

Methodological Challenges that Keep us Statistically Sharp: Modeling Associations between Repeated Patient and Physician Reported Outcomes

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Outline

- Scientific Question
- Statistical Challenges
- Statistical Solution
- Implications

Statistical Questions

- What relationships exist between symptoms reported by patients (ESAS) and physicians (CTCAE)?

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- How do these change over time?
- What about potential predictors?

Sample Characteristics

Patient visits

Visits	Baseline	2	3	4	5	6	7	8
n	261	163	92	59	41	17	8	1
%	40.7	25.4	14.3	9.2	6.4	2.7	1.3	0.2

Sample Characteristics

Patient visits

Time	Min	Q1	Median	Q3	Max	Mean	SD
Days	0	0	7	28	308	30.2	53
Months	0	0	0.2	0.9	10.1	1.0	1.7
Visits	1	1	2	3	8	2.3	1.5

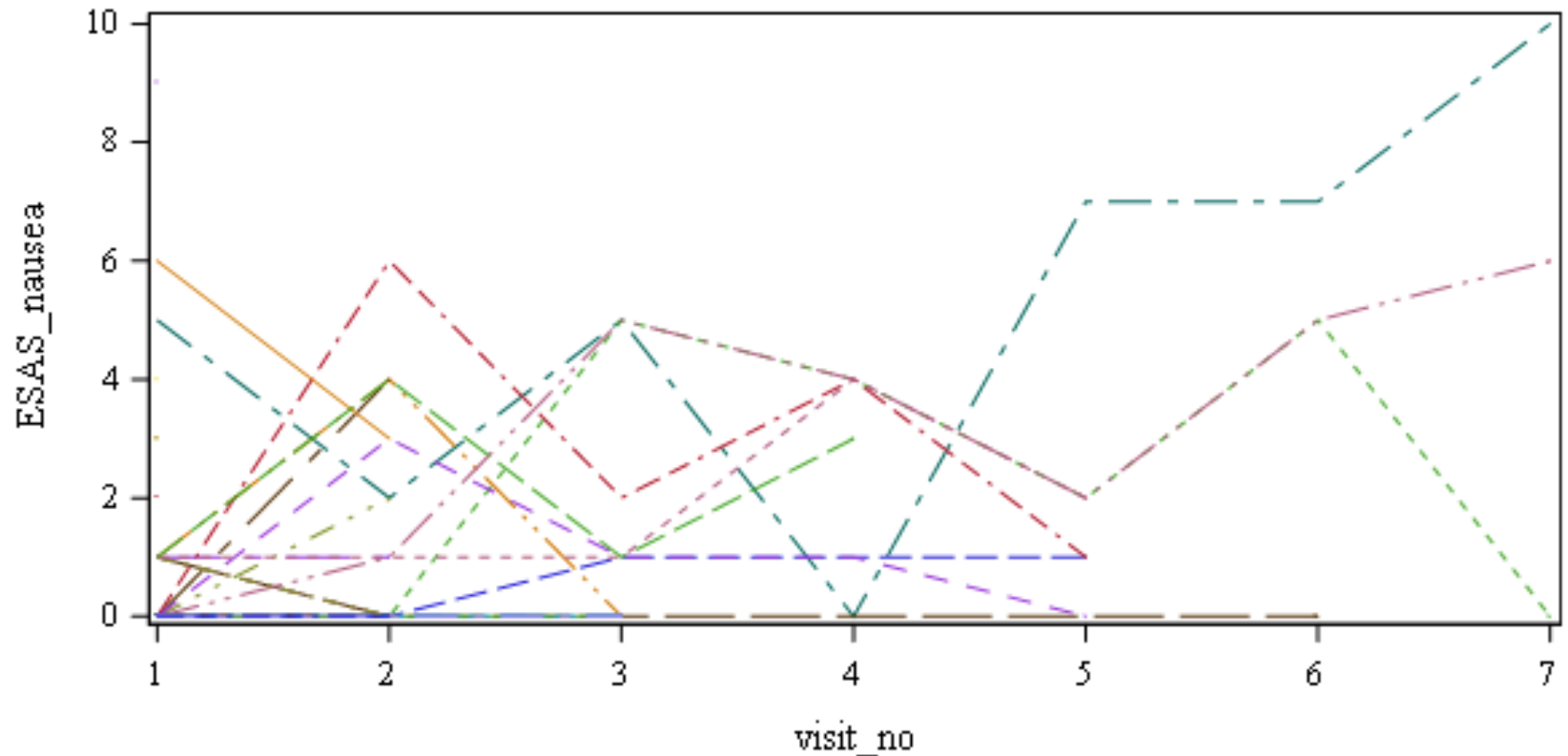
Sample Characteristics

- Potential predictors
 - Gender
 - Race
 - Ethnicity
 - Treatment type
 - Radiotherapy
 - Attending Physician

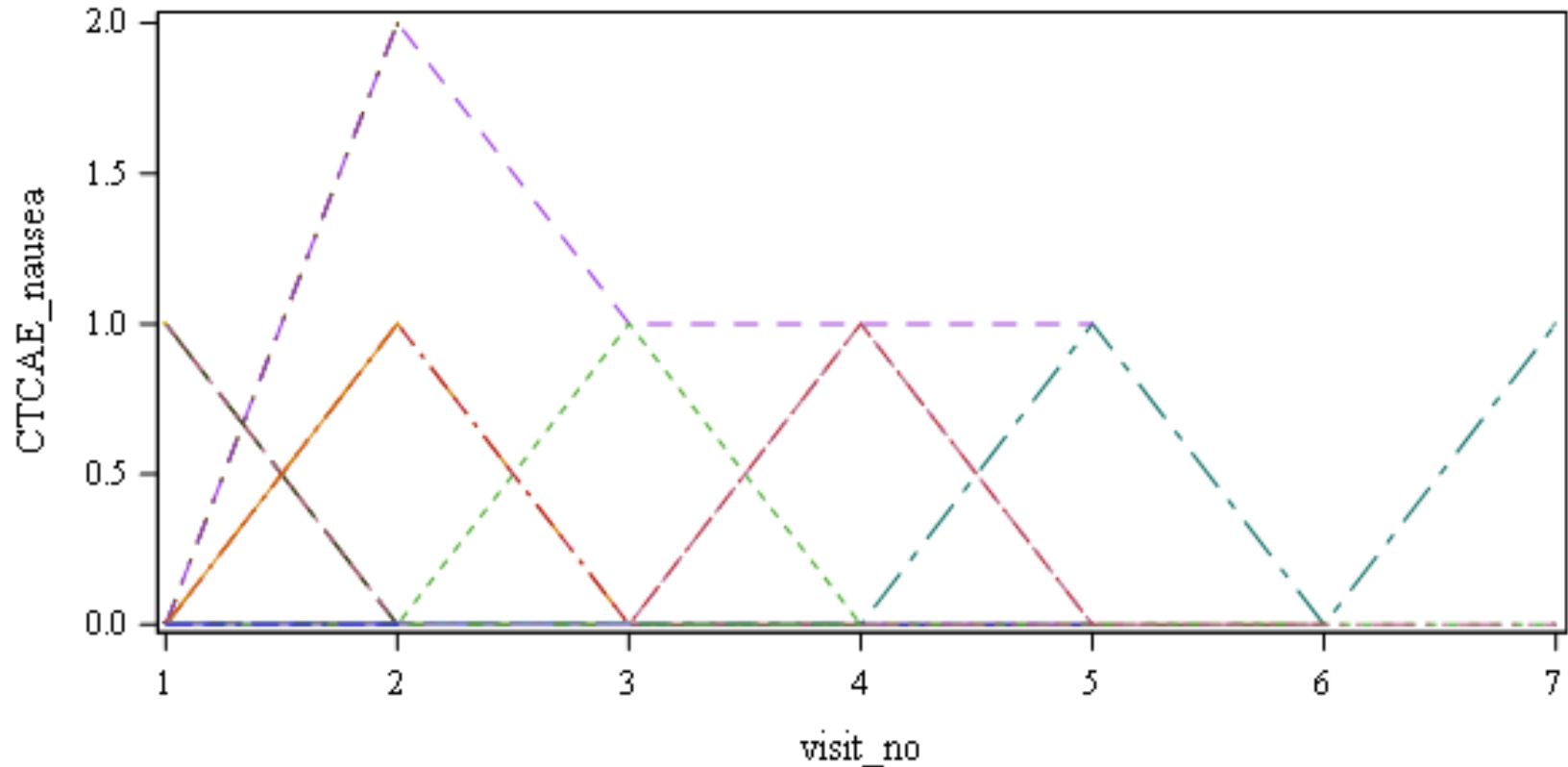
Outcomes

ESAS (0-10)	CTCAE (0-5)
Tiredness, drowsiness	Fatigue
Nausea	Nausea
Cough	Cough
Esophagitis	Esophagitis
Breath	Dyspnea

Example Spaghetti Plots



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Example Table: Esophogitis

CTCAE	ESAS										
	0	1	2	3	4	5	7	8	9	10	Total
0	545	2	2	2	3	4	1	1	1	1	562
1	37	0	0	2	1	2	1	0	1	1	45
2	31	0	0	0	0	0	1	1	0	0	33
3	2	0	0	0	0	0	0	0	0	0	2
Total	615	2	2	4	4	6	3	2	2	2	642

Just a Few Statistical Challenges

- Repeated Measures
 - Multivariate and longitudinal
 - Unbalanced
 - Different # of visits at different times
 - Different scales for CTCAE and ESAS
- Sparsity
 - Many patients rated symptom scores of zero, few had very high scores
- Variable Selection

Proposed Solutions

- Pearson and Spearman correlations on all raw scores (all time points collapsed)

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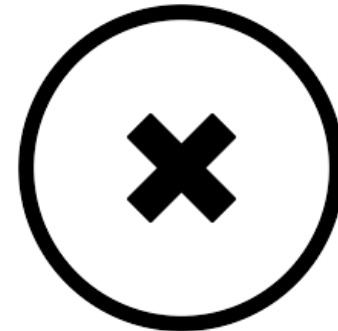
Proposed Solutions

- Pearson and Spearman correlations on all raw scores (all time points collapsed)
- Joint model of zero-inflated, multivariate, longitudinal scores



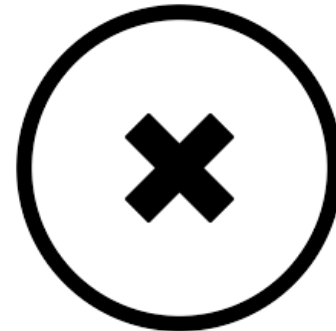
Proposed Solutions

- Pearson and Spearman correlations on all raw scores (all time points collapsed)
- Joint model of zero-inflated, multivariate, longitudinal scores



Proposed Solutions

- Pearson and Spearman correlations on all raw scores (all time points collapsed)
- Joint model (GLM) of zero-inflated, multivariate, longitudinal scores
- Joint model but dichotomize scores (high/low)
 - ESAS 0-2 vs. 3+
 - CTCAE 0-1 vs 2+



Analysis Overview

- Descriptive Statistics
- Proc GENMOD for each symptom pair (ESAS/CTCAE)
 - Backward Selection ($\alpha = 0.1$)
- Graphs of Predicted Probabilities

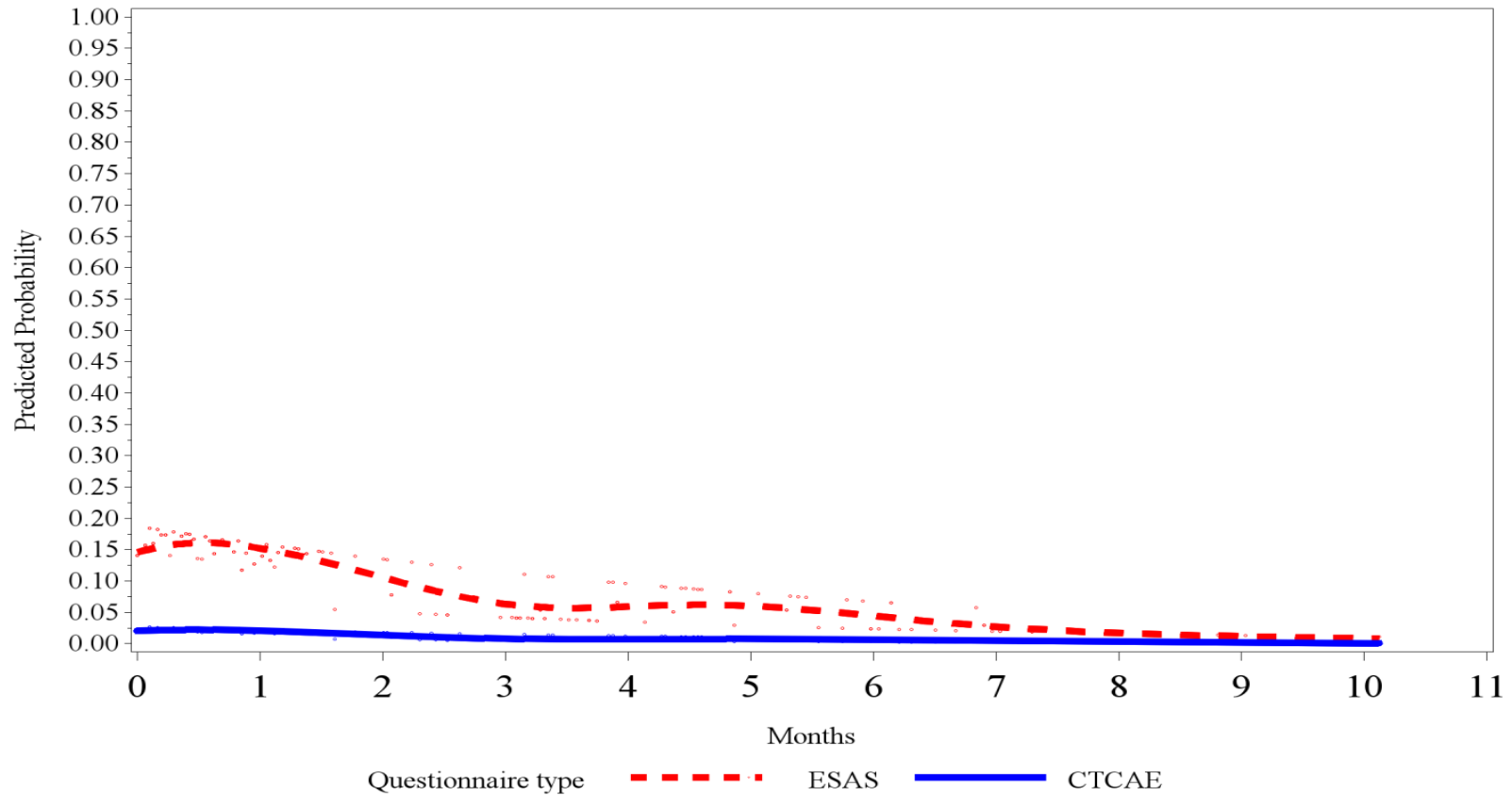
Descriptive Statistics

Variable	Level	N = 261	%
Physicians	Physician A	123	47
	Physician B	117	45
	Others	21	8
Gender	Female	121	46
	Male	140	54
Treatment	Definitive	153	63
	Palliative	88	37
	Missing	20	-
Race/Ethnicity	Non-URMM	200	77
	URMM	19	7
	Unknown	42	16
Radiation (SBRT)	Missing	33	13
	No	134	51
	Yes	94	36

Model: Nausea

<u>Parameter</u>	<u>Level</u>	<u>Estimate</u>	<u>SE</u>	<u>95% CI</u>		<u>P-value</u>
Intercept		-3.5925	0.3799	-4.3371	-2.8479	<.0001
Days		-0.0064	0.0028	-0.0119	-0.0008	0.0240
SBRT	Missing	-0.2878	0.6221	-1.5072	0.9315	0.6436
	Yes	-1.0732	0.3571	-1.7731	-0.3733	0.0027
Q_type	ESAS	2.1236	0.3211	1.4943	2.7529	<.0001

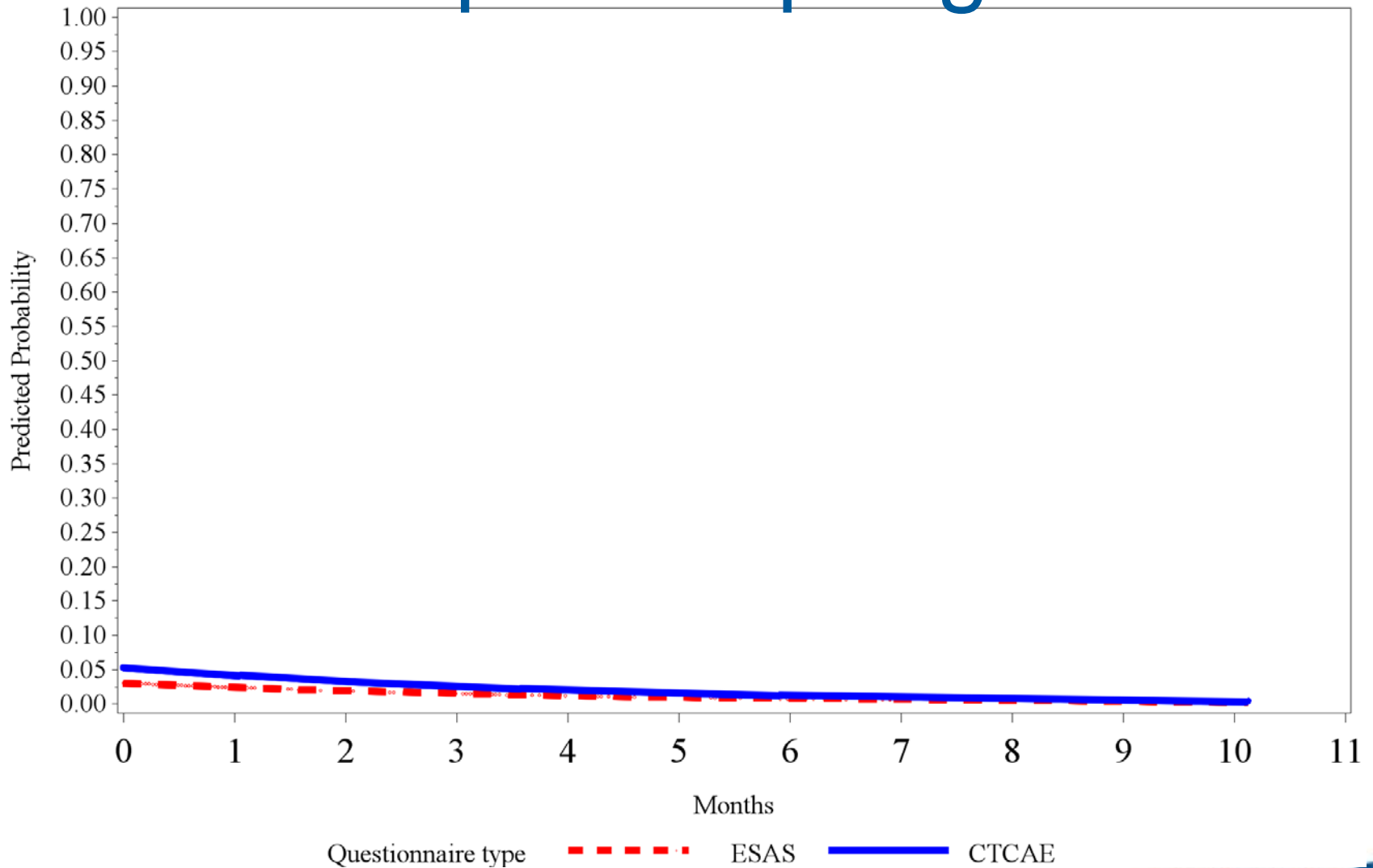
Graph: Nausea



Model: Esophagitis

<u>Parameter</u>	<u>Level</u>	<u>Estimate</u>	<u>SE</u>	<u>95% CI</u>		<u>P-value</u>
Intercept		-2.8804	0.2037	-3.2797	-2.4811	<.0001
Q_type	ESAS	-0.5711	0.3832	-1.3222	0.1800	0.1361
Days		-0.0080	0.0018	-0.0116	-0.0044	<.0001

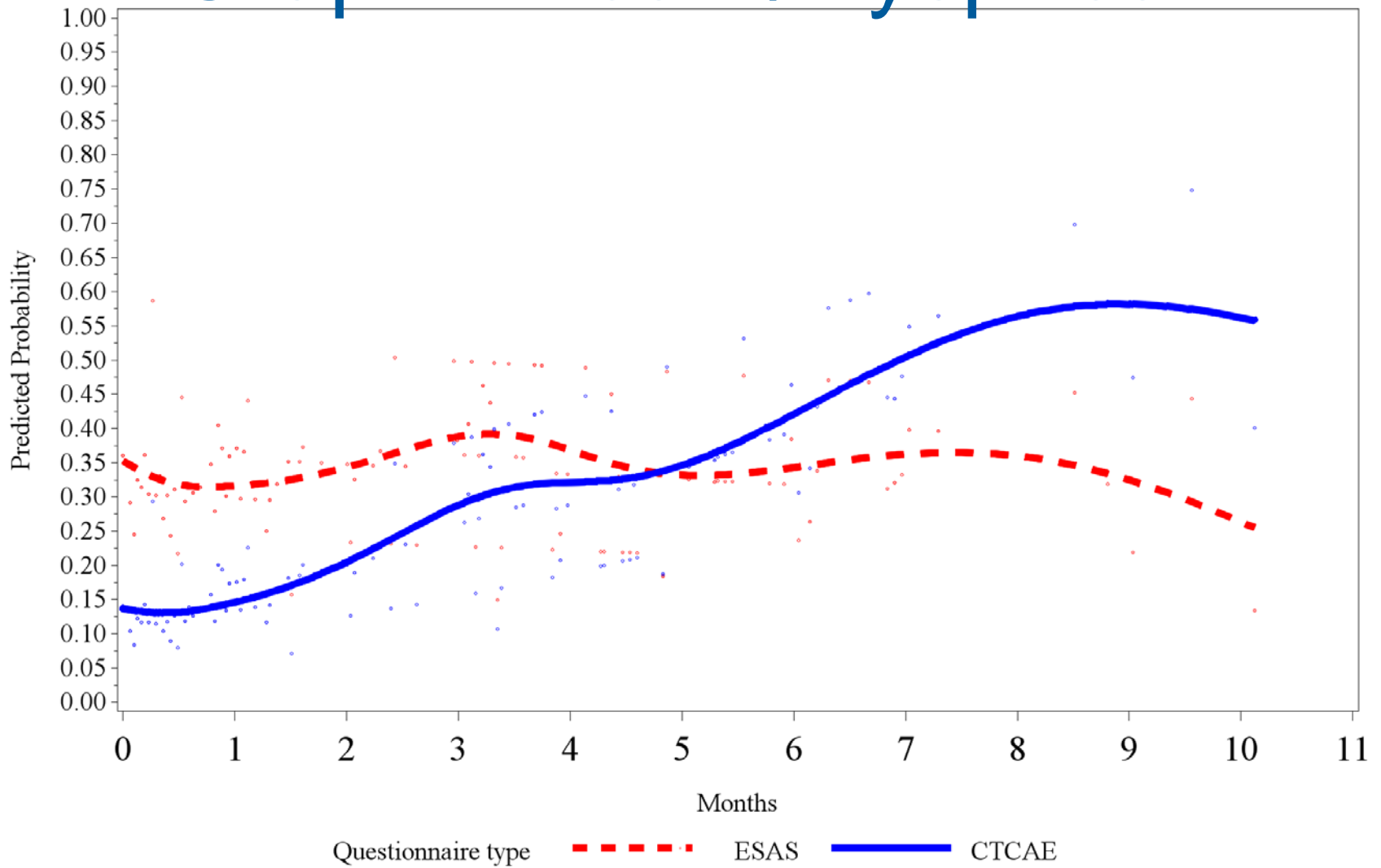
Graph: Esophagitis



Model: Breath/Dyspnea

<u>Parameter</u>	<u>Level</u>	<u>Estimate</u>	<u>SE</u>	<u>95% CI</u>		<u>P-value</u>
Intercept		-1.8612	0.1834	-2.2207	-1.5016	<.0001
URMM	Yes	-1.0651	0.4427	-1.9327	-0.1974	0.0161
	Unknown	-0.4451	0.3576	-1.1460	0.2558	0.2132
Gender	Female	-0.5602	0.2089	-0.9696	-0.1508	0.0073
SBRT	Missing	0.9202	0.3664	0.2020	1.6383	0.0120
	Yes	0.6546	0.2324	0.1990	1.1102	0.0049
Days		0.0079	0.0022	0.0035	0.0123	0.0004
Q_type	ESAS	1.3000	0.1796	0.9481	1.6520	<.0001
Days *	ESAS	-0.0090	0.0019	-0.0127	-0.0053	<.0001
Q_type						

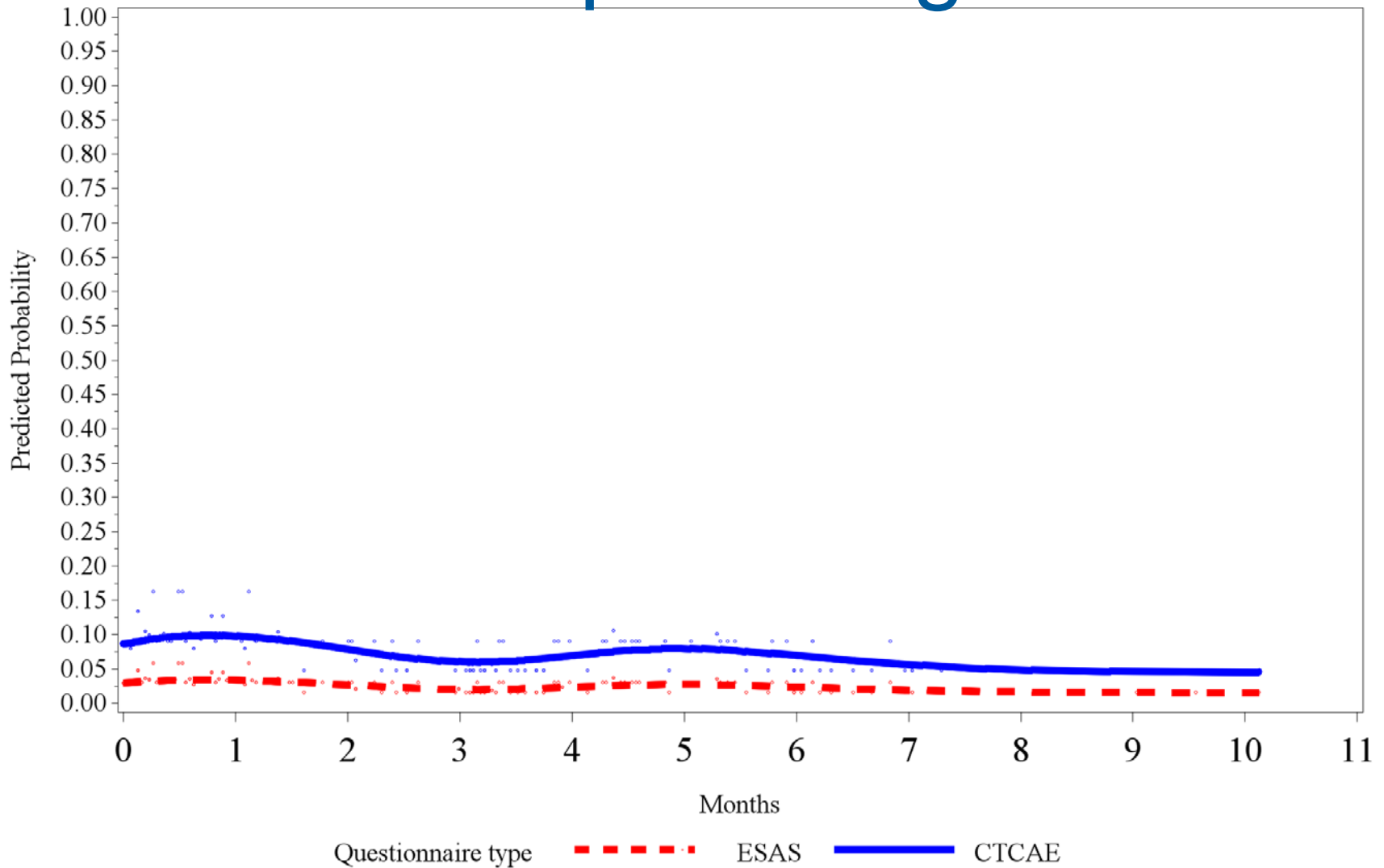
Graph: Breath/Dyspnea



Model: Cough

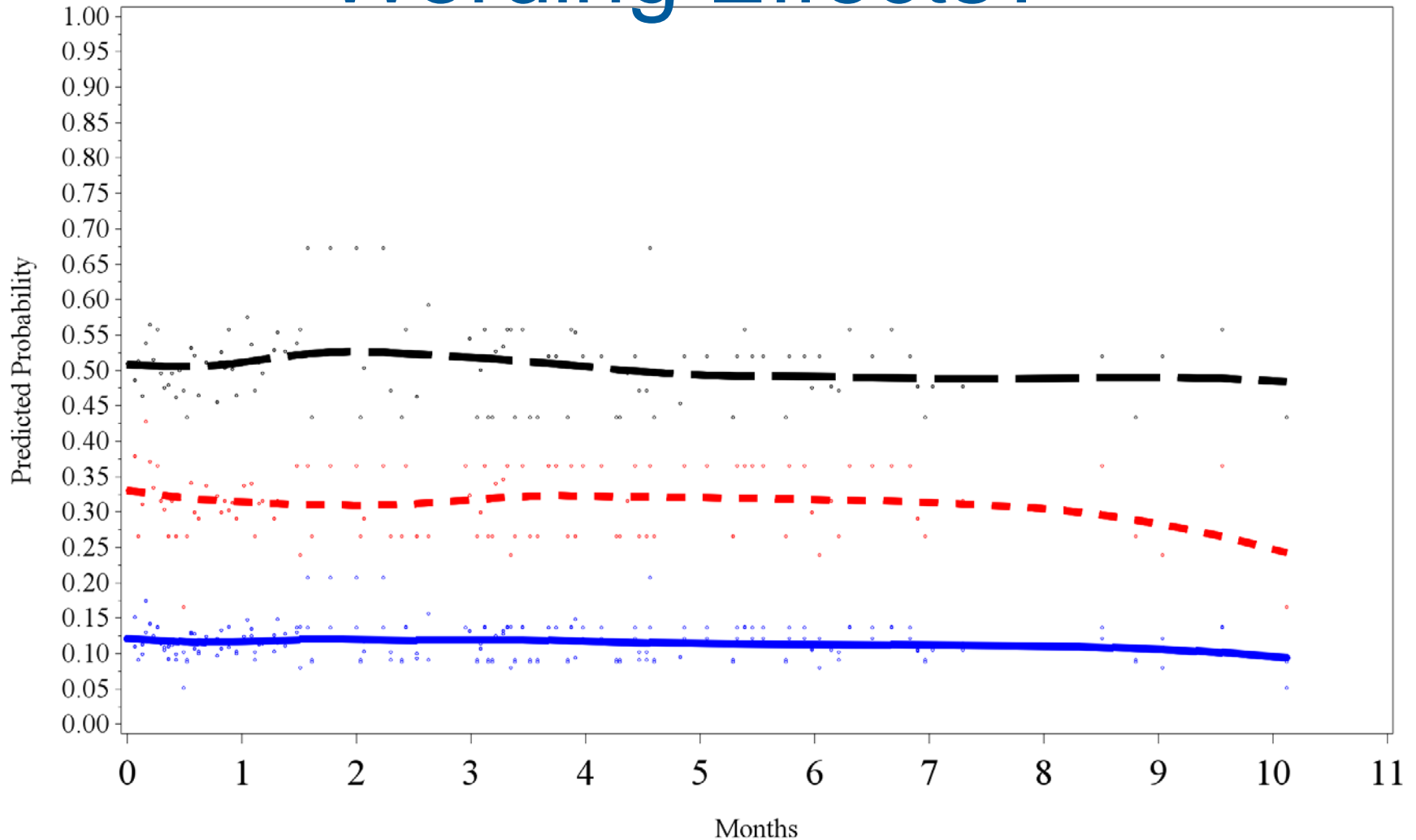
<u>Parameter</u>	<u>Level</u>	<u>Estimate</u>	<u>SE</u>	<u>95% CI</u>		<u>P value</u>
Intercept		-2.3061	0.2100	-2.7177	-1.8945	<.0001
SBRT	Missing	0.6730	0.5140	-0.3344	1.6803	0.1904
	Yes	-0.6739	0.3875	-1.4335	0.0856	0.0820
Q_type	ESAS	-1.1394	0.3167	-1.7602	-0.5187	0.0003

Graph: Cough



Questionnaire type  ESAS  CTCAE

Wording Effects?



Questionnaire type **—** CTCAE Fatigue **- - -** ESAS Drowsiness **- - -** ESAS Tiredness

Model of Tiredness/fatigue

<u>Parameter</u>	<u>Level</u>	<u>Estimate</u>	<u>SE</u>	<u>95% CI</u>		<u>P value</u>
Intercept		-1.3415	0.2289	-1.7901	-0.8929	<.0001
Gender	Female	-0.3449	0.2015	-0.7398	0.0500	0.0870
Physician	A	-0.6401	0.2449	-1.1200	-0.1602	0.0089
	B	-0.4889	0.2588	-0.9961	0.0183	0.0588
Q_type	ESAS	2.0612	0.1595	1.7485	2.3739	<.0001

Model of Drowsy/fatigue

<u>Parameter</u>	<u>Level</u>	<u>Estimate</u>	<u>SE</u>	<u>95% CI</u>	<u>P value</u>
Intercept		-1.8381	0.1932	-2.2168 -1.4594	<.0001
URMM	Yes	-0.6021	0.3897	-1.3660 0.1617	0.1224
	Unknown	0.5192	0.3178	-0.1038 1.1421	0.1024
Gender	Female	-0.4623	0.2198	-0.8932 -0.0315	0.0355
Q_type	ESAS	1.2853	0.1609	0.9699 1.6008	<.0001

Interpretation

- Outcomes sometimes change over time
 - Nausea, Esophagitis, Dyspnea
- Patients often report more/worse symptoms than physicians
 - Nausea, tiredness, fatigue
 - Not always (Esophagitis, Cough, Dyspnea)
- Predictors vary
 - Gender, URMM, SBRT, physician
 - Not treatment?!

Conclusion

- Originally proposed analyses suboptimal
 - Ignore important structure in the data OR
 - Computationally infeasible
- Our analysis better answered the question
 - Retained much of the structure
 - Simplifying data with PI for interpretability
 - Visualizations helped
- Team is happy
- Paper in preparation



Big Picture Lessons

- Understand the research question
- Consider methodology options
 - Common methods may have fatal flaws
 - Additional existing methods may be available
 - We are trained to develop new methods too
- Providing reasonable analyses with methods that are:
 - Valid and feasible
 - Reflect data structure fully but simply

Key Skills

- Collaboration
 - Even complex models can be well-received
- Communication
 - Meetings
 - Presentations
 - Visuals
 - Papers

Thank you!

Research Team

- Naomi Brownstein
- Mahrukh Naqvi
- Michael Yu
- Tom Dilling
- Daniel Oliver