

Part I

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

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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: 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
 - Motivation and definition
 - Examples
 - Code available in GitHub Repo
- Slides Part II:
 - Preview of Statistical Properties
 - False discovery rates
 - Study Planning
 - Connection with Equivalence tests
 - Code available in GitHub Repo

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Resources

- GitHub with Slides and Code
 - <http://www.github.com/murraymegan/SGPV-ASA-Short-Course-2022>
- RStudio Desktop
 - www.rstudio.com/products/rstudio/download
- Interrupt or use Zoom chat for questions!

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Outline



- Evidential Metrics
- Second-generation p -value
- Introductory examples
- High-dimensional examples

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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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Second-generation *p*-value

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

- Statistical properties important for study planning
- False discovery rates <> Reliability of results

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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

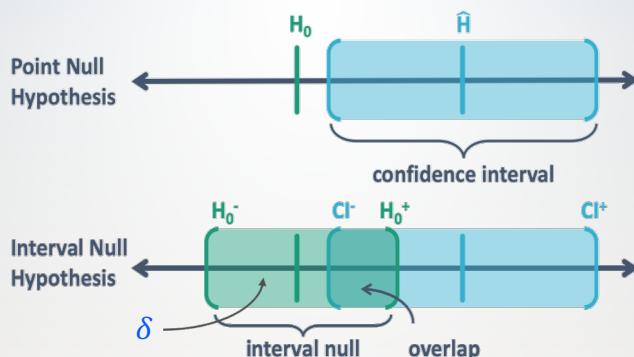
- ✓ Number between 0 and 1 →
 - near 0 supports alt
 - near 1 supports null
 - near $\frac{1}{2}$ inconclusive
- ✓ Smaller \Rightarrow support for an alternative hypothesis
 - Larger \Rightarrow data ~~are inconclusive~~ support null
 - Clinical significance is ~~ignored~~ incorporated
- ✗ Sample size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



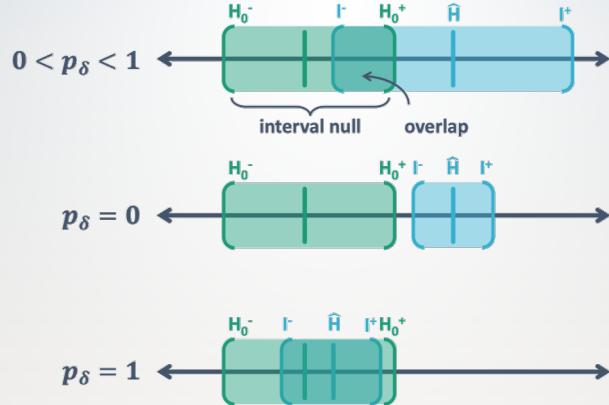
Point null hypothesis H_0 and interval null hypothesis $[H_0^-, H_0^+]$

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

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Illustration

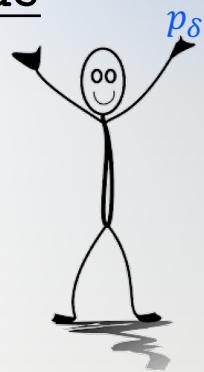


Works with confidence, credible, and support intervals

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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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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

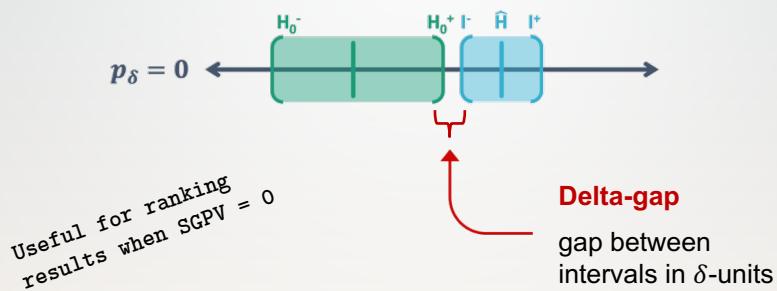
when $|I| > 2|H_0|$

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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 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



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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

Abstract

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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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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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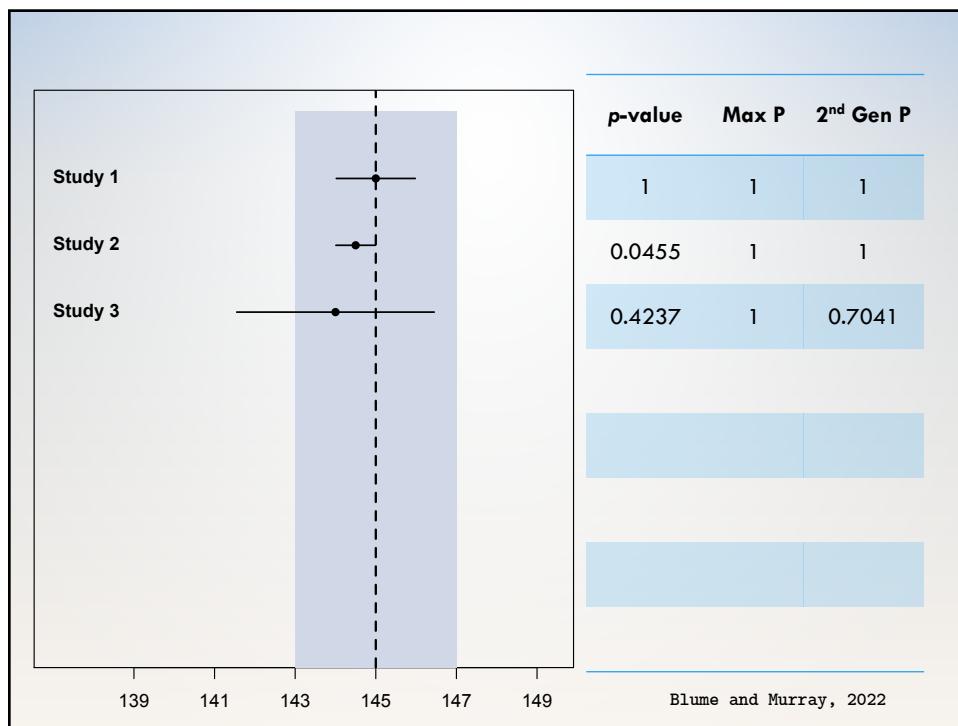
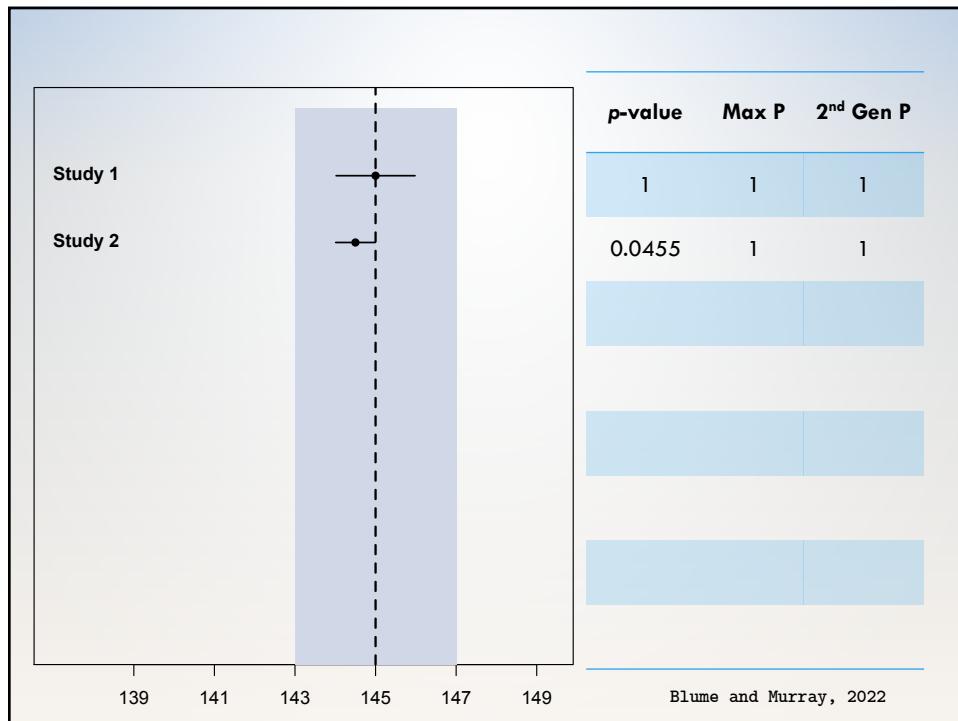
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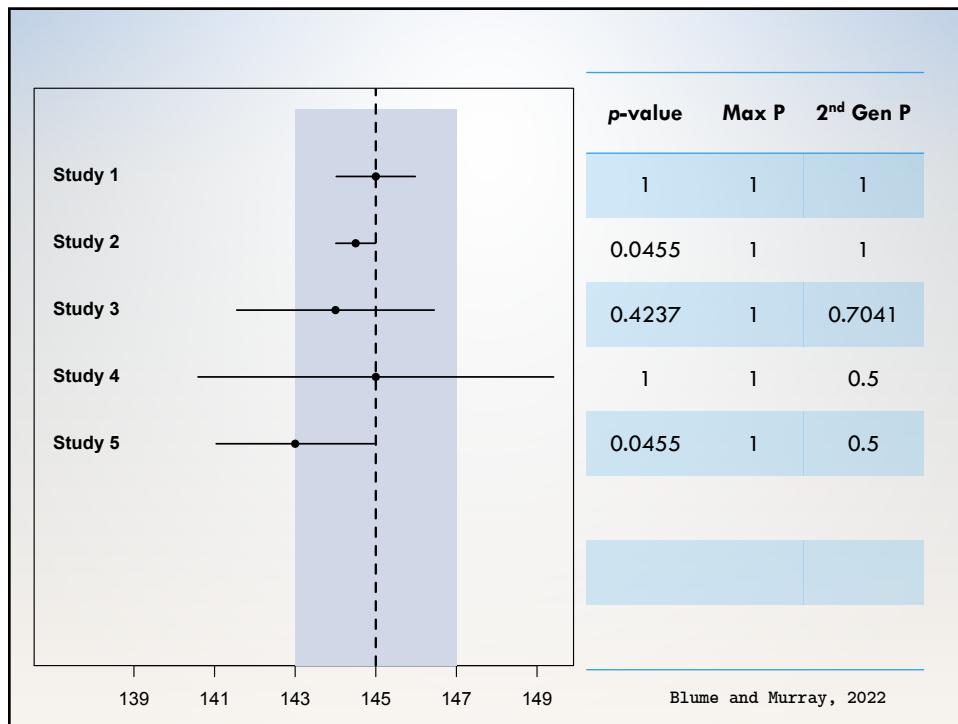
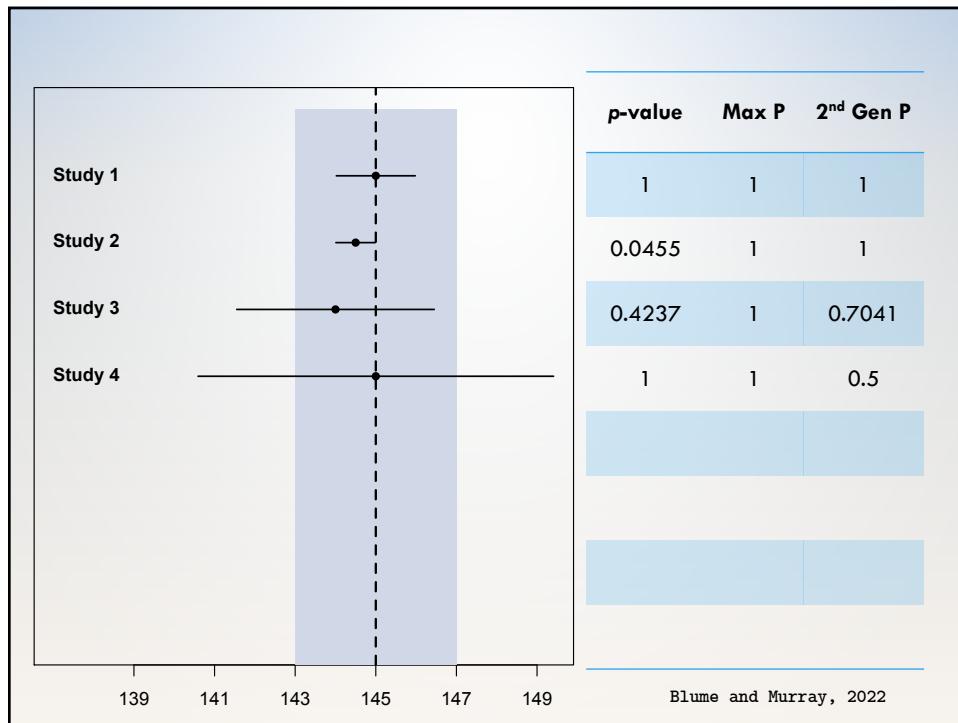
Study 1

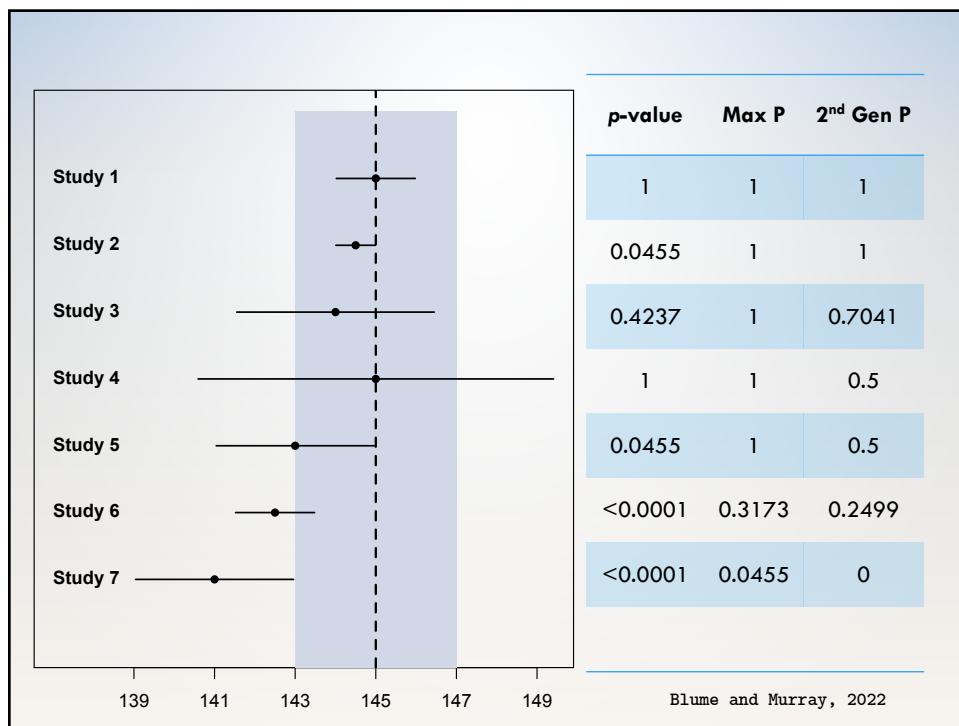
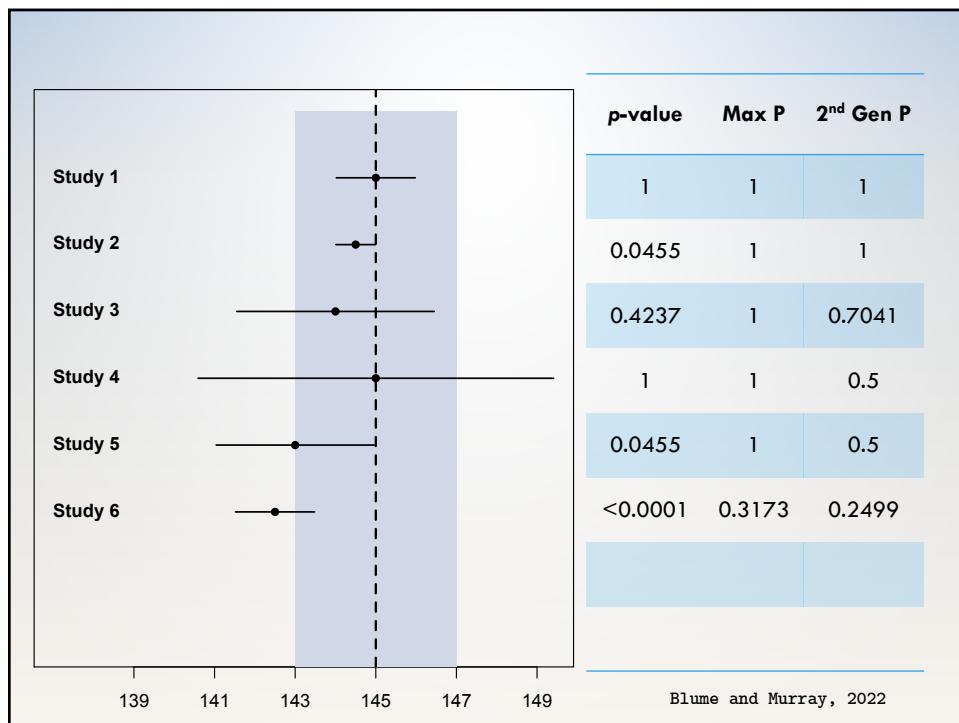
139 141 143 145 147 149

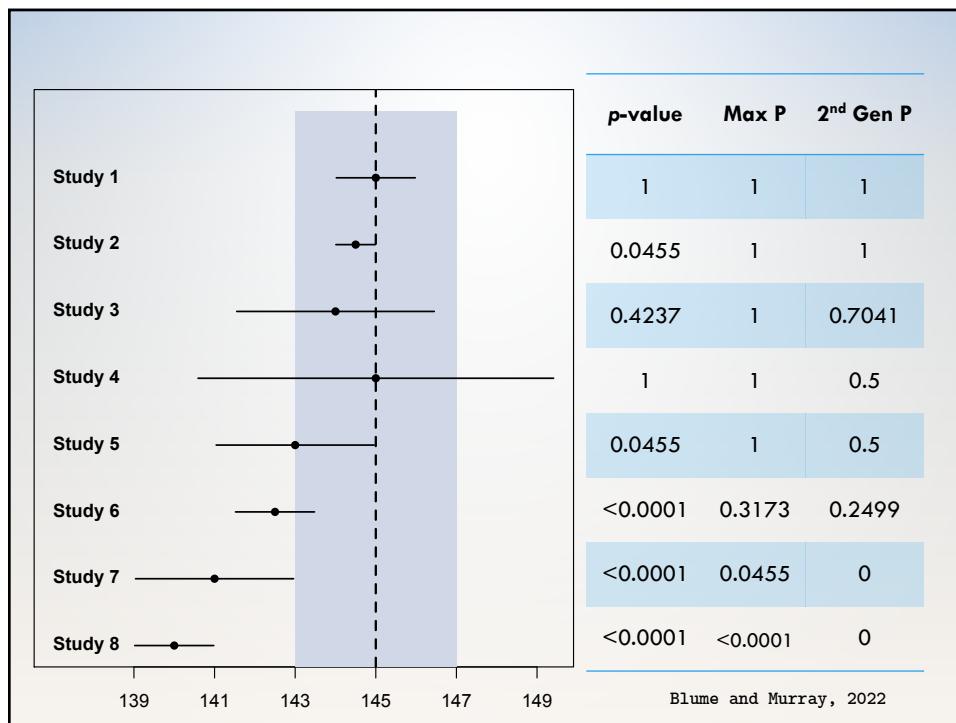
p-value	Max P	2 nd Gen P
1	1	1

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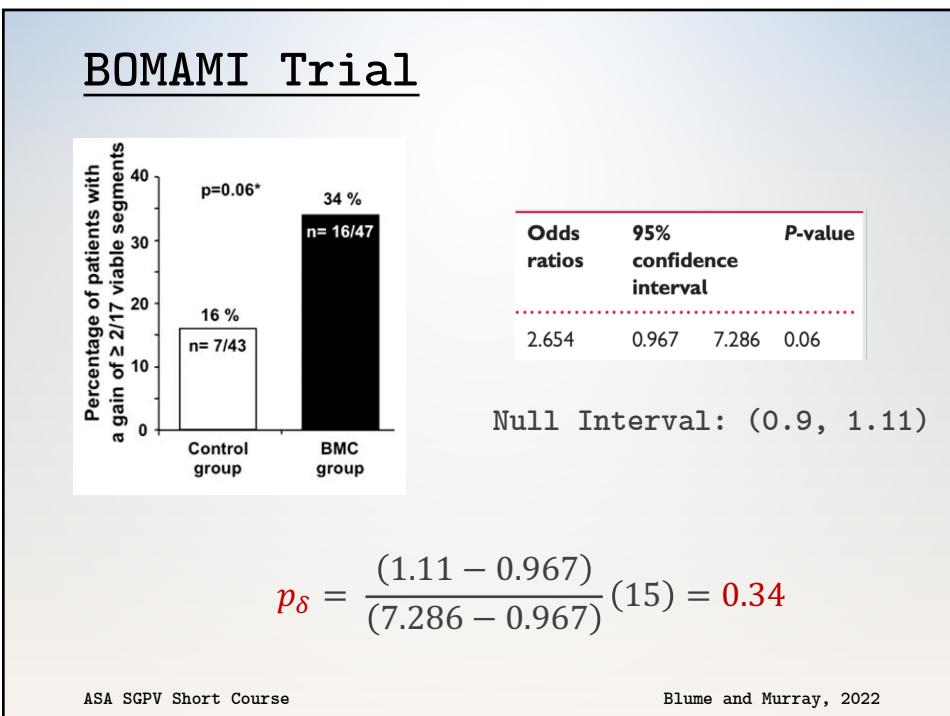




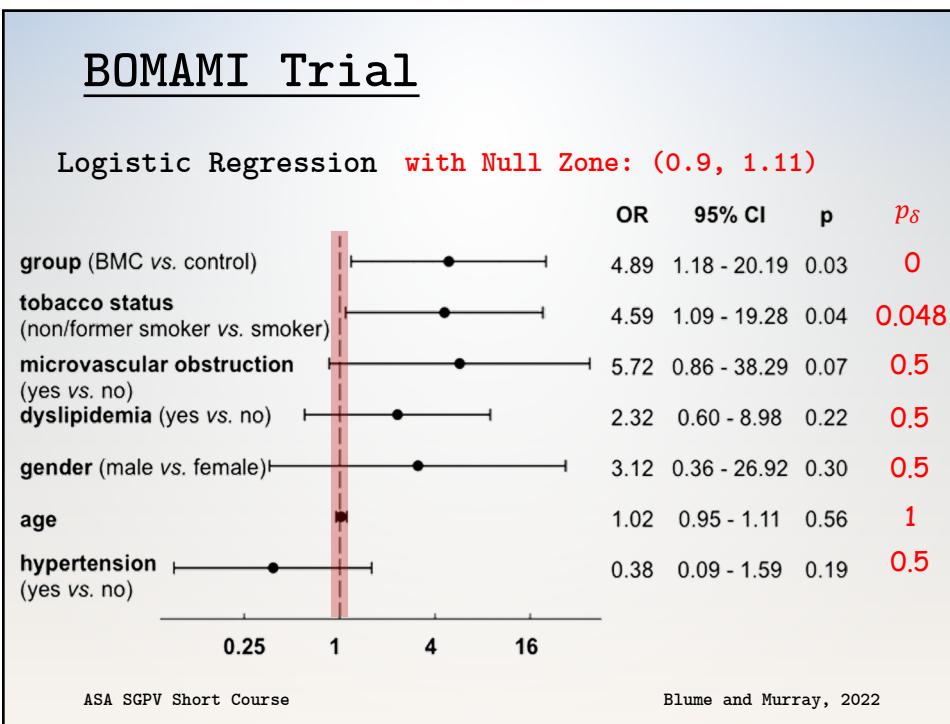


Bone Marrow in Acute Myocardial Infarction (BOMAMI)

- 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)



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

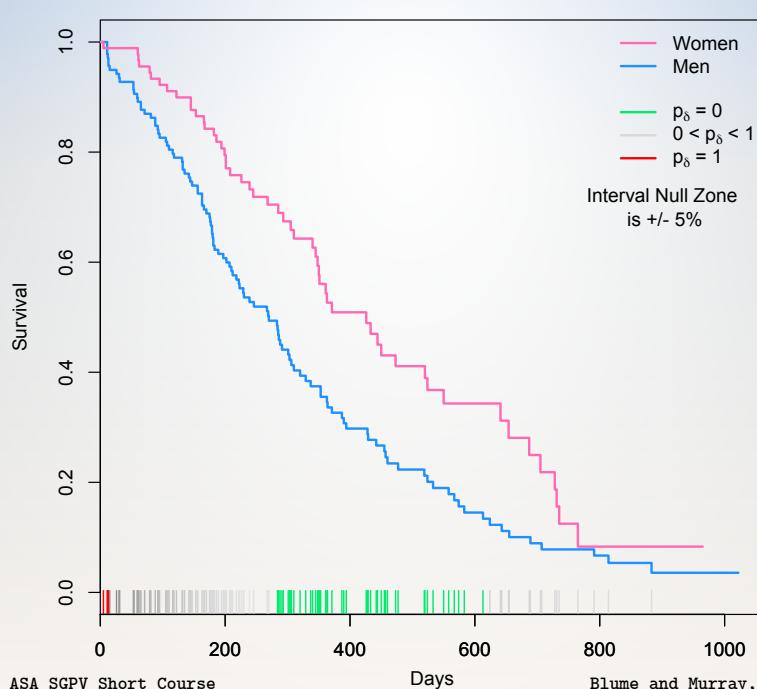


Lung Cancer Survival

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

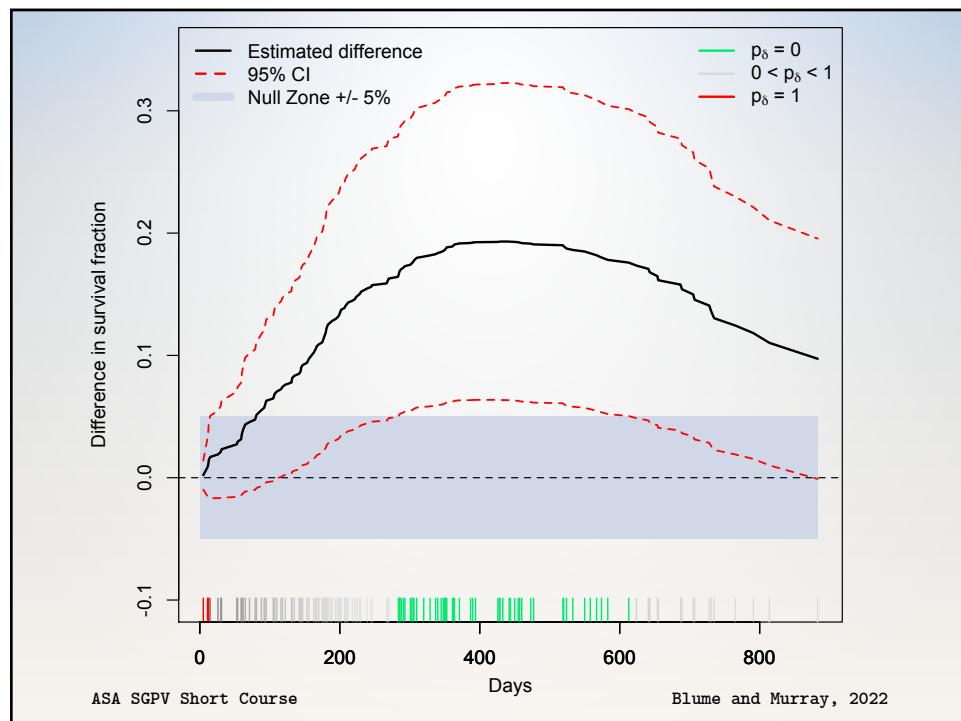
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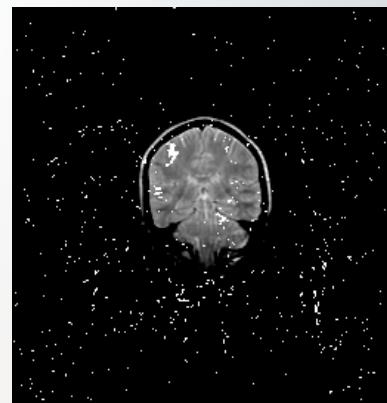
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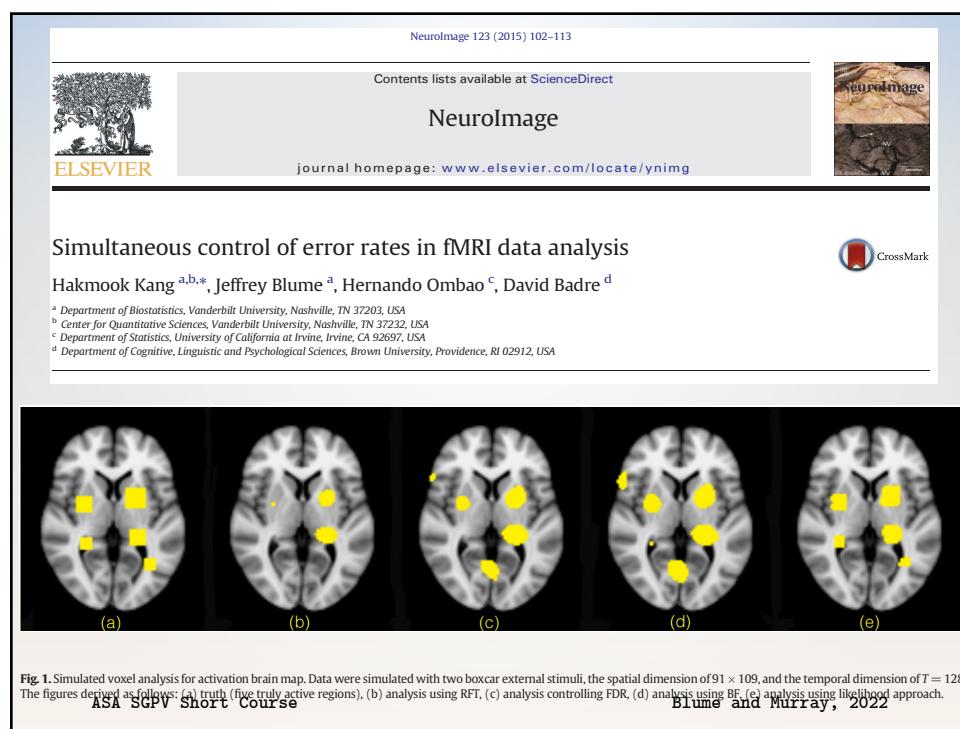
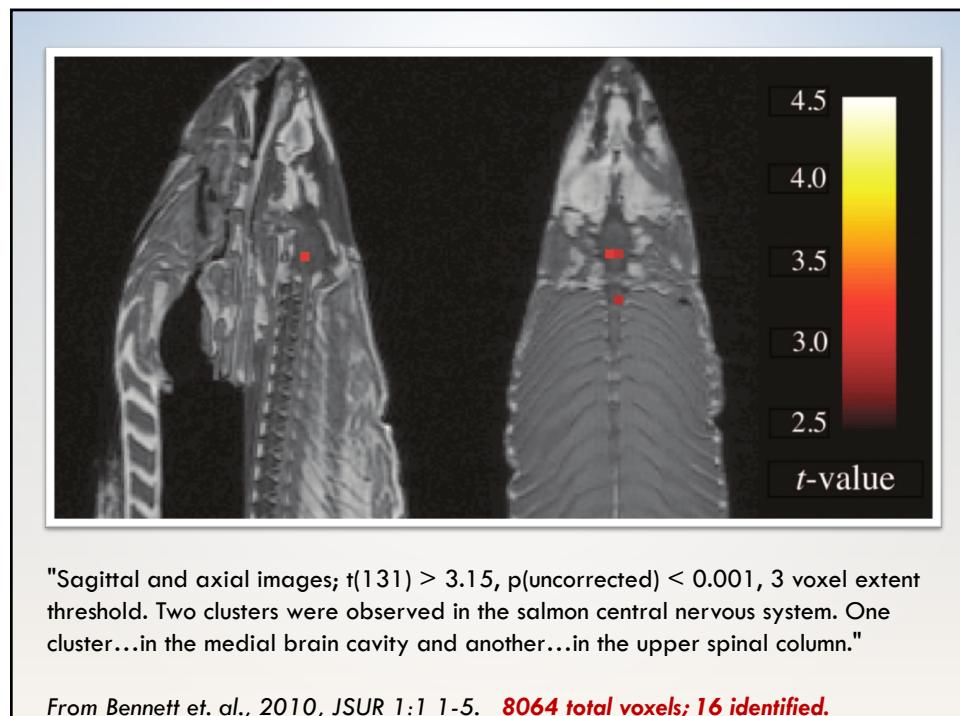
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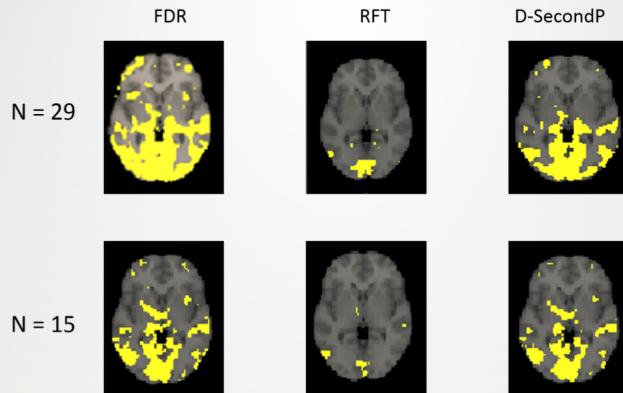
Setting interval null

- 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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SGPV in Action!



[Surg Endosc.](#), Author manuscript; available in PMC 2021 Jun 1.

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Published in final edited form as:

NIHMSID: NIHMS1700788

[Surg Endosc. 2020 Jun; 34\(6\): 2613–2622.](#)

PMID: 31346754

Published online 2019 Jul 25. doi: [10.1007/s00464-019-07032-1](https://doi.org/10.1007/s00464-019-07032-1)

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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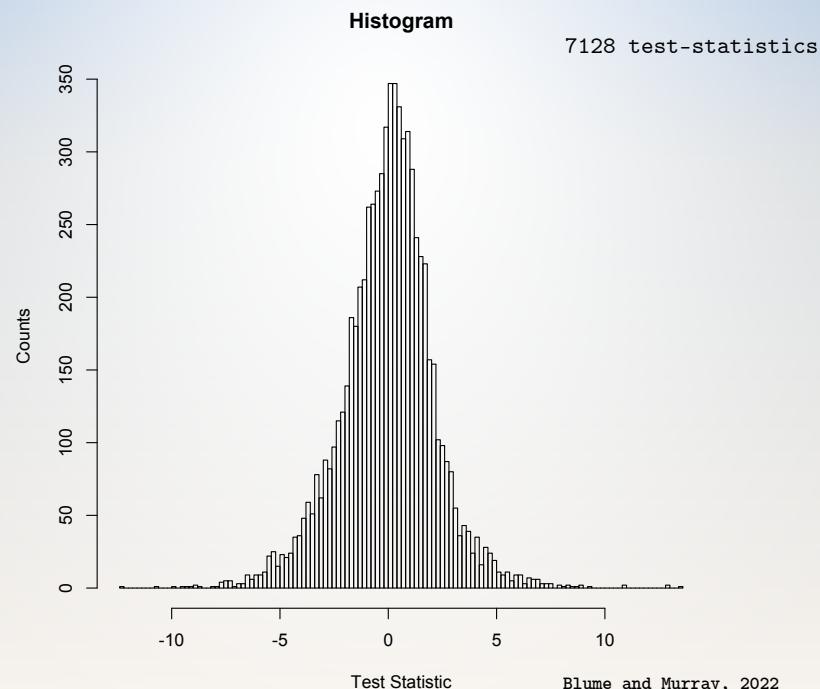
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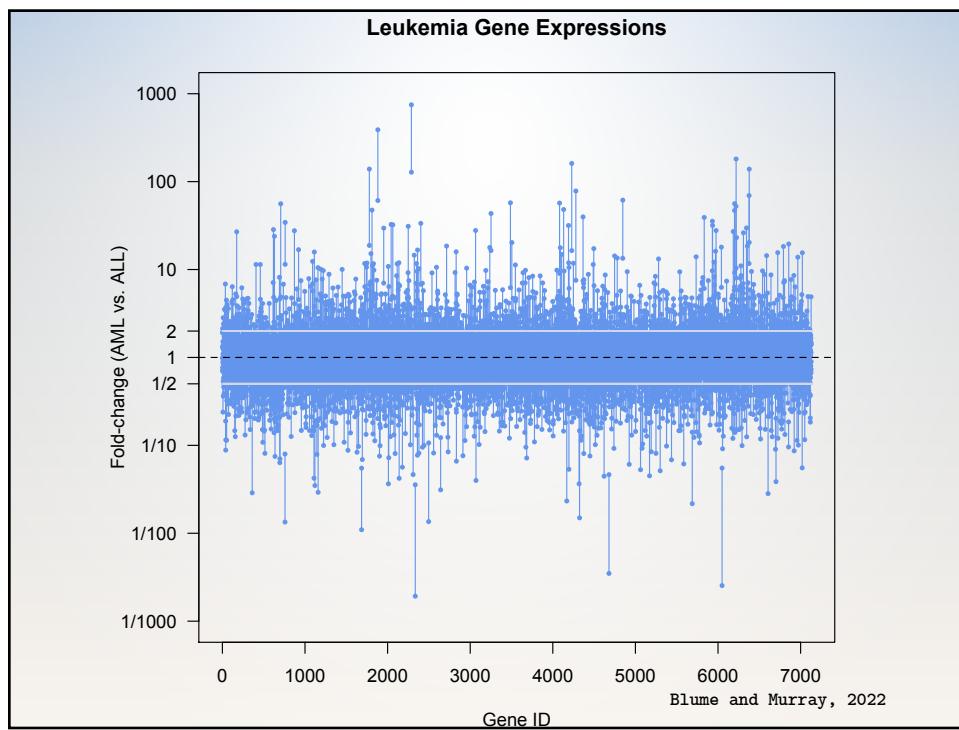
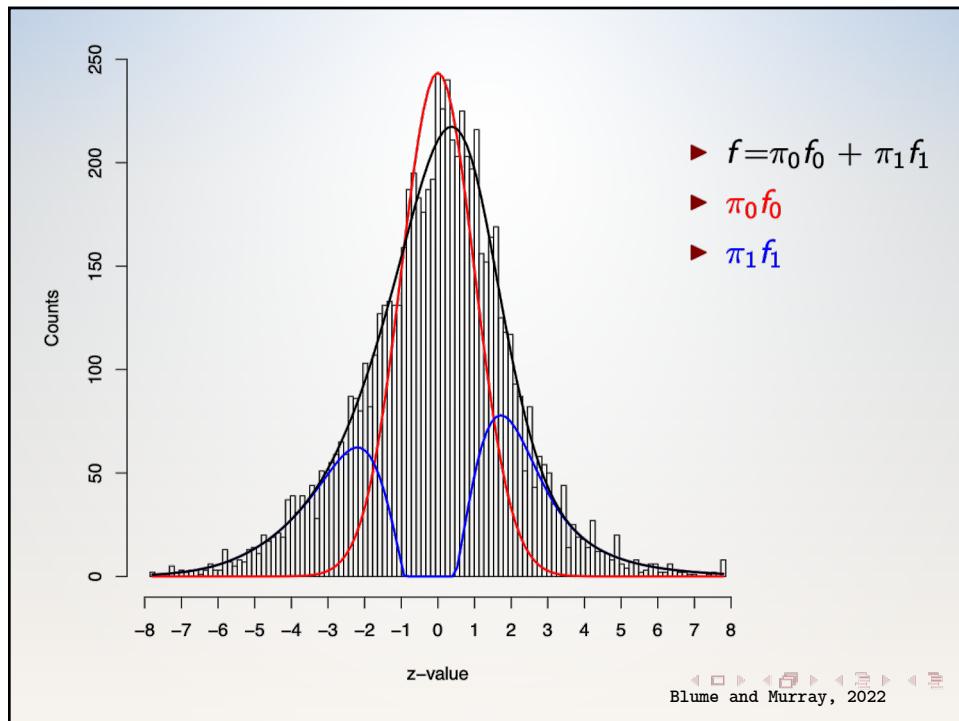
High-Dimensional Data: Leukemia gene expression

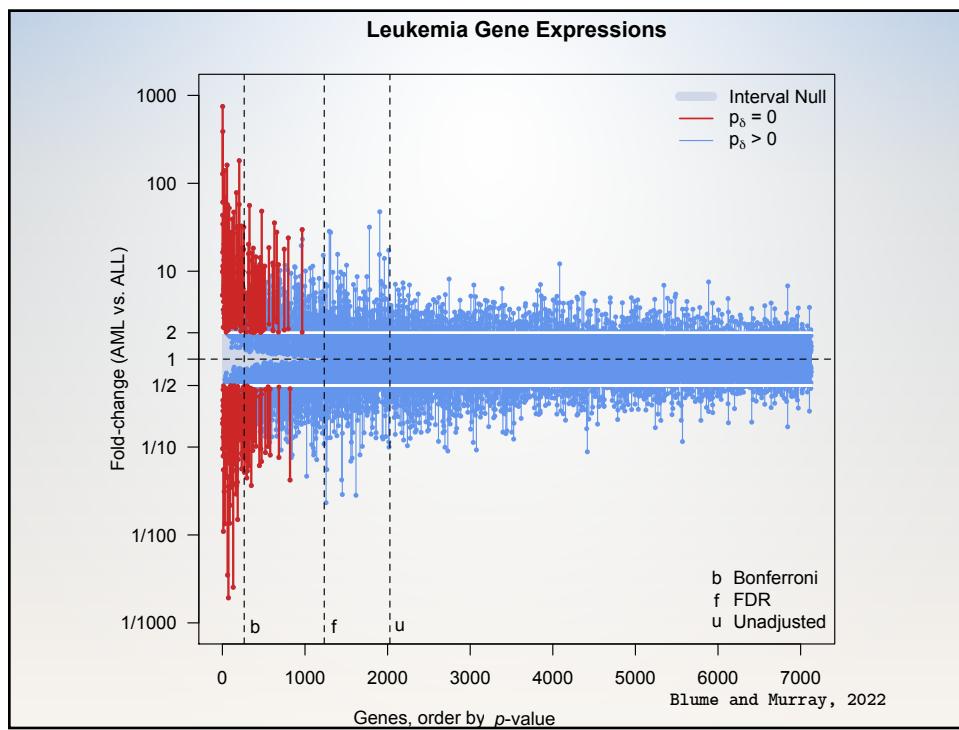
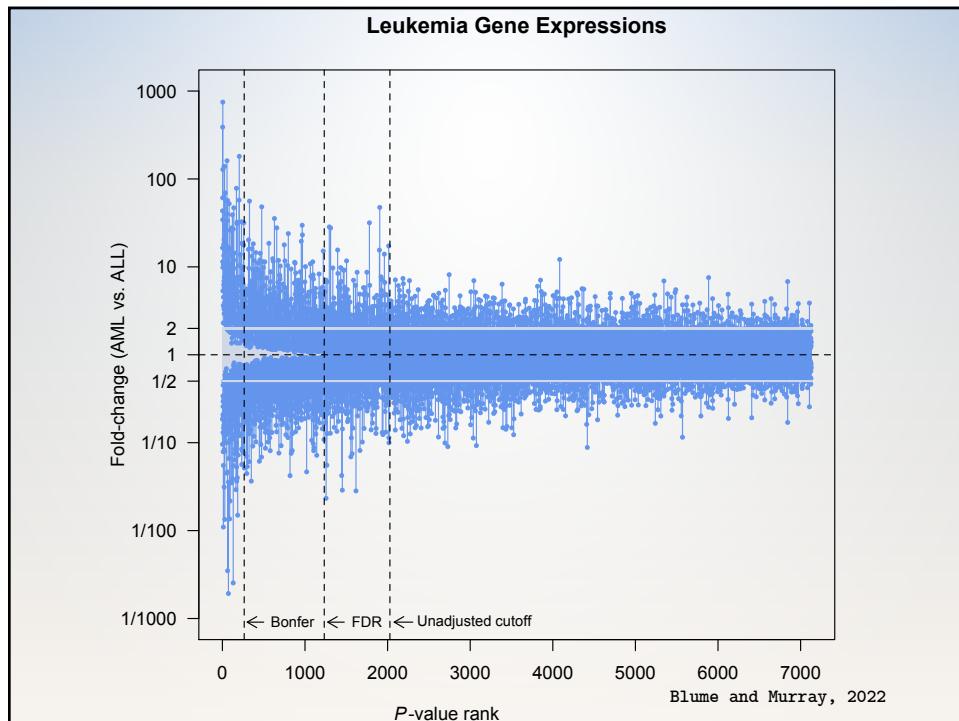
- Classifying acute leukemia by precursors
(Golub 1999, *Science*)
- 7128 genes ; 72 patients (47 ALL and 25 AML)
- Affymetrix chip collected expression levels
- Goal: Identify 'interesting' genes whose expression levels differ between All and AML subjects.
- Looking for fold changes of 2 or more

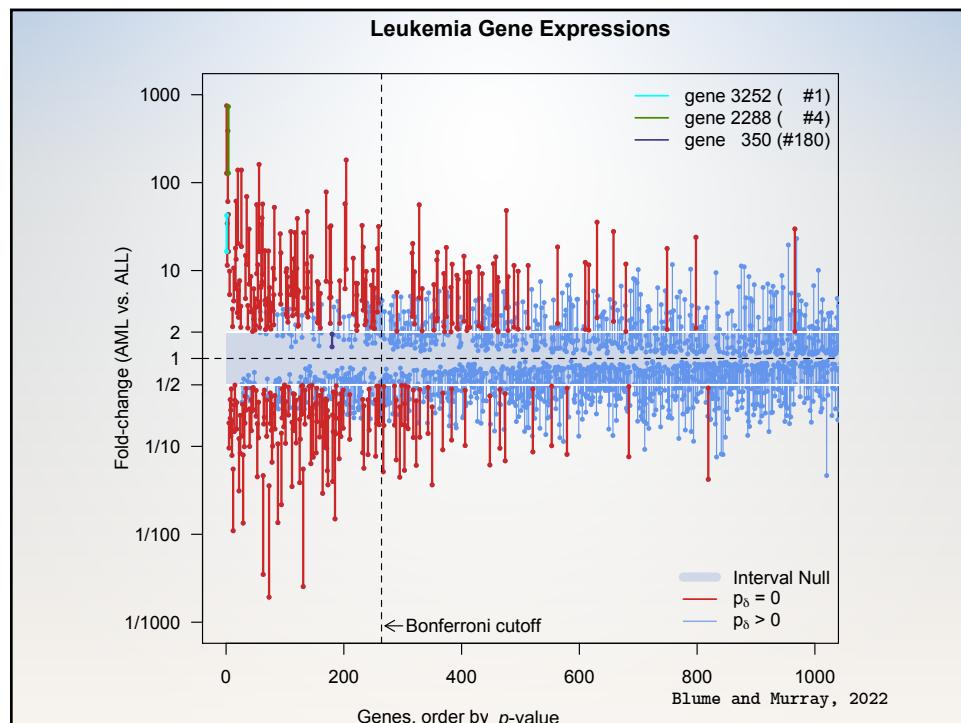
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Cross-Tabulation of Leukemia Results

- Bonferroni vs Second Generation p -values

		1/2 < Fold Change < 2 ($\delta = 0.3$)		
		$p_\delta = 0$	$p_\delta > 0$	Total
$p_{bon} < 0.05$		164	100	264
$p_{bon} > 0.05$		65	6799	6864
Total		229	6899	7128

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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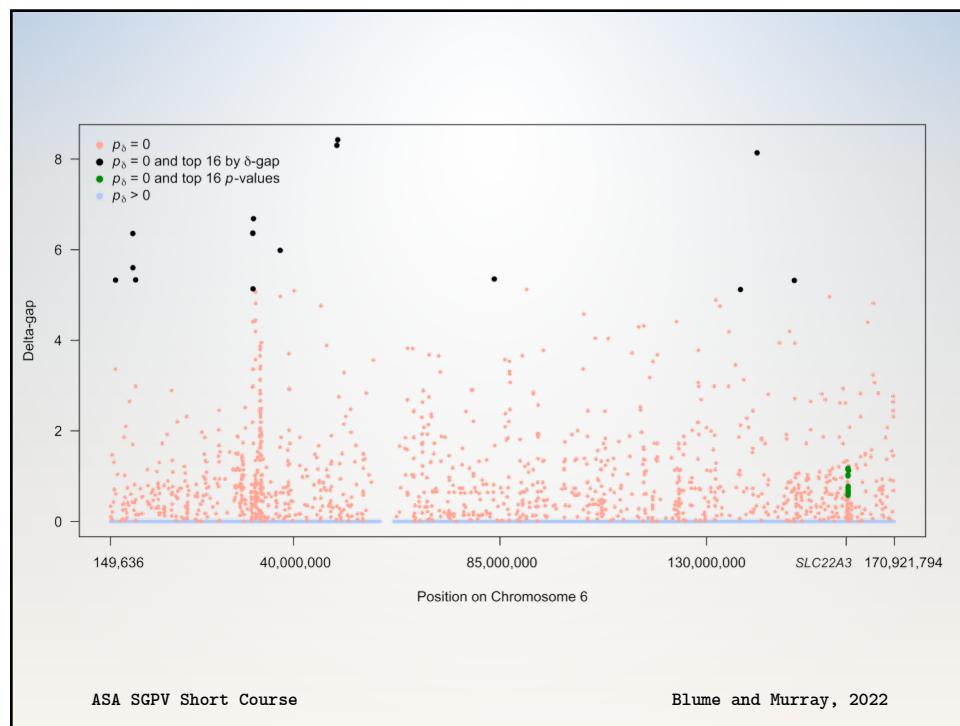
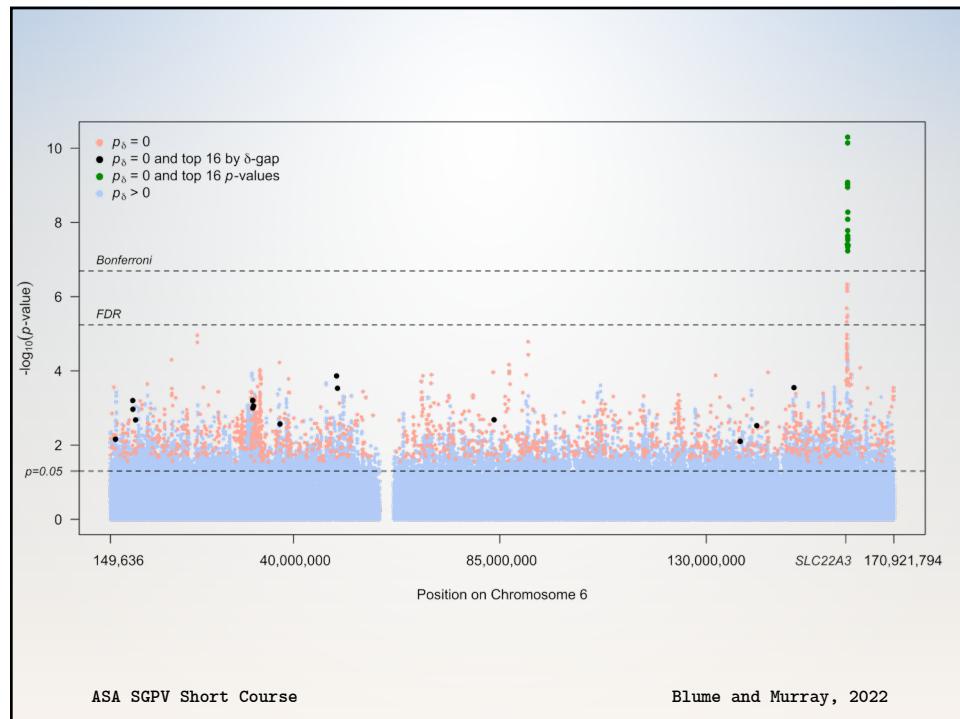
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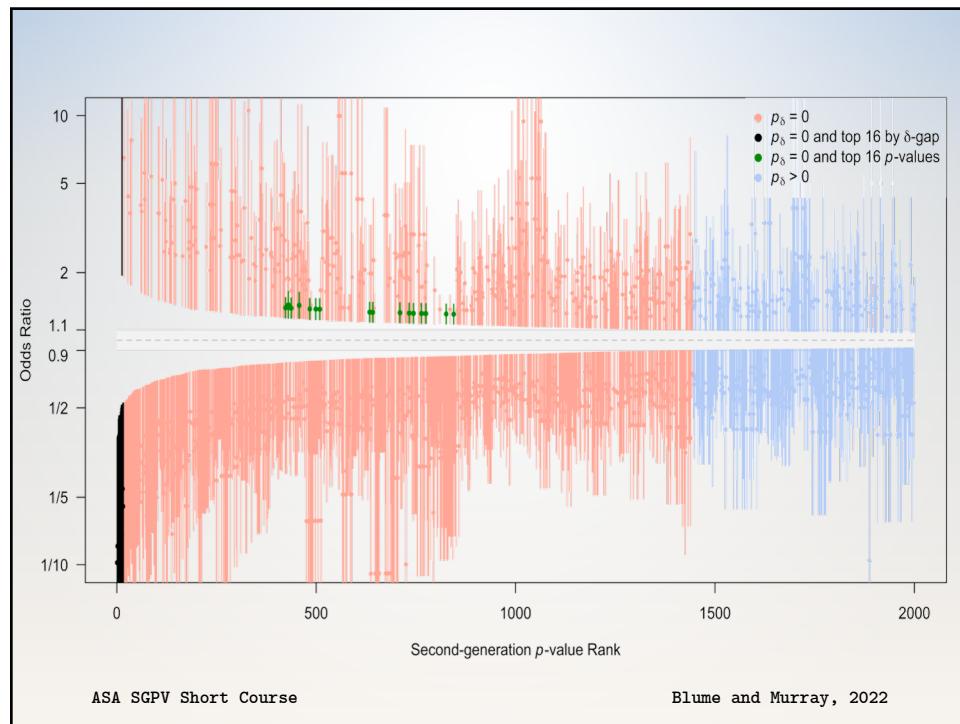
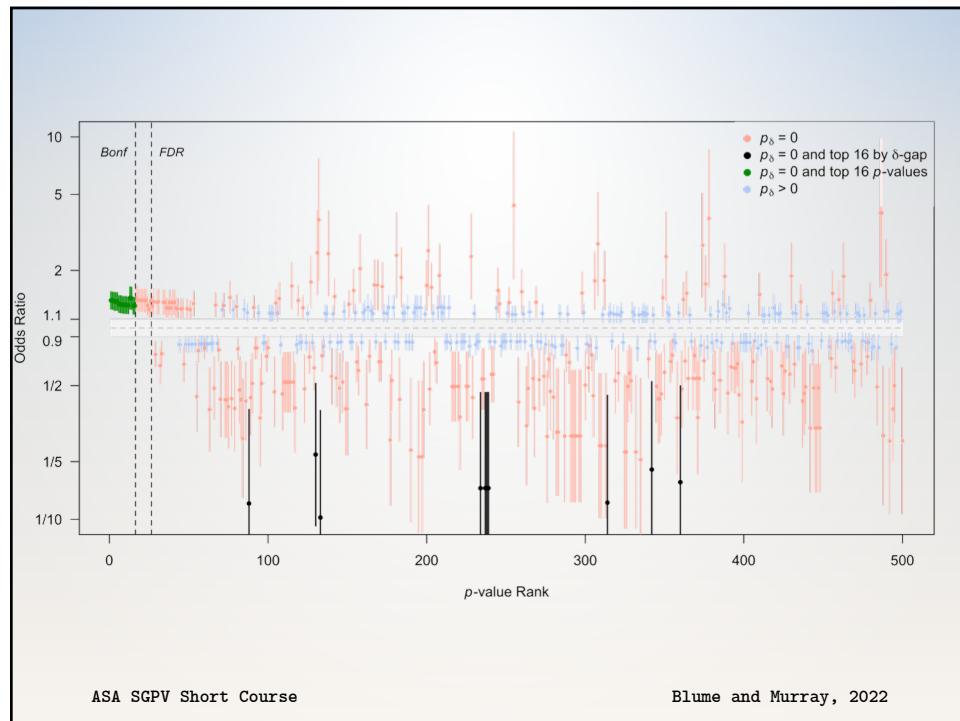
Prostate Cancer SNPs

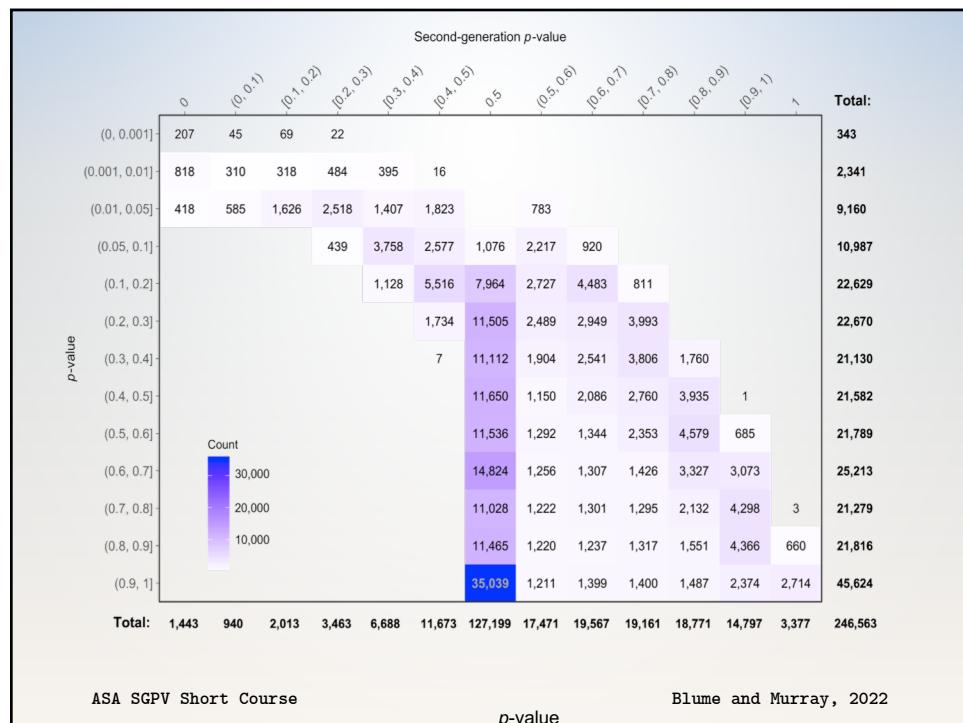
- International Consortium for Prostate Cancer Genetics (Schaid and Chang 2005; ICPCG 2018)
- 3,894 subjects: 2,511 cases & 1,383 controls
- 247,000 single-nucleotide polymorphisms (SNPs) from Chromosome 6
- Goal: Identify ‘interesting’ SNPs potentially associated with prostate cancer
- Looking for odds ratios of <0.9 or >1.11

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End of Part 1!