

Approaches to assess impact of misclassification bias in real-world observational study

When validation data is not available



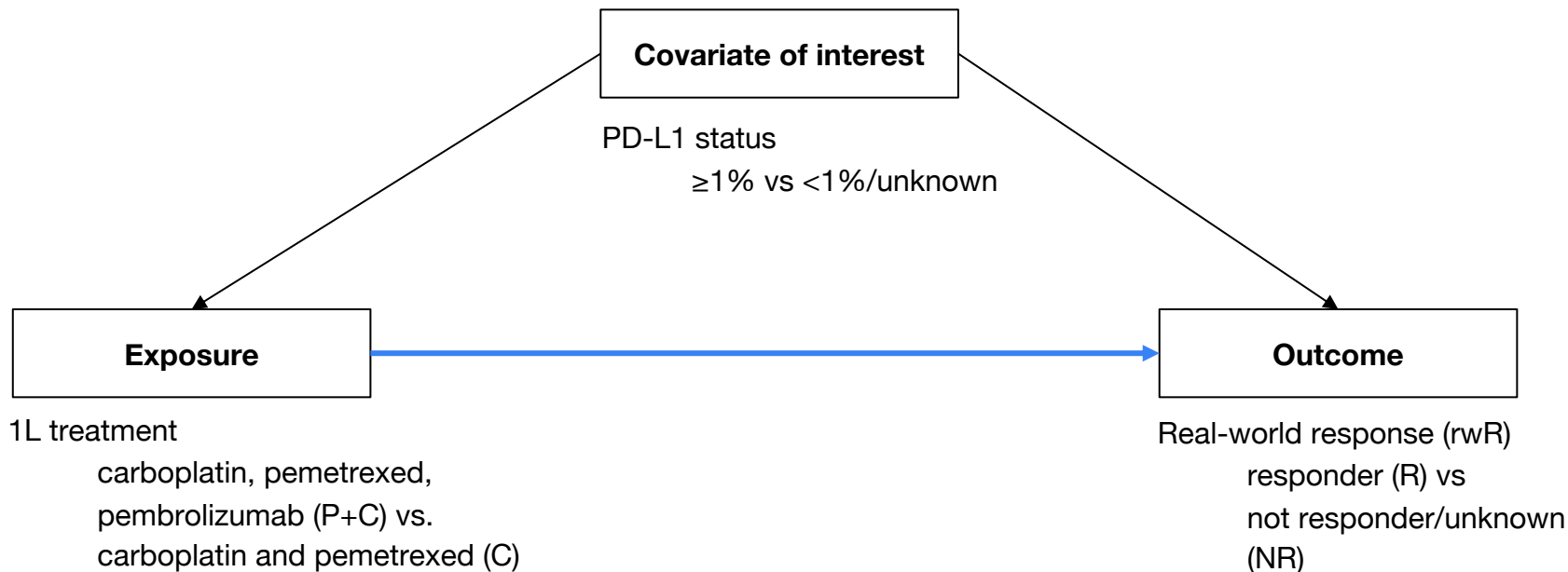
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Flatiron Health, Inc.

Case study

To assess the association between front-line treatment and real-world response among patients with de novo metastatic non-small cell lung cancer (mNSCLC)

Key Variables of Interest

Include 3,082 patients with de novo mNSCLC from the nationwide Flatiron Health research database.



Step 0: Naive (Observed) Study Results

Model	OR	95% CI
Naive	1.55	1.33, 1.82

Reviewer may have questions on the uncertainty of the naive result

Model	OR	95% CI
Naive	1.55	1.33, 1.82

Reviewer Questions: Did the measurements of key variables **introduce uncertainty** to the observed estimates? If so, **to which direction and what extent** would they affect the estimated effect size and study conclusion?

How would you address these concerns about the use of this RWD?
QBA (Probabilistic bias analysis)

What we aim to achieve by applying QBA

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Naive	1.55	1.33, 1.82

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How would you address these concerns about the use of this RWD?
QBA (Probabilistic bias analysis)

Desired Results from QBA: **Our study conclusion remains the same:** The association remains statistically significant even in the presence of significant misclassification bias.

Step 1: Estimate bias parameters

**Observed
2x2 Table**

		1L Treatment	
		Pembro+Chemo (P+C)	Chemo (C)
Real-world Response	Responder (R)	a	b
	Non-responder (NR)	c	d

1L Treatment

		True Status	
		P+C	C
Observed	P+C	Se	1- Sp
	C	1-Se	Sp

**Adjusted
2x2 Table**

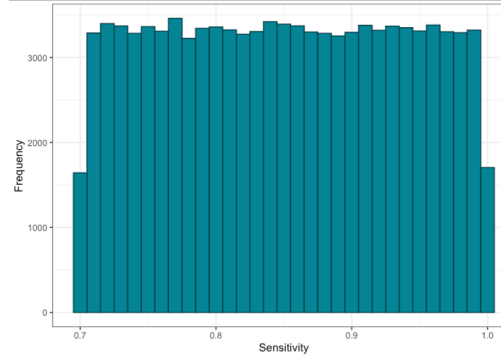
		1L Treatment	
		Pembro+Chemo (P+C)	Chemo (C)
Real-world Response	Responder (R)	A	B
	Non-responder (NR)	C	D

Step 2: Specify a probability distribution for each bias parameter

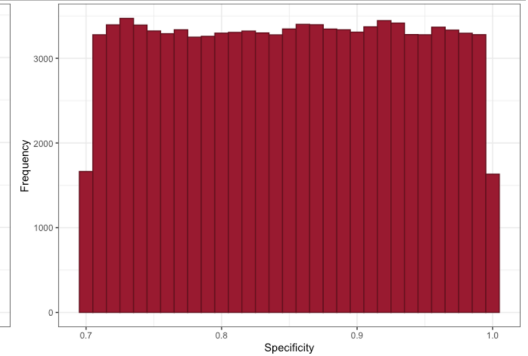
Uniform distribution [0.7, 1.0] of sensitivity and specificity of treatment variable.

Responder

Sensitivity of treatment

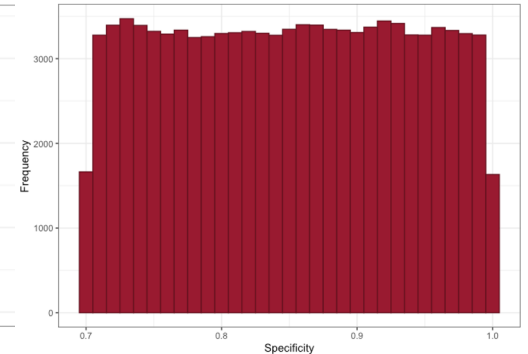
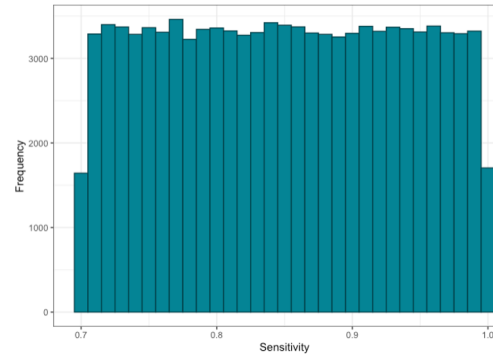


Specificity of treatment



Non-differential misclassification between response groups

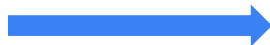
**Non-responder/
unknown**



Step 3: Sample from each bias parameter distribution

PID	rwR	Treatment_Obs	PD-L1	Covariates
1	R	P+C		
2	NR	P+C		
3	R	C		
4	NR	C		
...	...			

$se_i \sim \text{dist}(\text{iter}, \dots)$
 $sp_i \sim \text{dist}(\text{iter}, \dots)$



PID	rwR	Treatment_Obs	Treatment_Adj
1	R	P+C	P+C
2	NR	P+C	P+C
3	R	C	P+C
4	NR	C	C
...	...		

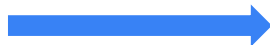
Naive OR:

$$\text{logit}(rwR) = \text{Treatment_Obs} + \text{PD-L1} + \text{Age} + \text{Sex} + \dots$$

Step 4: Use the sampled bias parameter values to correct the naive study estimate

PID	rwR	Treatment_Obs	PD-L1	Covariates
1	R	P+C		
2	NR	P+C		
3	R	C		
4	NR	C		
...	...			

$se_i \sim dist(iter, \dots)$
 $sp_i \sim dist(iter, \dots)$



PID	rwR	Treatment_Obs	Treatment_Adj
1	R	P+C	P+C
2	NR	P+C	P+C
3	R	C	P+C
4	NR	C	C
...	...		

Naive OR:

$$\text{logit}(rwR) = \text{Treatment_Obs} + \text{PD-L1} + \text{Age} + \text{Sex} + \dots$$

Treatment Bias-Adjusted ORs:

$$\text{logit}(rwR) = \text{Treatment_Adj} + \text{PD-L1} + \text{Age} + \text{Sex} + \dots$$

Step 5: Save the bias-adjusted estimate and repeat steps 3 and 4 to generate a frequency distribution of bias-adjusted effect estimates

PID	rwR	Treatment_Obs	Treatment_Adj
1	R	P+C	P+C
2	NR	P+C	P+C
3	R	C	P+C
4	NR	C	C
...	...		

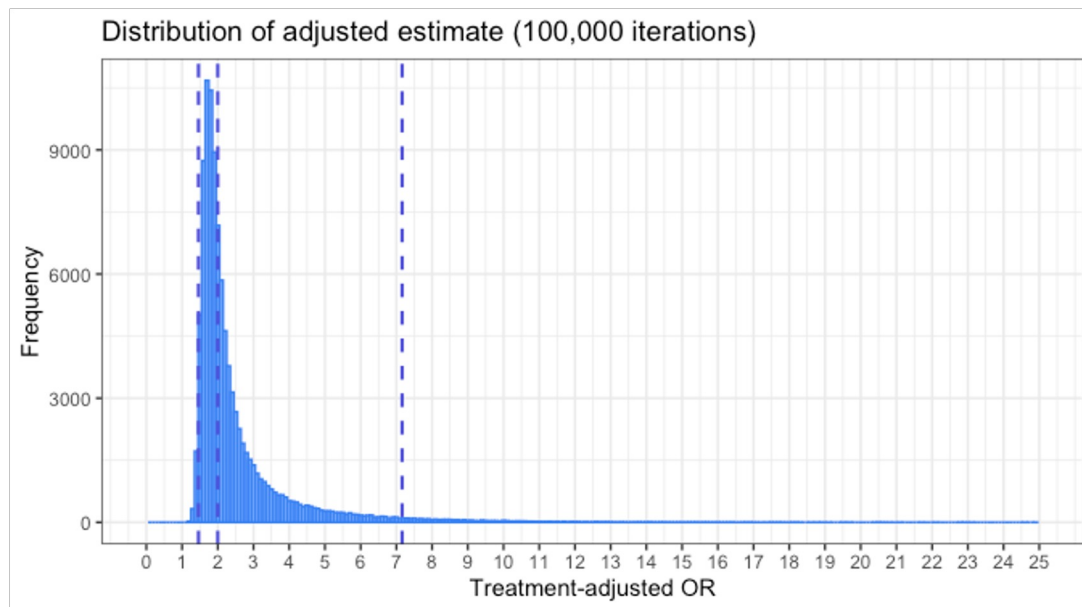


iter	se ₀	se ₁	sp ₀	sp ₁	OR _{adj}	OR _{total}
1						
2						
3						
4						
5						
...	...					

Step 6: Summarize bias-adjusted ORs and 95% simulation interval that accounts for random and systematic sources of error

Treatment bias-adjusted

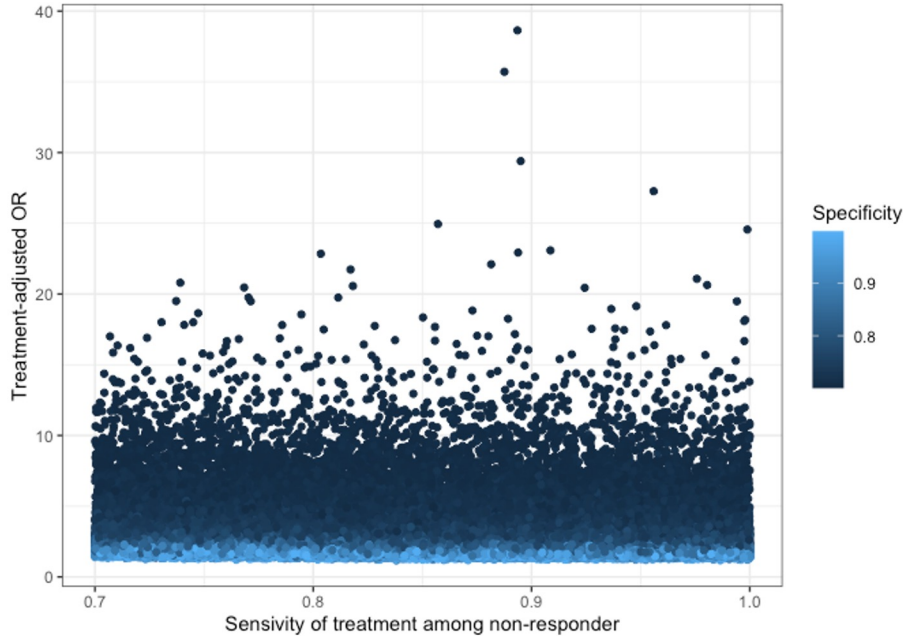
- OR = 2.00
- 95% CI: 1.46, 7.16
- Range: 1.17, 38.6



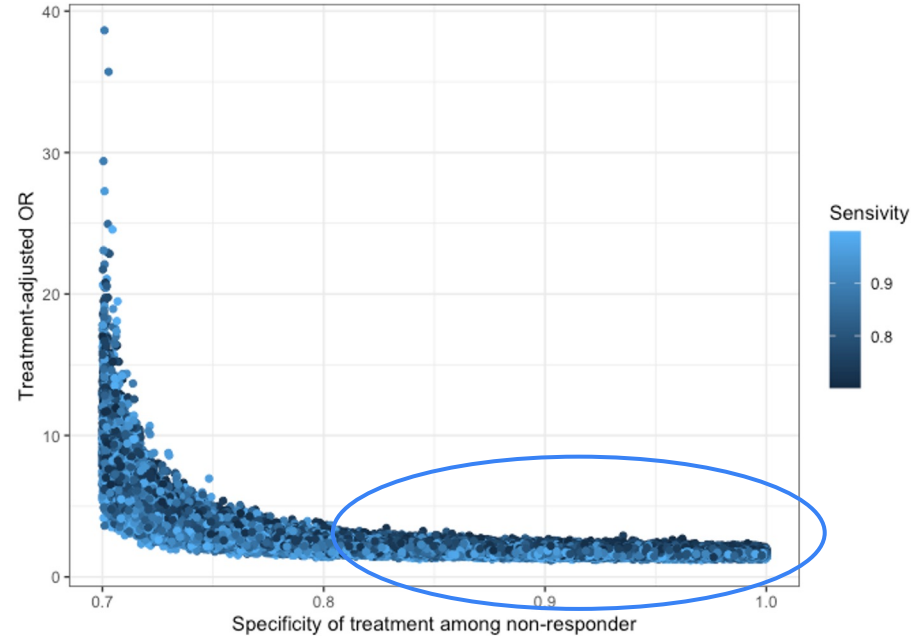
* Purple line: median, 2.5th and 97.5th percentile; Extreme estimates > 25 are omitted.

Stronger correlation between specificity of treatment and treatment bias-adjusted ORs

Scatterplot between sensitivity and adjusted OR

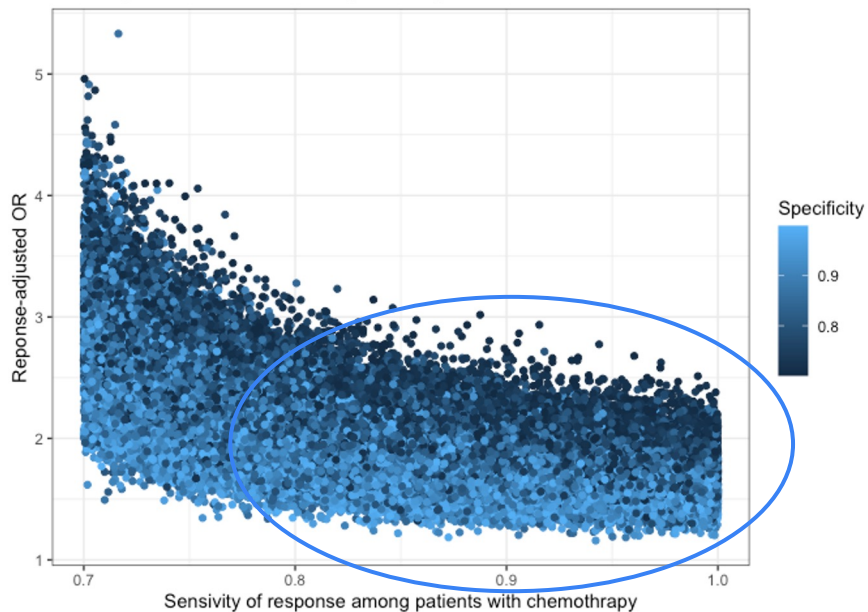


Scatterplot between specificity and adjusted OR

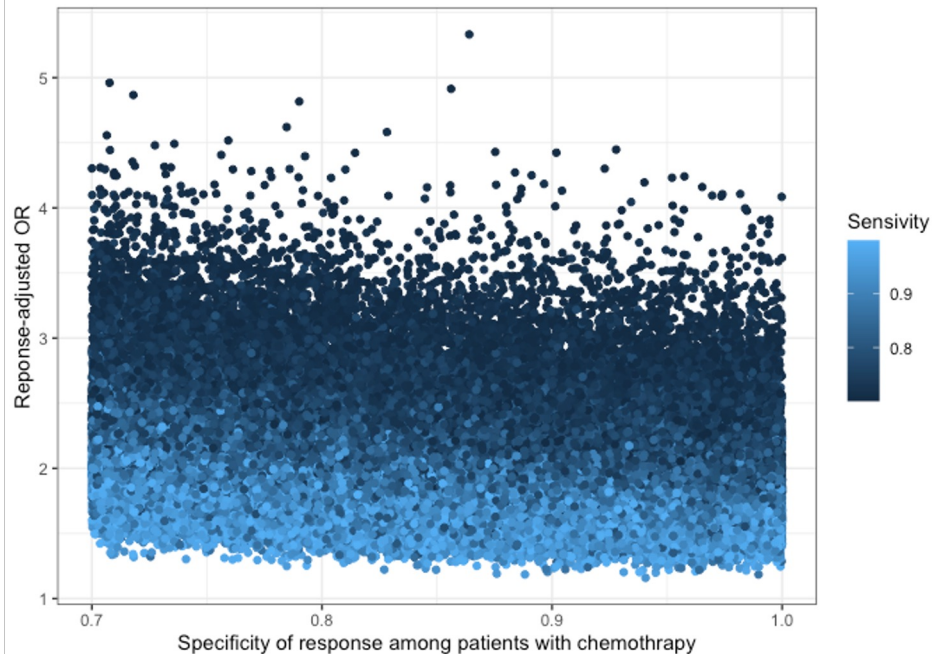


Stronger correlation between sensitivity of response and response bias-adjusted ORs

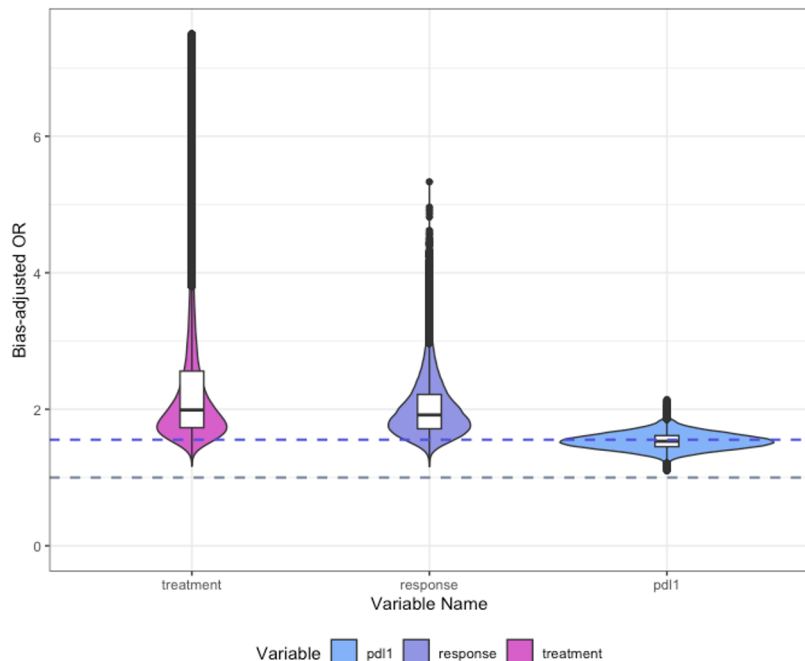
Scatterplot between sensitivity and adjusted OR



Scatterplot between specificity and adjusted OR



Misclassification bias in treatment has the largest impact on the effect estimates



* Purple line: naive OR; Grey line: OR = 1; Extreme estimates > 7.5 are omitted.

Model	OR	95% CI
Naive	1.55	1.33, 1.82
Bias adjusted		
Treatment	2.00	1.46, 7.16
Response	1.92	1.46, 3.09
PD-L1	1.53	1.31, 1.79

Step 7+: Generate “fully adjusted” estimates by adding repeating the process using partial adjusted datasets

PID	rwR	Treatment_Obs	Treatment_Adj
1	R	P+C	P+C
2	NR	P+C	P+C
3	R	C	P+C
4	NR	C	C
...	...		

$se_i \sim dist(iter, \dots)$
 $sp_i \sim dist(iter, \dots)$



PID	rwR	Treatment_Adj	rwR_Adj
1	R	P+C	NR
2	NR	P+C	NR
3	R	P+C	R
4	NR	C	R
...	...		

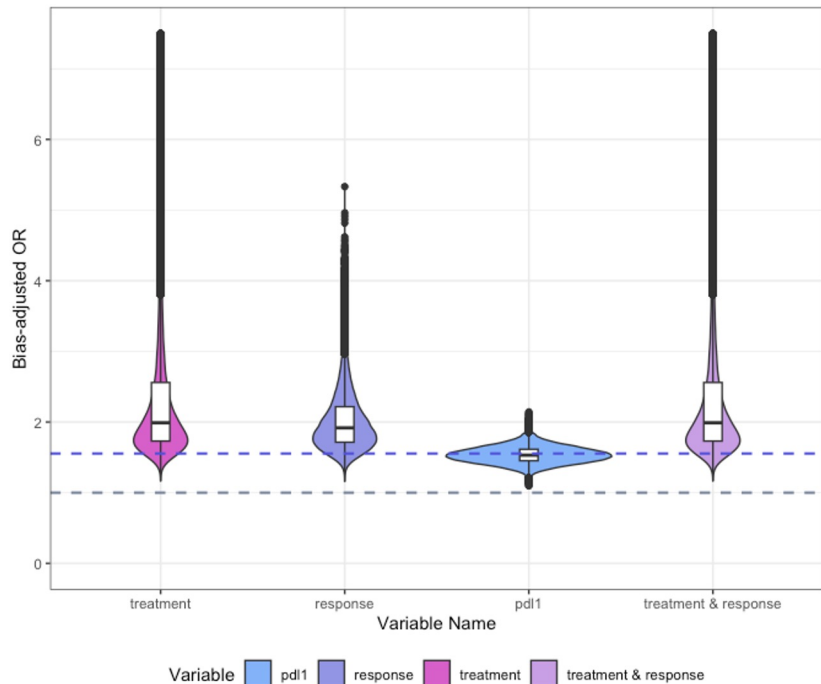
Treatment Adjusted ORs:

$$\text{logit}(rwR) = \textit{Treatment_Adj} + PD-L1 + \textit{Age} + \textit{Sex} + \dots$$

Treatment and Response Adjusted ORs:

$$\text{logit}(rwR_Adj) = \textit{Treatment_Adj} + PD-L1 + \textit{Age} + \textit{Sex} + \dots$$

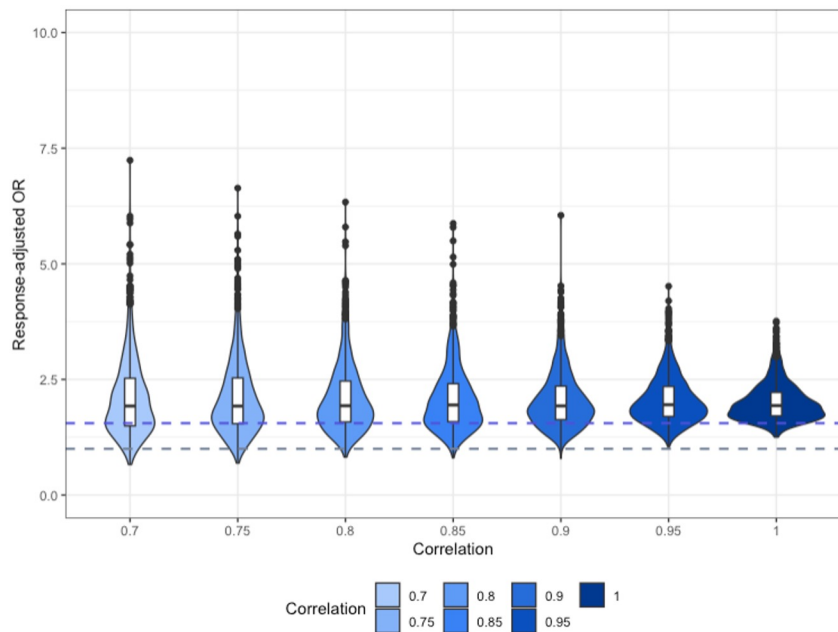
Misclassification biases in multiple variables can result in larger changes in the effect estimates



* Purple line: naive OR; Grey line: OR = 1; Extreme estimates > 7.5 are omitted.

Model	OR	95% CI
Naive	1.55	1.33, 1.82
“Partial adjusted”		
Treatment	2.00	1.46, 7.16
Response	1.92	1.46, 3.09
PD-L1	1.53	1.31, 1.79
“Fully adjusted”		
Treatment & Response	2.43	1.64, 5.67

Bonus: Differential misclassification has larger impact on 95% CIs and can result in change of conclusion



Model	OR	95% CI
Naive	1.55	1.33, 1.82
Response-adjusted		
$\rho = 0.7$	1.93	0.98, 4.19
$\rho = 0.75$	1.92	1.00, 4.13
$\rho = 0.8$	1.93	1.13, 3.91
$\rho = 0.85$	1.95	1.15, 3.80
$\rho = 0.9$	1.93	1.25, 3.73
$\rho = 0.95$	1.95	1.34, 3.36
$\rho = 1.0$ (non-diff)	1.93	1.47, 3.05

* Purple line: naive OR; Grey line: OR = 1

* Estimates are based on 1,000 iterations in each analysis.

Key Results Summary

Reviewer Questions: Did the measurements of key variables **introduce uncertainty** to the observed estimates? If so, **to which direction and what extent** would they affect the estimated effect size and study conclusion?

Key Results:

Our study conclusion remains the same: The association remains statistically significant even in the presence of significant misclassification bias.

We found that the true association between rwR and pembrolizumab + chemotherapy is likely **larger** than the observed OR after accounting for misclassification bias.

Bias parameters of different variables are correlated with effect estimates in different ways. In this study, the sensitivity of response variable should be **prioritized**.

Severe differential misclassification may impact the study conclusions, but it is unlikely to be the case in this study.

Conclusions and Future Directions

Probabilistic quantitative bias analysis is a useful tool, especially as a first step, for assessing the impact of misclassification bias.

This approach is **flexible and applicable** to various use cases and data sources.

It is possible to assess the **direction and magnitude of biases** due to misclassifications in both single and multiple variables, under different assumptions.

It can be computationally intensive when assessing multiple variables.

Other distributions may be more realistic and relevant for specific use case.

Exploring **different bias distributions** is recommended.

Domain knowledge remains critical to inform QBA methods and decisions.

Acknowledgement

The author thanks **Brett Wittmershaus, BSE, Melissa Estevez, MS, Niquelle Wadé, PhD, Aaron Cohen, PhD** and **Margaret Musumeci, MPH** of Flatiron Health, Inc, for providing scientific expertise, and **Catherine Au-Yeung, MS** for providing presentation design support, which was all funded by Flatiron Health, Inc. in accordance with Good Publication Practice (GPP3) guidelines (<http://www.ismpp.org/gpp3>).

The methods applied in this presentation are adopted from Fox MP, MacLehose R, Lash TL. [Applying Quantitative Bias Analysis to Epidemiologic Data](#). R codes used in the case study are adopted from the publicly available sample SAS and R codes [here](#).

All analyses are performed using R version 4.1.3.