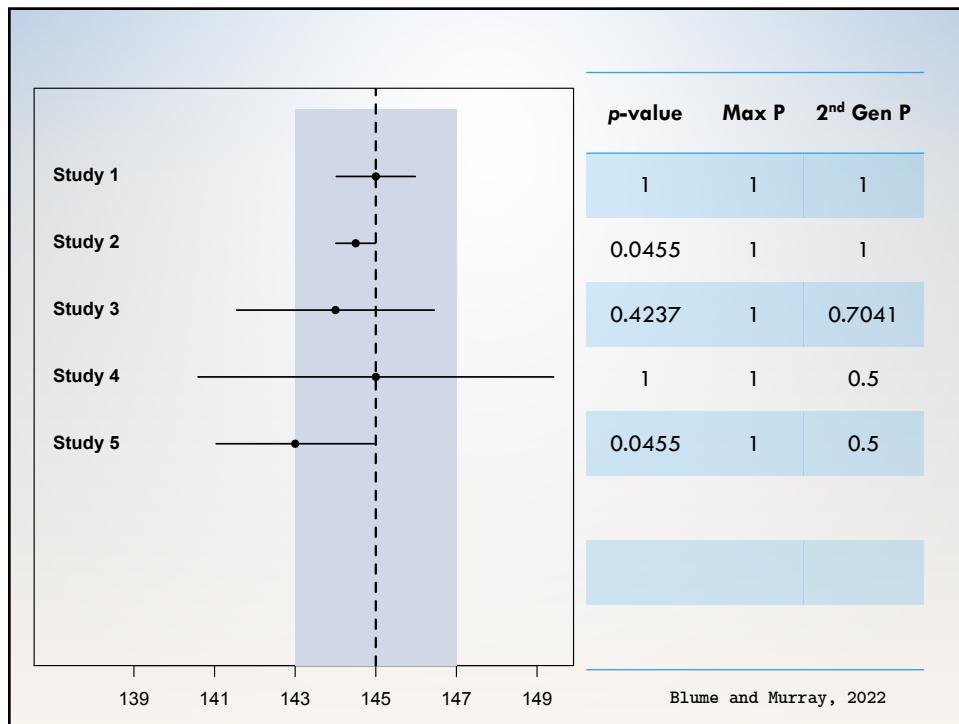
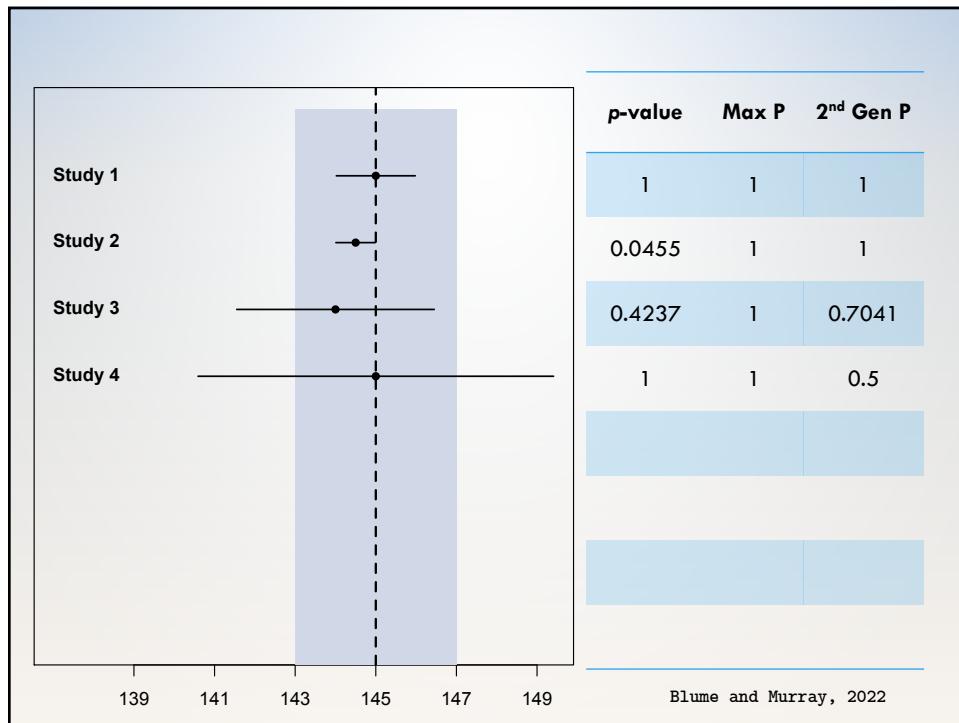
139 141 143 145 147 149

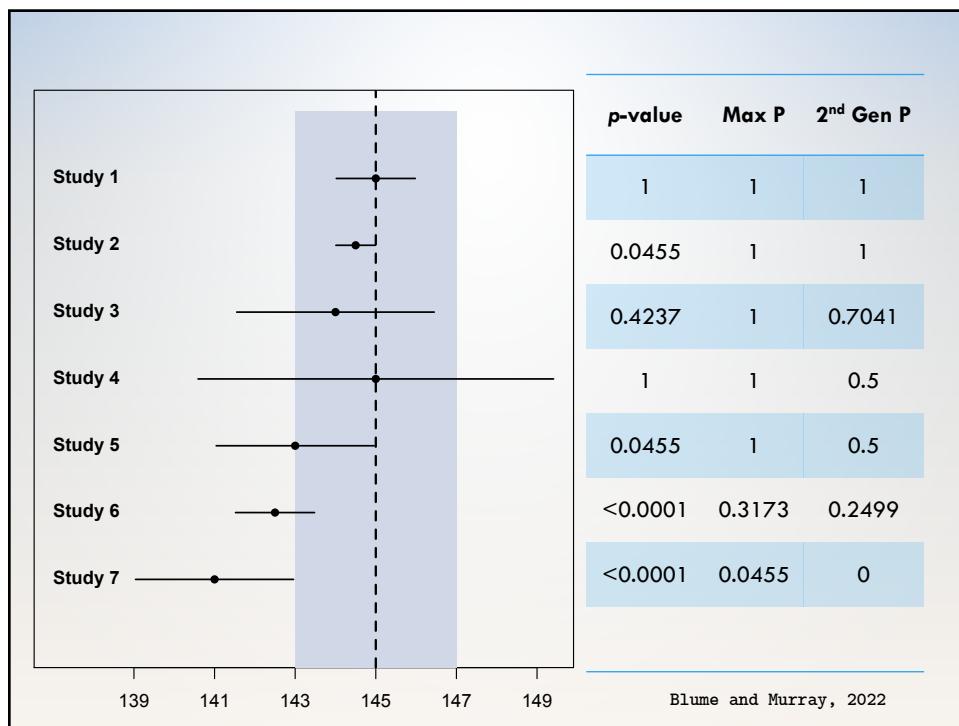
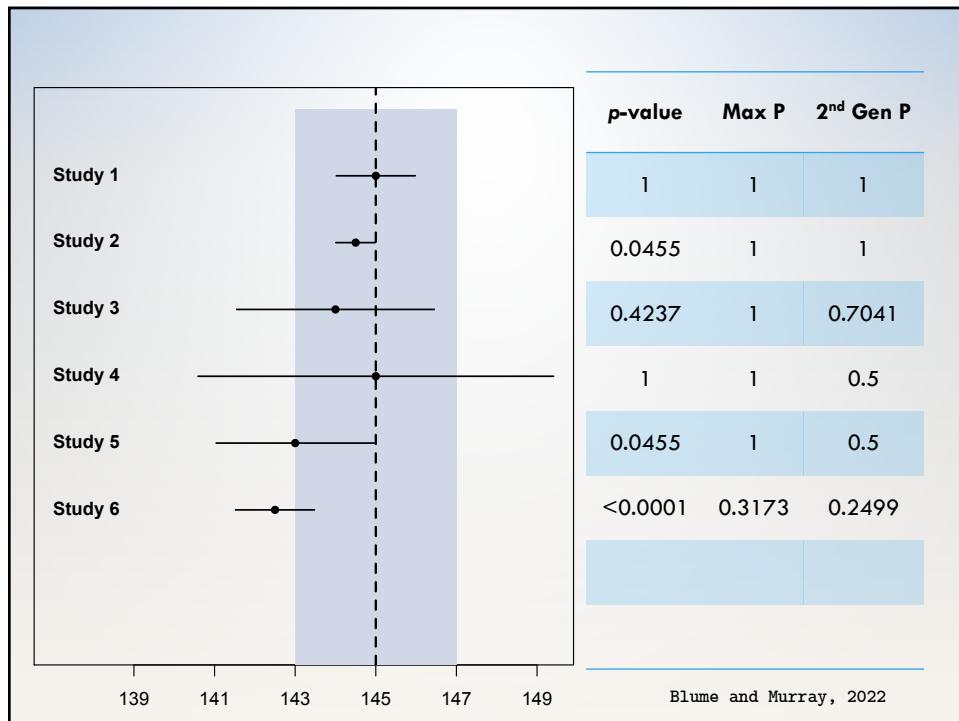
p-value Max P 2nd Gen P

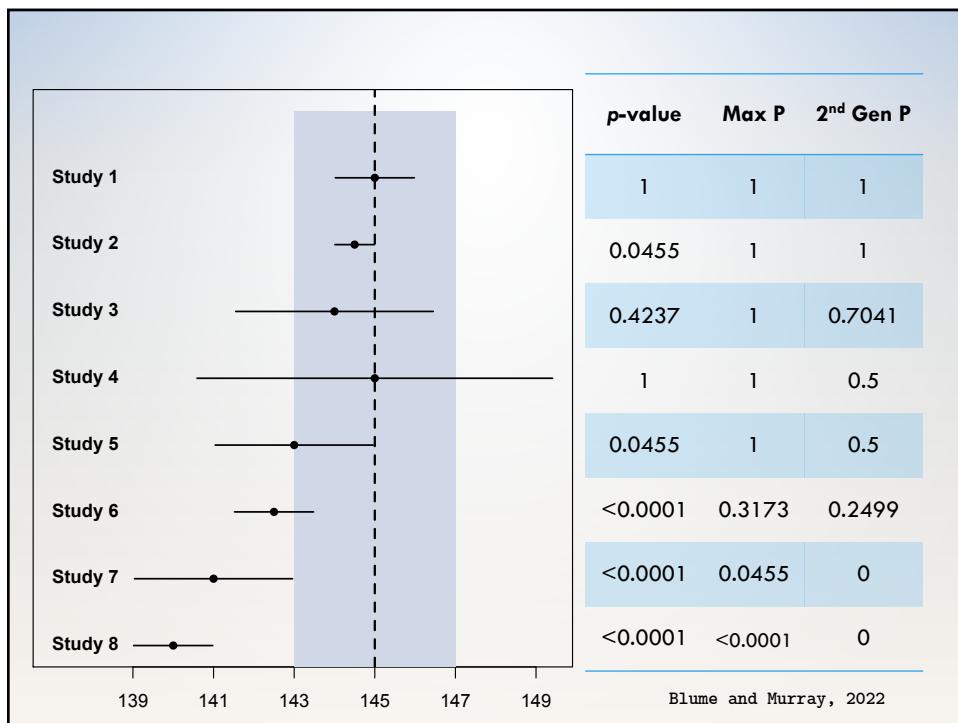
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2x2 Tables & Odds Ratios

Exposure	Outcome	
	No	Yes
Exposed	35	65
Unexposed	50	50

- Scale can be important for inconclusive results
- A p_δ of 0 or 1 will always remain the same
- An inconclusive p_δ will vary slightly

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)

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

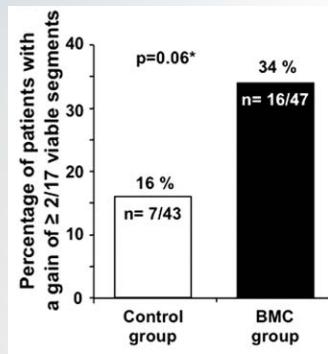
Bone Marrow in Acute Myocardial Infarction (BOMAMI)

- 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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BOMAMI Trial



Odds ratios	95% confidence interval	P-value
2.654	0.967 - 7.286	0.06

Null Interval: (0.9, 1.11)

$$p_\delta = \frac{(1.11 - 0.967)}{(7.286 - 0.967)} (15) = 0.34$$

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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)

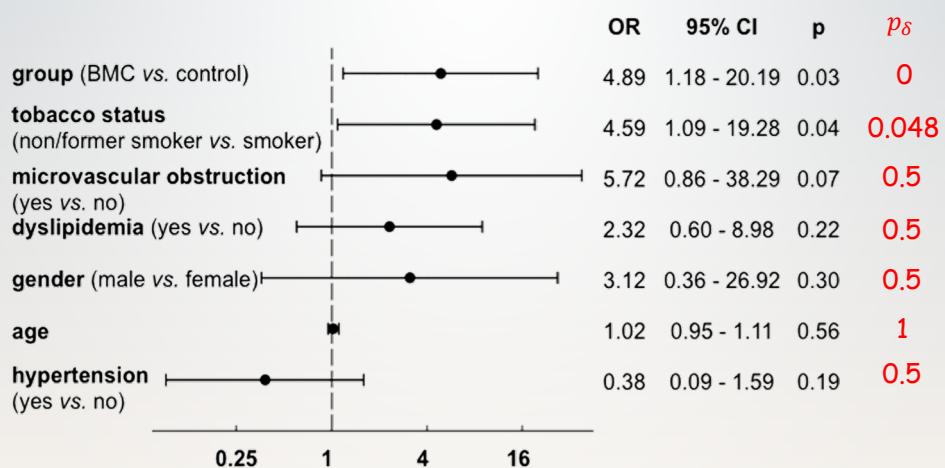
	Estimate	CI Lower	CI Upper	SGPV
Odds Ratio	2.65	0.967	7.286	0.34
Risk Ratio	2.09	0.953	4.589	0.37
Risk Difference	0.18	0.003	0.352	0.24

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BOMAMI Trial

Logistic Regression with Null Zone: (0.9, 1.11)



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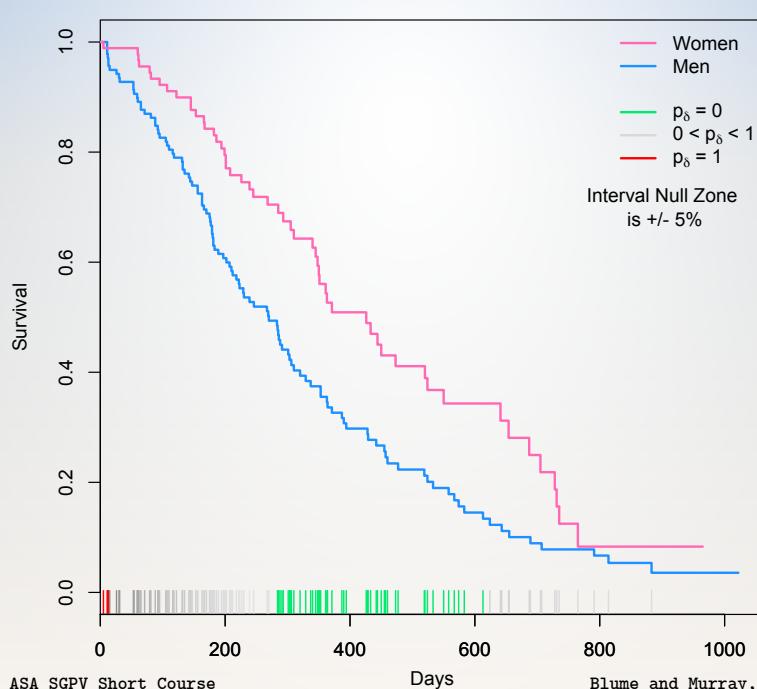
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Lung Cancer Survival

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

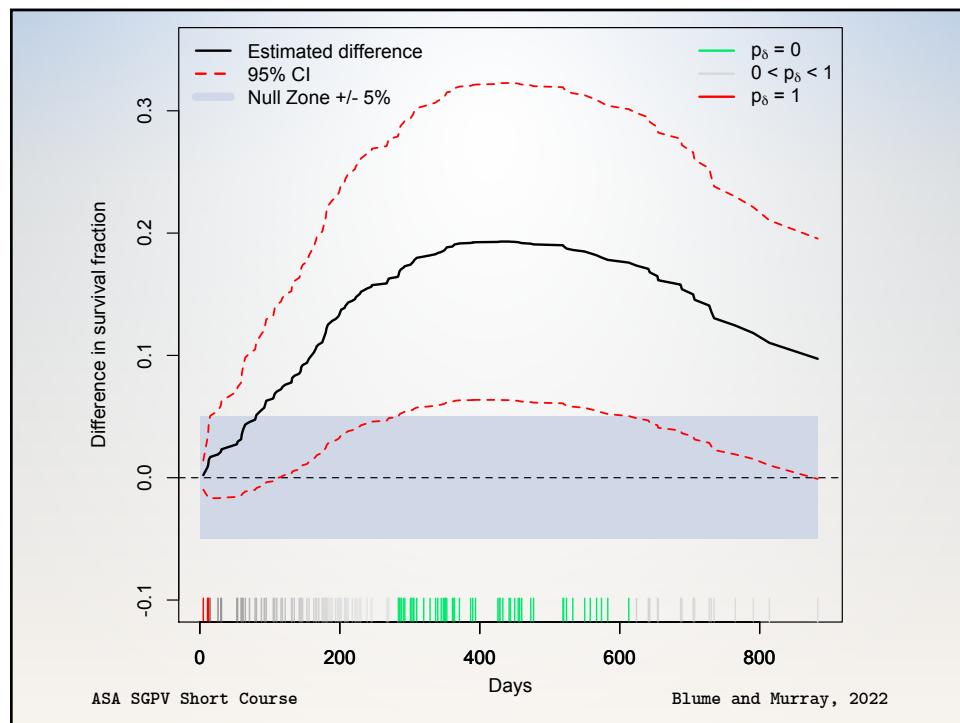
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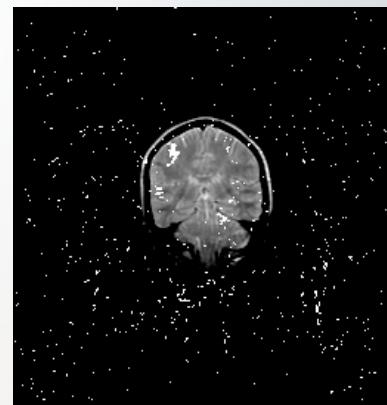
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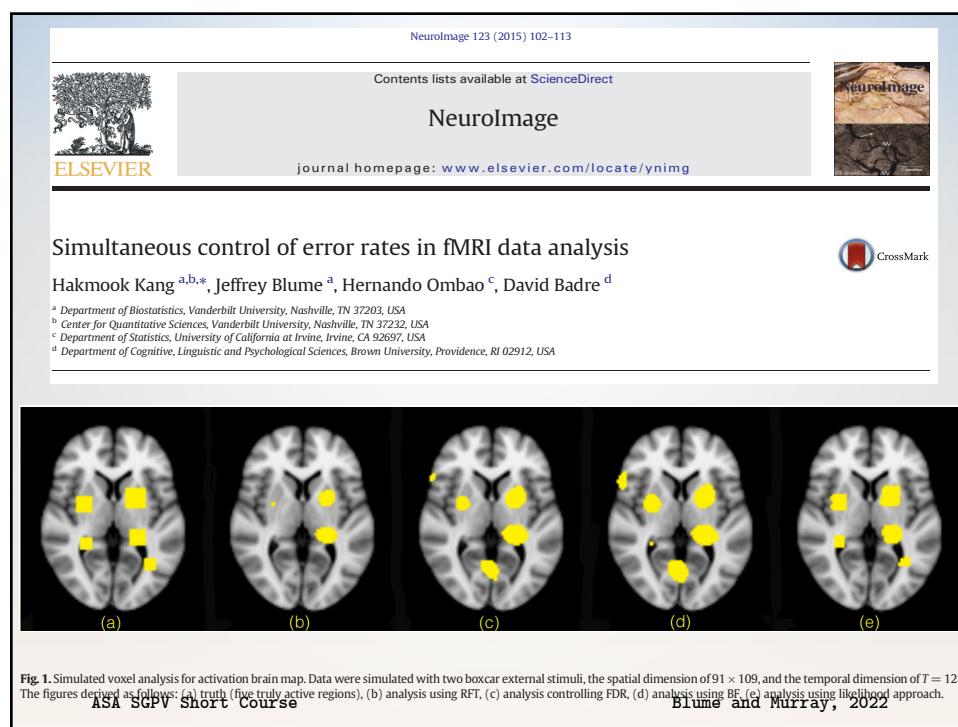
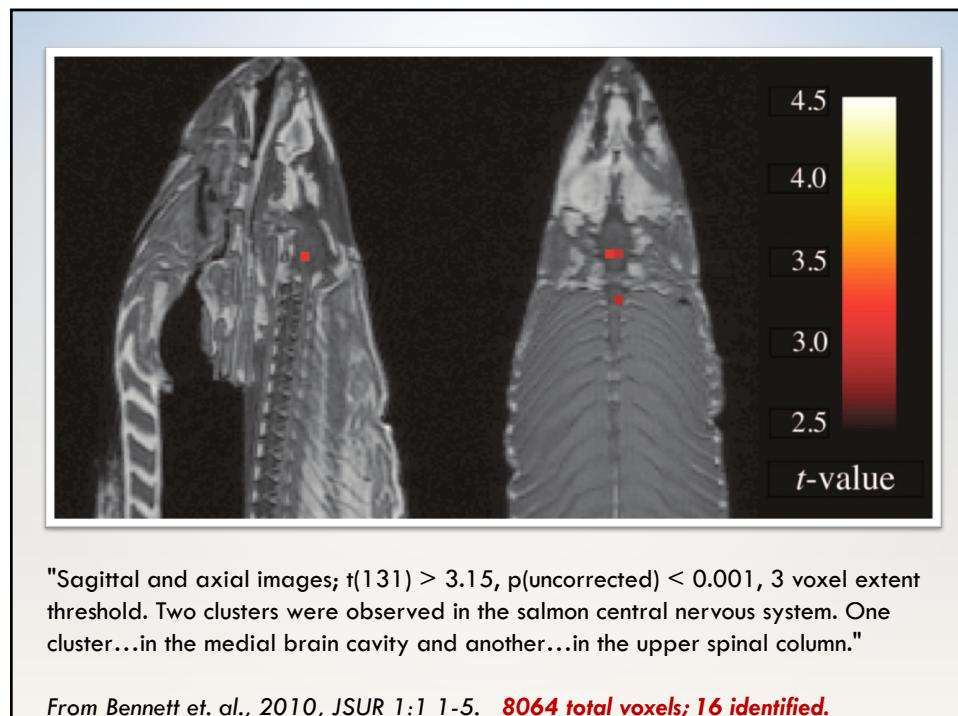
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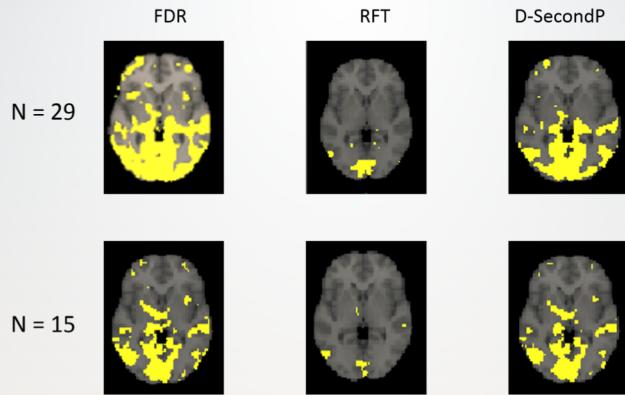
Setting interval null

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





SGPVs for Functional MRI Data



Lisa Lin Dissertation 2021: Data decimation results of activation maps for the 37th axial slice. The yellow blobs indicate activated areas resulted from FDR (first column), RFT (second column) and D-SecondP (third column). The first row corresponds to the activation maps with full sample size at 29. The second row corresponds to the activation maps with a randomly selected sample of size 15.

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Reference of real world SGPV Example

- “Comparing pathologic outcomes for robotic versus laparoscopic Surgery in rectal cancer resection: a propensity adjusted analysis of 7616 patients”
 - By Hopkins et. al
 - Surgical Endoscopy 2020
 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8117669/>

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Surg Endosc. Author manuscript; available in PMC 2021 Jun 1.
Published in final edited form as:
[Surg Endosc. 2020 Jun; 34\(6\): 2613–2622.](#)
Published online 2019 Jul 25. doi: [10.1007/s00464-019-07032-1](https://doi.org/10.1007/s00464-019-07032-1)

PMCID: PMC8117669
NIHMSID: NIHMS1700788
PMID: [31346754](#)

Comparing pathologic outcomes for robotic versus laparoscopic Surgery in rectal cancer resection: a propensity adjusted analysis of 7616 patients

M. Benjamin Hopkins,¹ Timothy M. Geiger,¹ Alva J. Bethurum,¹ Molly M. Ford,¹ Roberta L. Muldoon,¹ David E. Beck,¹ Thomas G. Stewart,² and Alexander T. Hawkins¹

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Statistical Analysis Paragraph 1

- “...The primary hypothesis was tested using a second generation p value ($p\delta$), in which the confidence interval for the log-odds of the outcome (and marginalized difference in probability) for robotic versus laparoscopic approach was compared to the region of practical equivalence specified prior to the analysis [11, 12]...”

Statistical Analysis Paragraph 2

- “... We implemented the second generation p value in this analysis because it avoids a common limitation of many traditional statistical tests related to the interpretation of null results. Take the t test as an example...”

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Time for Code Part 1b!

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10 Minute Break!

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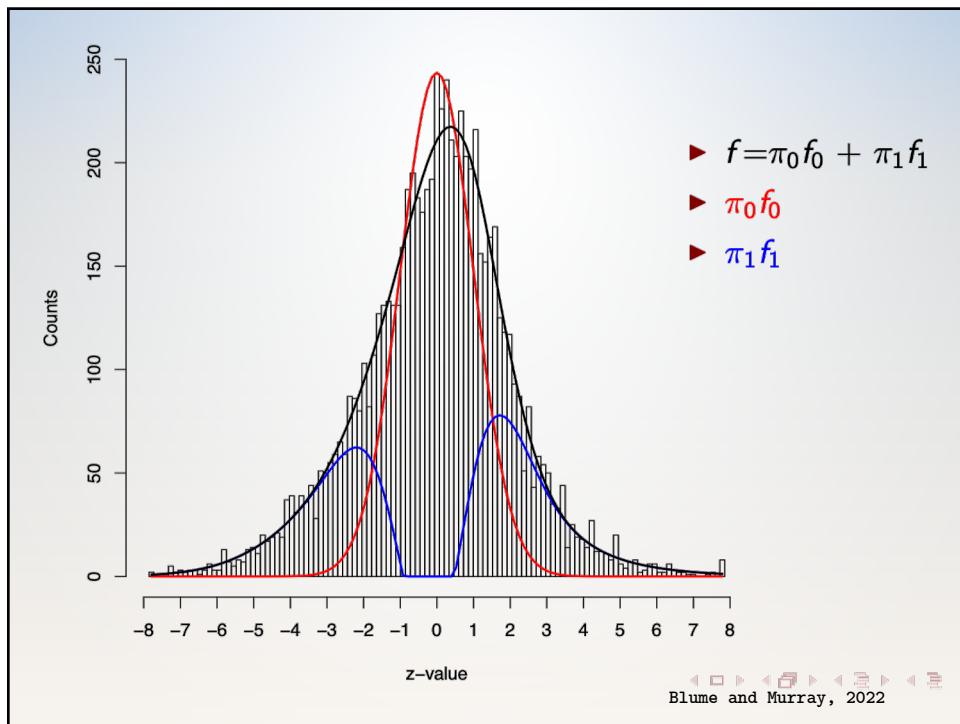
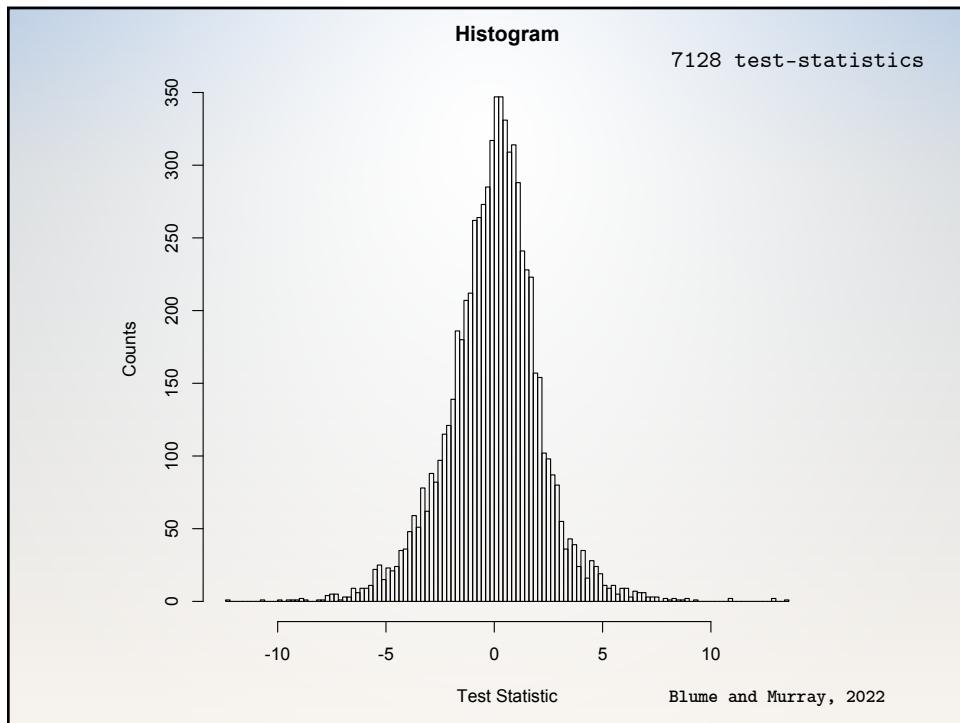
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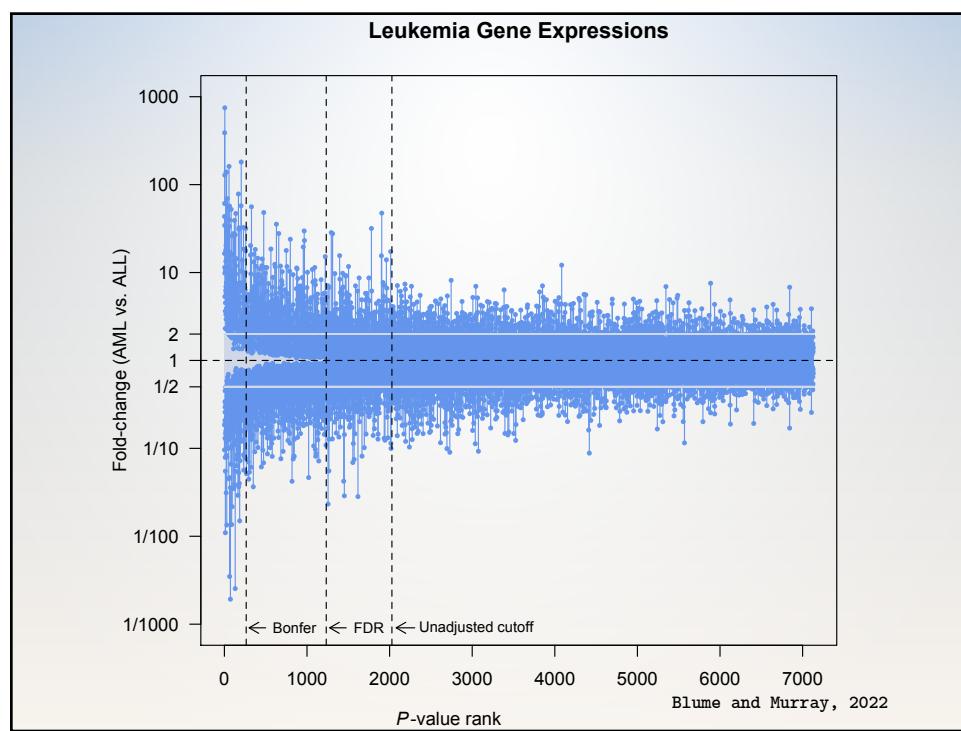
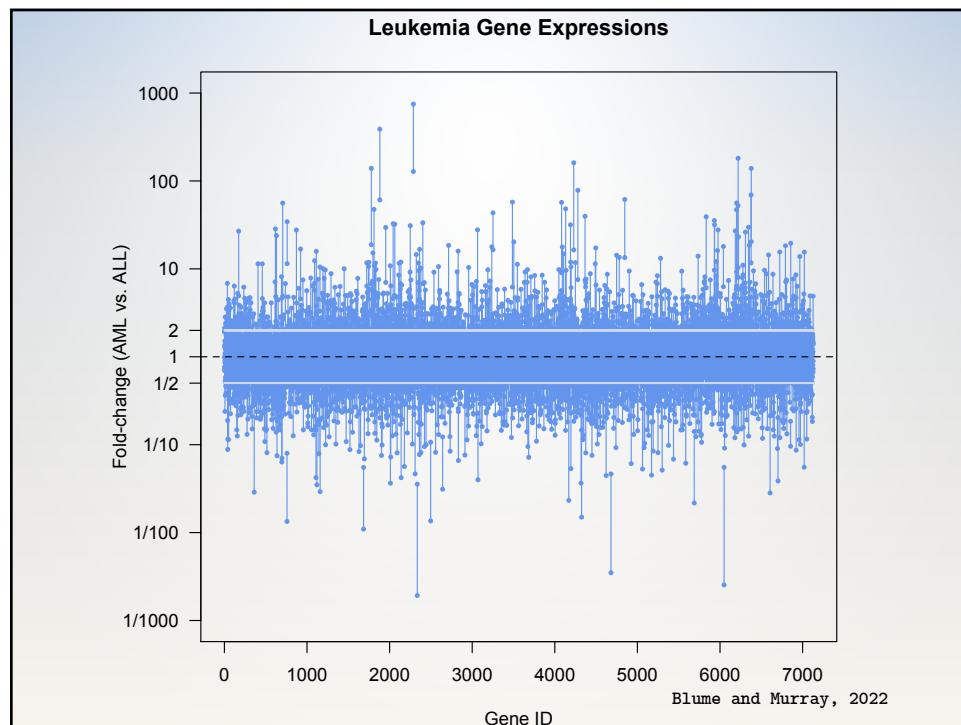
High-Dimensional Data: Leukemia gene expression

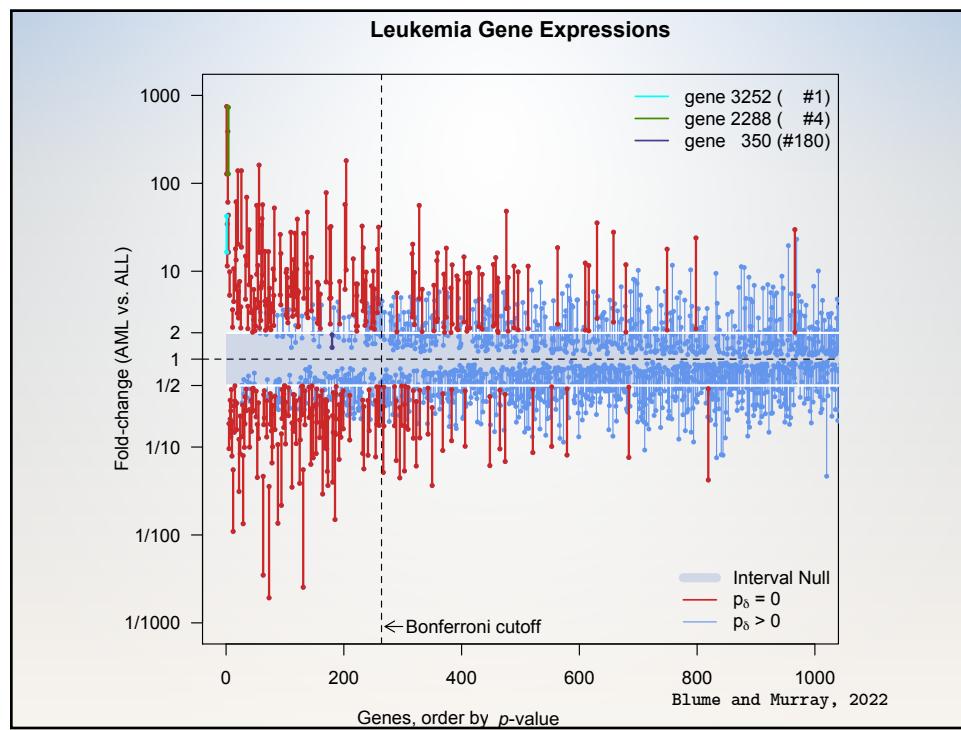
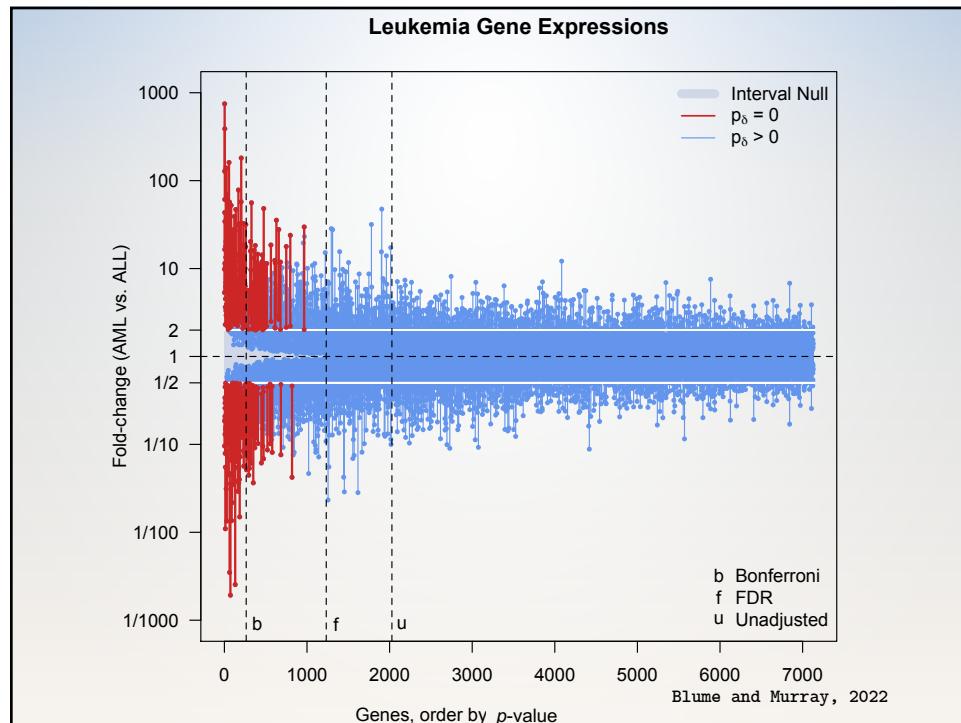
- Classifying acute leukemia by precursors
(Golub 1999, *Science*)
- 7128 genes ; 72 patients (47 ALL and 25 AML)
- Affymetrix chip collected expression levels
- Goal: Identify 'interesting' genes whose expression levels differ between All and AML subjects.
- Looking for fold changes of 2 or more

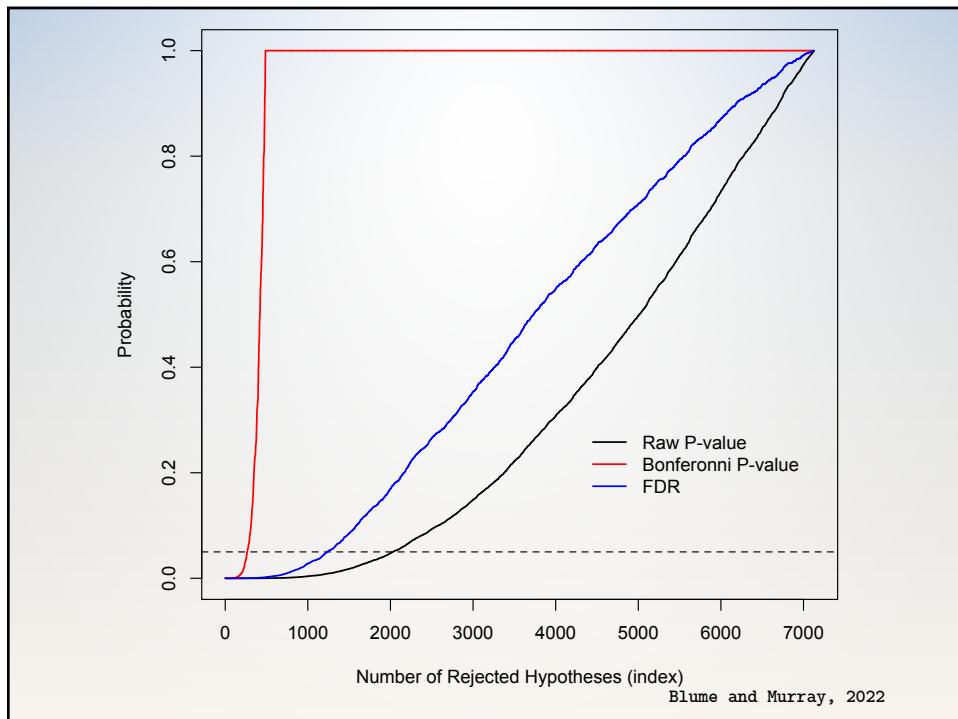
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Cross-Tabulation of Leukemia Results

- Bonferroni vs Second Generation p -values

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

Leukemia study findings

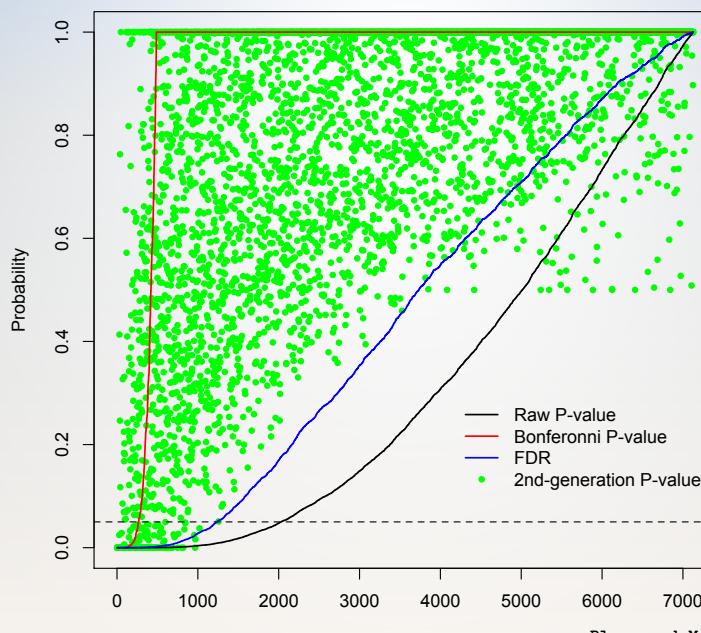
- Findings: Bonferroni 264, SGPV 229
 - Agree on 164 findings
 - Bonferroni +100, SGPV +65
- Effective Type I error rate: 0.037 vs. 0.032
- FDR of 2.45% captures all $p_\delta = 0$, 737 others
- Moving cutoff trades Type I for Type II errors
- SGPV changes the *ranking* of findings
 - Three categories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

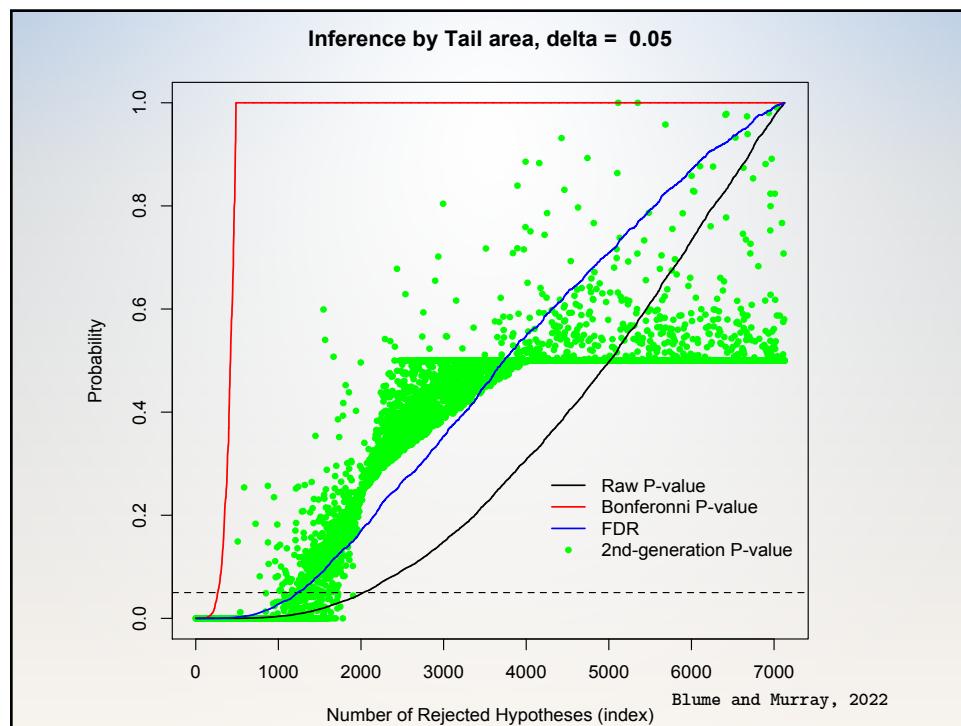
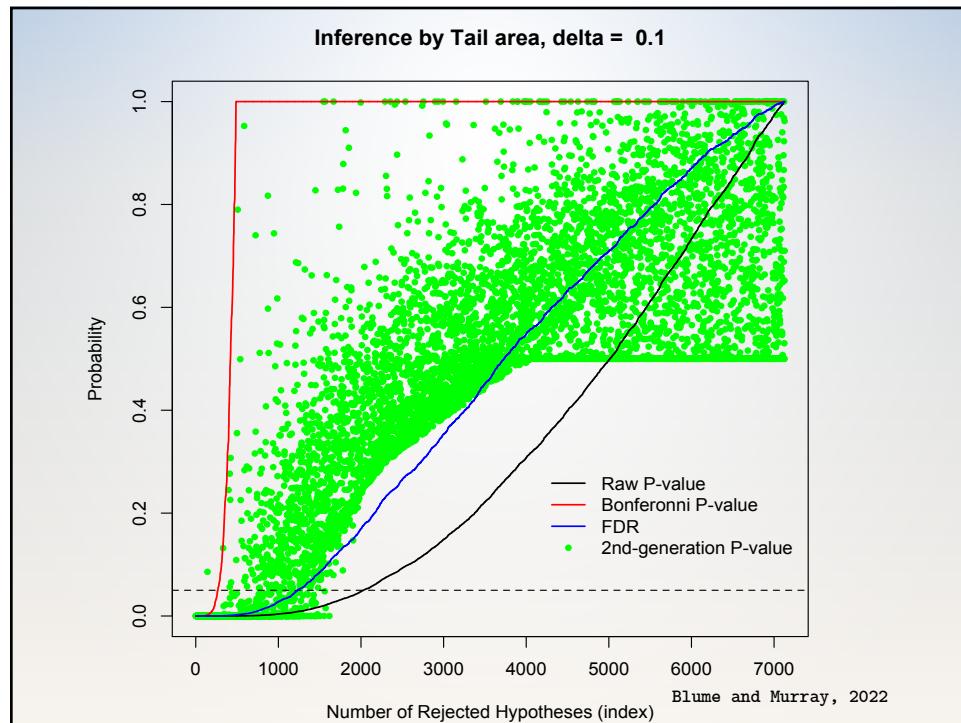
Some SGPV findings
have a priori
published validation

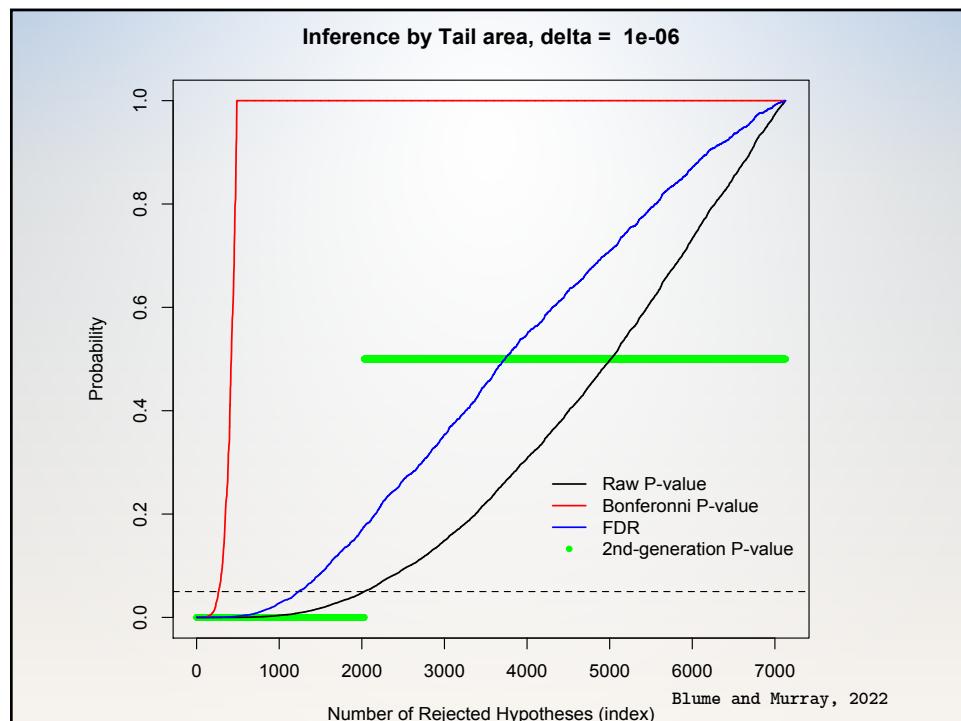
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Inference by Tail area, delta = 0.3

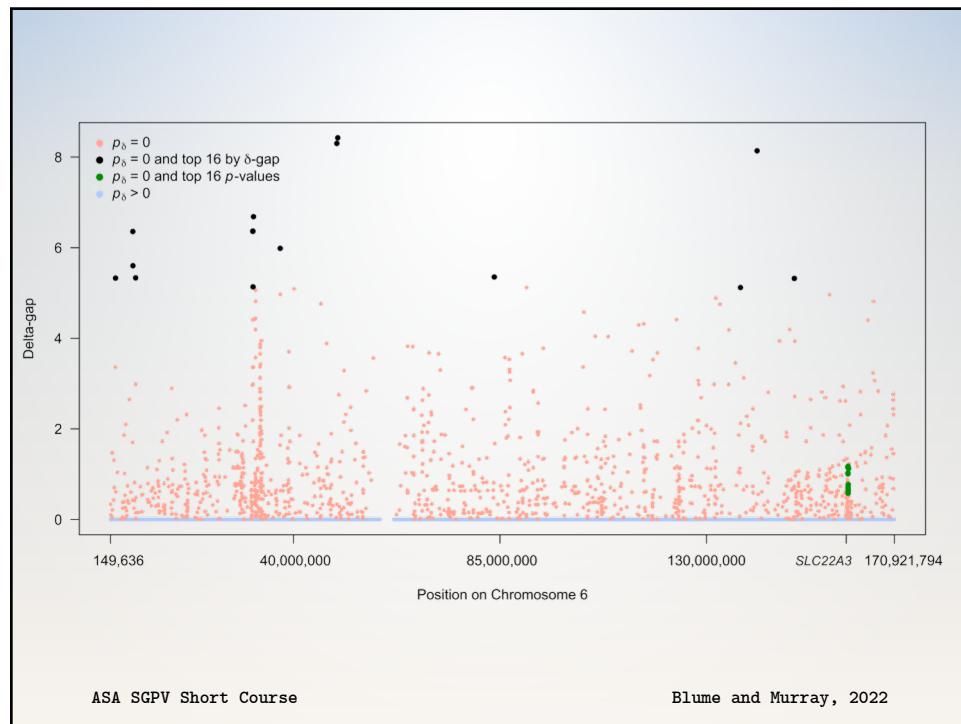
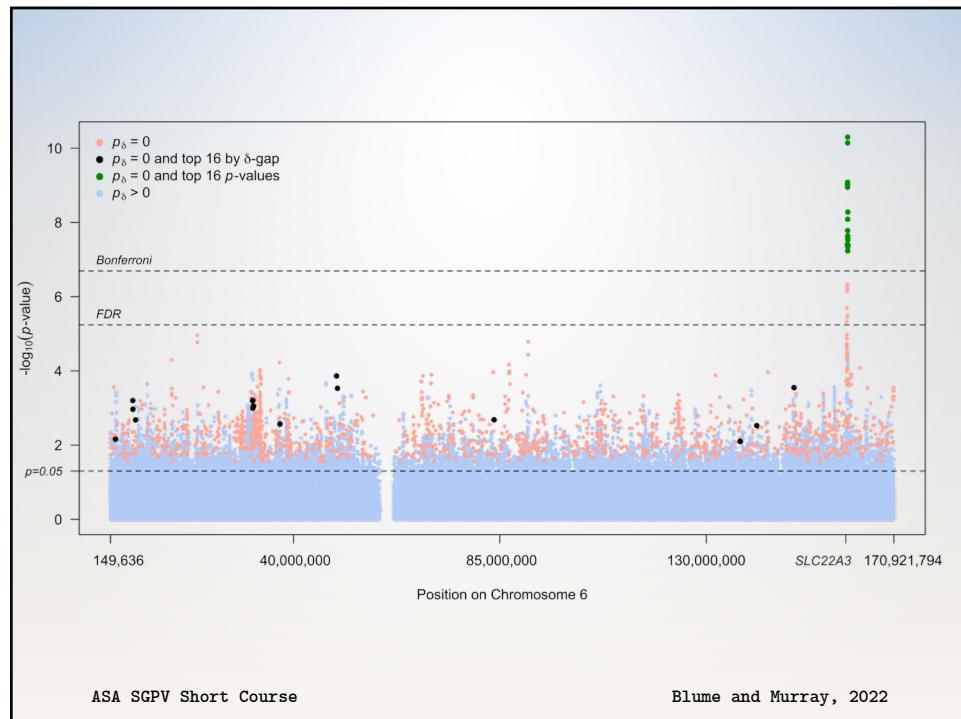


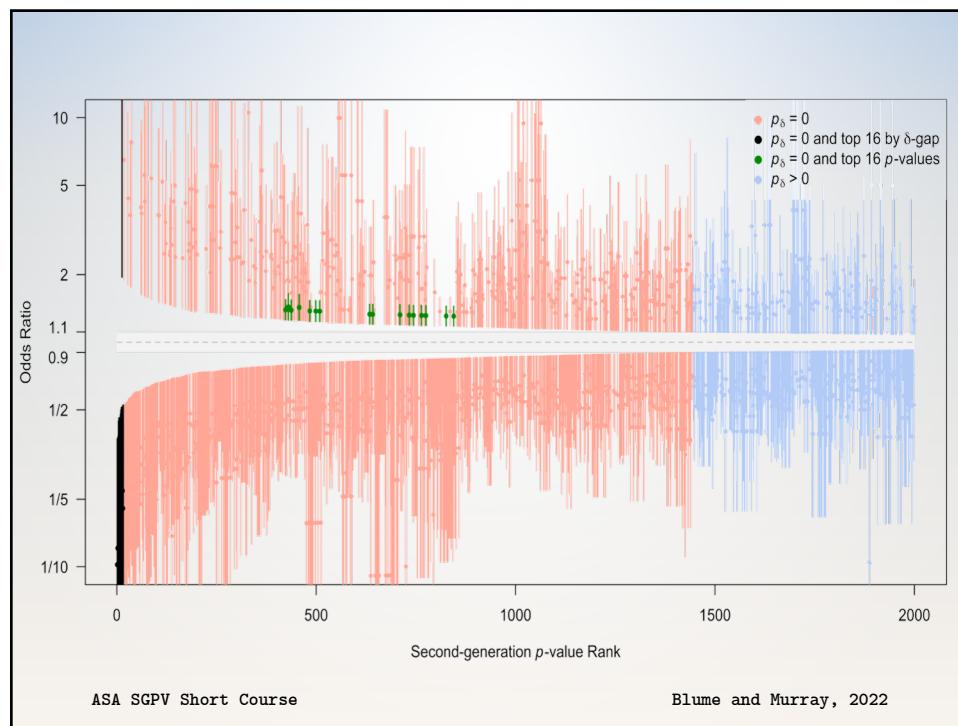
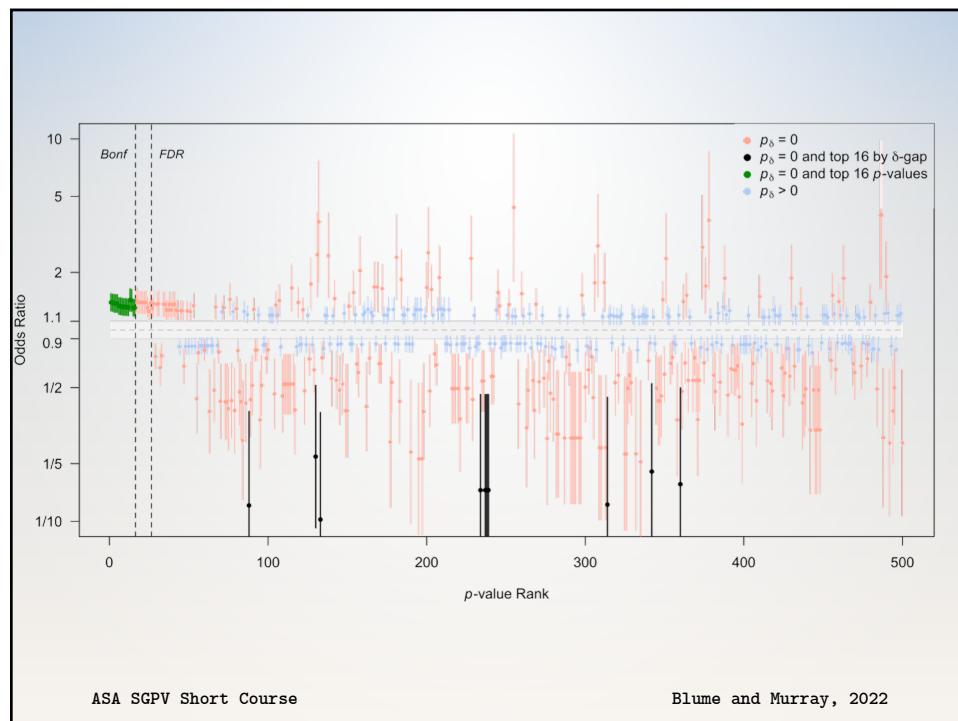


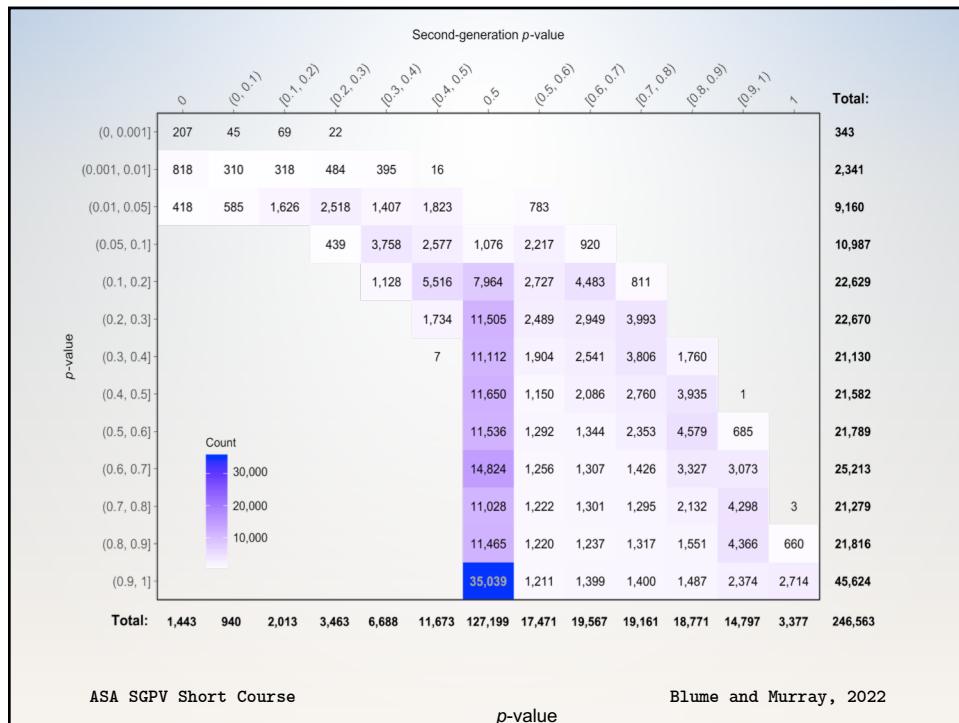


Prostate Cancer SNPs

- 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







Outrageous Claim

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

Discussion?

Time for Code Part 1c!

ASA SGPV Short Course

Blume and Murray, 2022

Lunch Time!

ASA SGPV Short Course

Blume and Murray, 2022