

# Obesity & Postmenopausal Breast Cancer

Project : 4

Rochita Das, Sandipan Pramanik & Pallavi Ray

Class presentation

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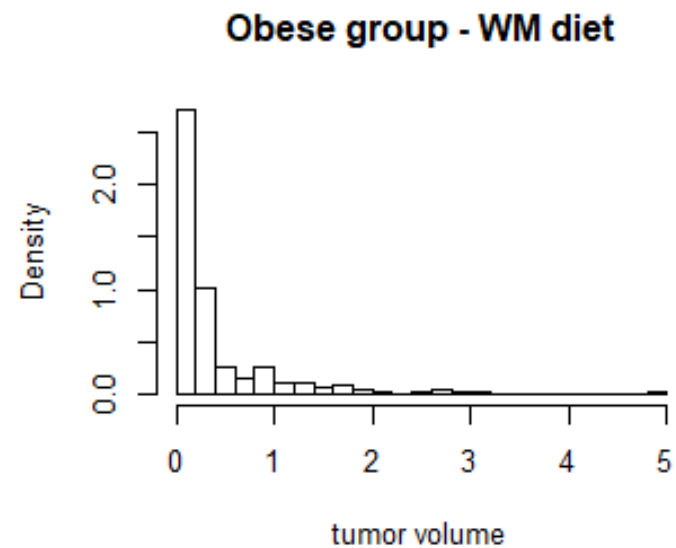
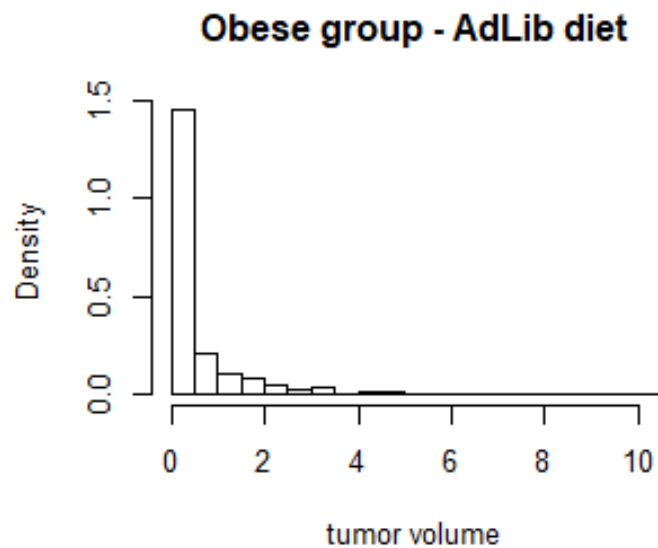
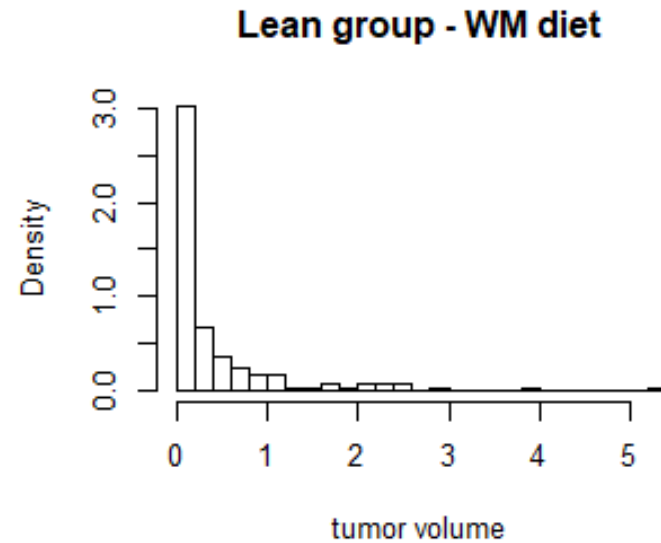
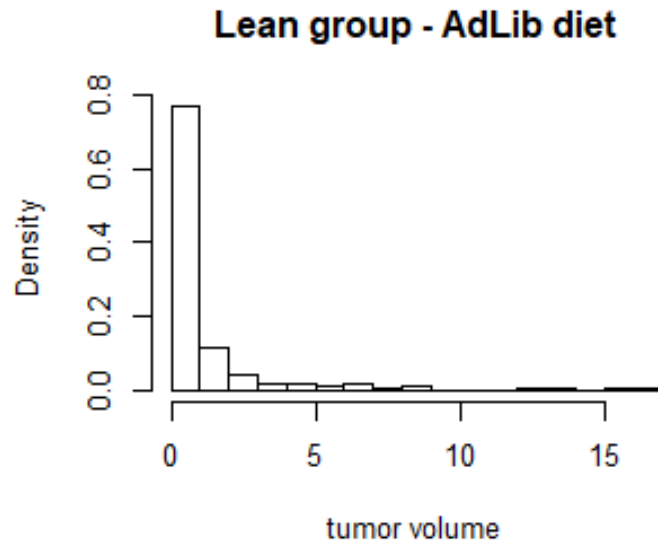
# Data description and objective

- **Test subjects:** 66 rats
- **Variable of interest:** tumor volume (ccm or cm<sup>3</sup>)
- **Weight groups:** Lean (L) and Obese (OB)
- **Diet groups:** Ad libitum (AdLib) and **Weight Maintaining** (WM)
- Tumor volumes were monitored for **9 weeks**

rat_ID	tumor_ID	weight	group	diet	group	week0	week1	week2	week3	week4	week5	week6	week7	week8
401	1		OB		WM	1.05	0.44	0.31	0.31	0.36	0.06	0.06	0.03	0.02
402	3		OB		AdLib	1.48	0.76	0.64	0.52	0.76	0.44	0.64	0.27	0.16
414	1		OB		WM	4.82	1.80	1.37	0.55	0.41	0.69	0.97	0.86	0.50
414	2		OB		WM	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
416	1		L		WM	5.33	4.00	1.05	1.20	0.43	0.38	0.18	0.22	0.33
416	2		L		WM	0.44	1.00	0.24	0.30	0.01	0.00	0.00	0.00	0.00

- **2 × 2 experimental design:** “weight” as block effect and “diet” as treatment effect
- **Objective:** whether dietary intervention (preventing weight gain) decreases tumor volume

# Zero inflated data

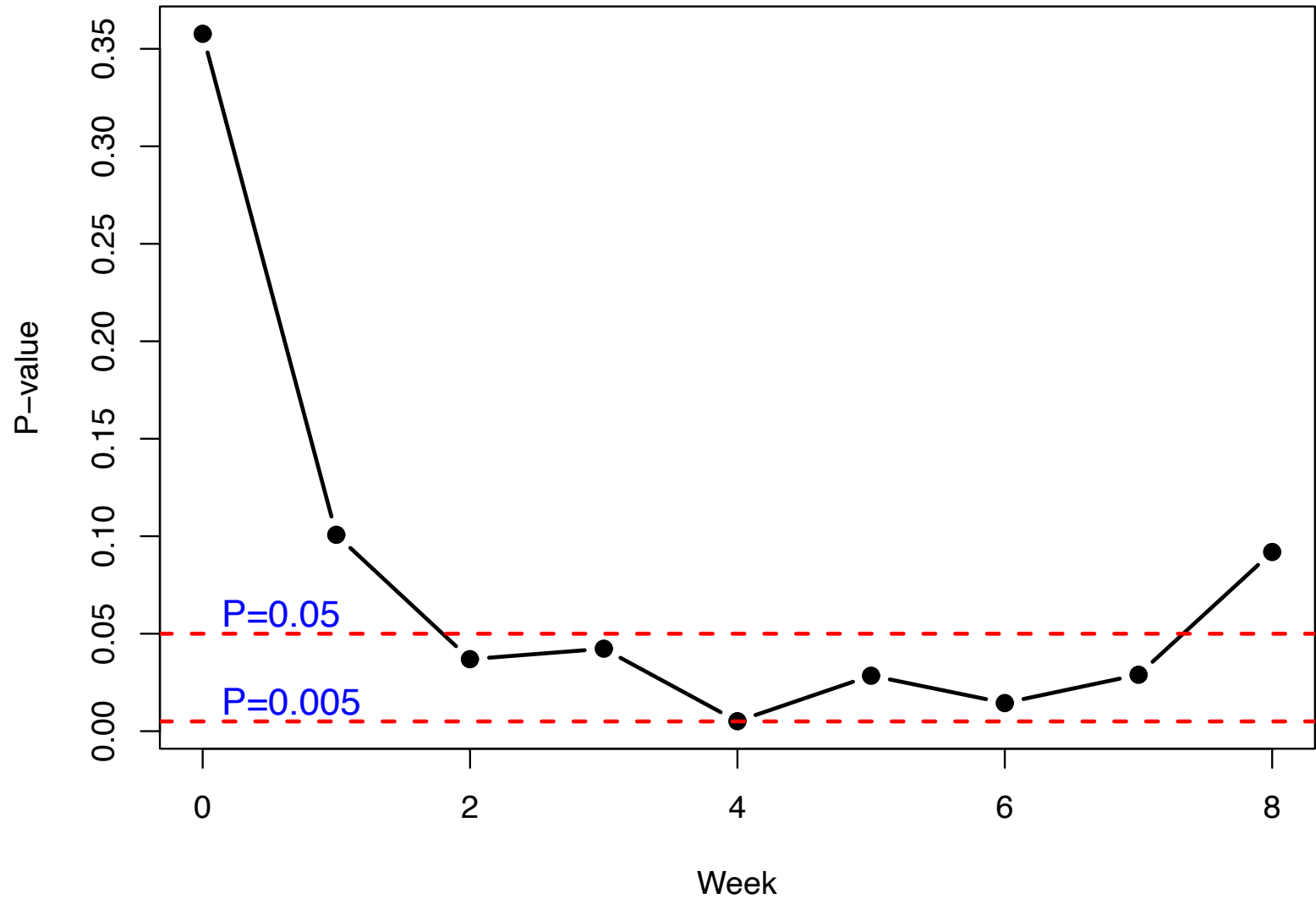


# Zero-inflated Gamma model

- Tumor volume (y) in ccm has **abundance of 0's** due to measurement limitations.
- Tumor volume is a **positive continuous** random variable.
- The histograms of y vs combinations of block (weight groups: Lean or Obese) and treatment (diet groups: AdLib or WM) are very similar to a **gamma distribution** with **zero-inflation**.
- We implemented a **Zero-inflated generalized gamma regression** with **mixed effects**.
- **Model:** For  $i^{\text{th}}$  week, where  $i = 0, 1, 2, \dots, 8$ ,  

```
glmmTMB(tumor_vol ~ block * treat + (1|rat_ID),  
        data = subset(data, week==i), ziformula = ~1,  
        family = ziGamma(link = "log"))
```

## Statistical significance of WM over week



# LR test for fixed week effects

## Full model:

```
glmmTMB(tumor_vol ~ block * treatment + week +  
        (1|rat_ID/tumor_nos), ziformula = ~1,  
        family = ziGamma(link = "log"))
```

- Test 1:

**H<sub>0</sub>:** No fixed effect of **Week** (P-value 4.16e-81)

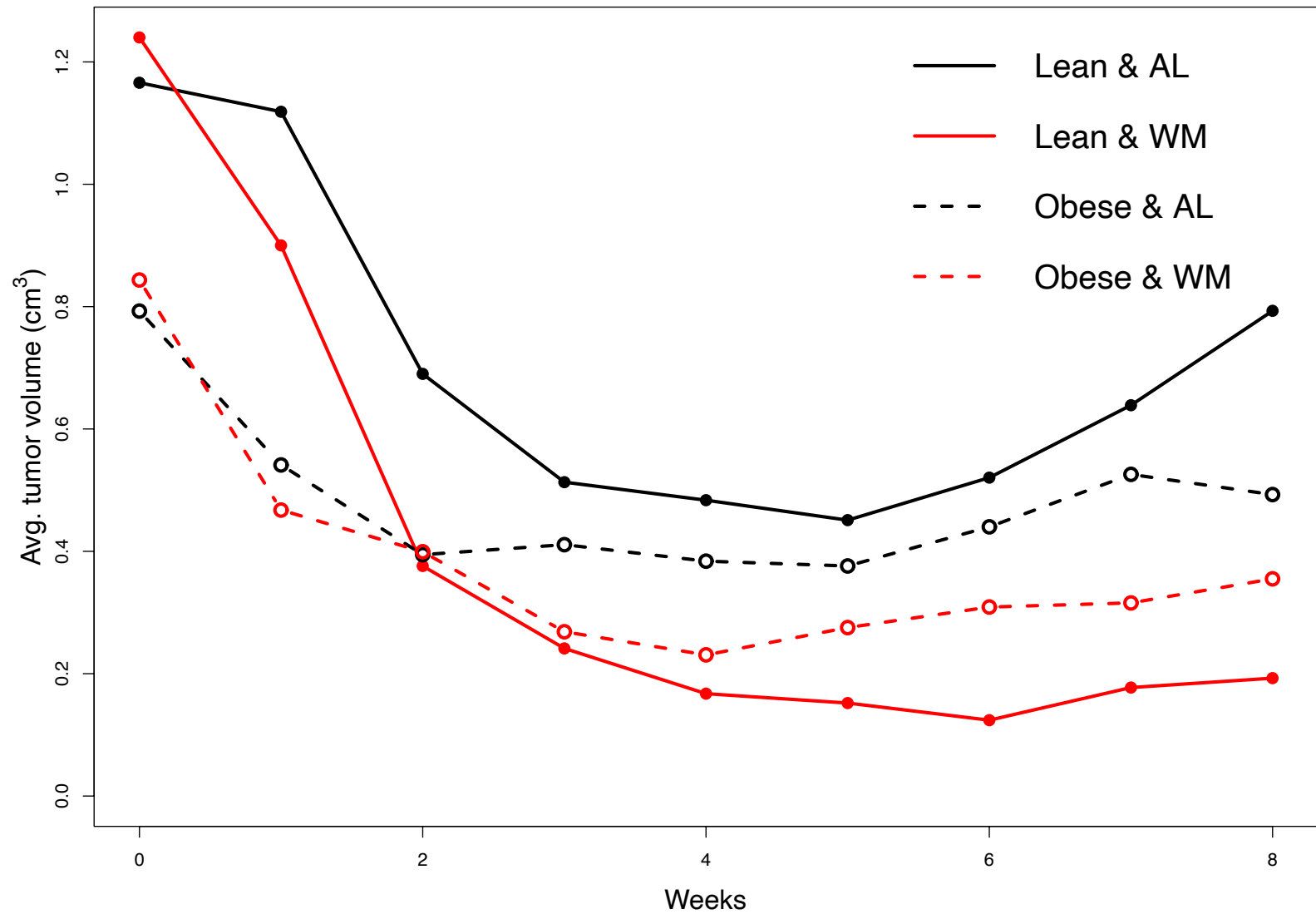
Conclusion: We **reject H<sub>0</sub>**, i.e. **week has significant effect**

- Test 2:

**H<sub>0</sub>:** No fixed effect of **block** and **treatment** (P-value 0.54)

Conclusion: We **fail to reject H<sub>0</sub>**, i.e. **week explains more** variability than **block** and **treatment together**

# Quadratic week effects



# LR test for quadratic week effects

## Full model:

```
glmmTMB(tumor_vol ~ block * treatment +  
        week + weeks2 + (1|rat_ID/tumor_nos),  
        ziformula = ~1,  
        family = ziGamma(link = "log"))
```

### • Test 1:

**H<sub>0</sub>:** No quadratic effect of **Week** (P-value 7.92e-87)

Conclusion: We **reject H<sub>0</sub>**, i.e. **week has significant quadratic effect**

### • Test 2:

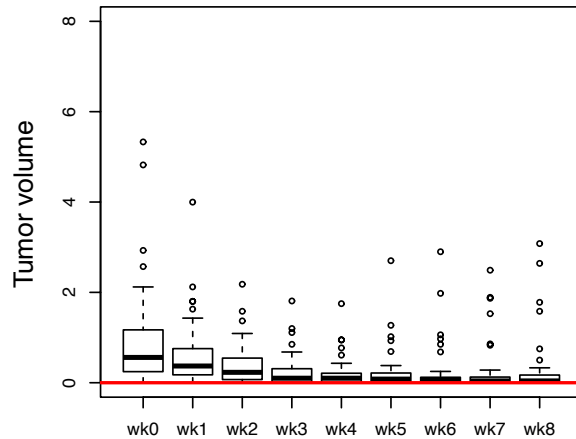
**H<sub>0</sub>:** No fixed effect of **block** and **treatment** (P-value 0.5377)

Conclusion: We **fail to reject H<sub>0</sub>**, i.e. **week explains more** variability than **block** and **treatment together**

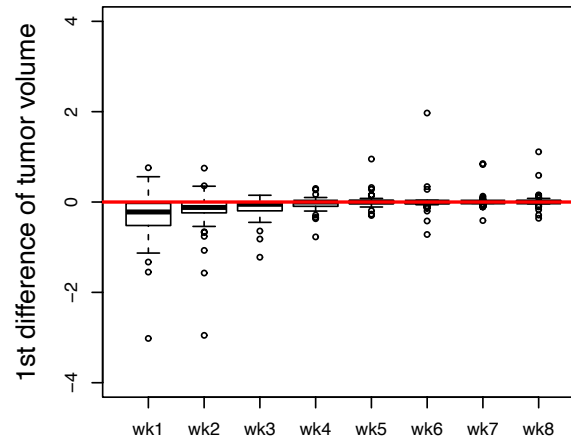


# De-trending time effects

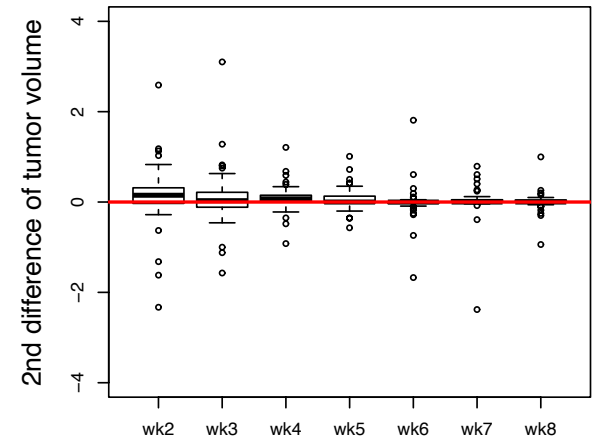
**Diet WM : No diff**



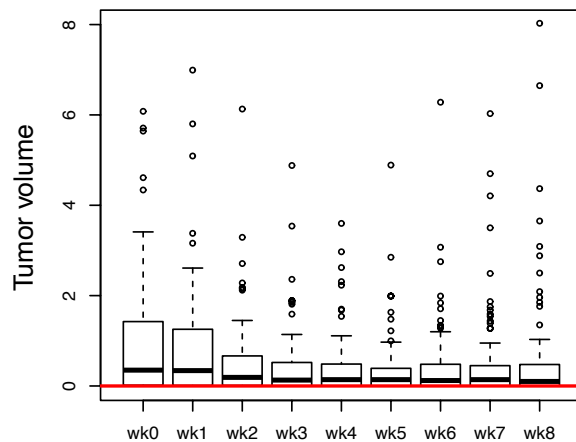
**Diet WM : 1st diff**



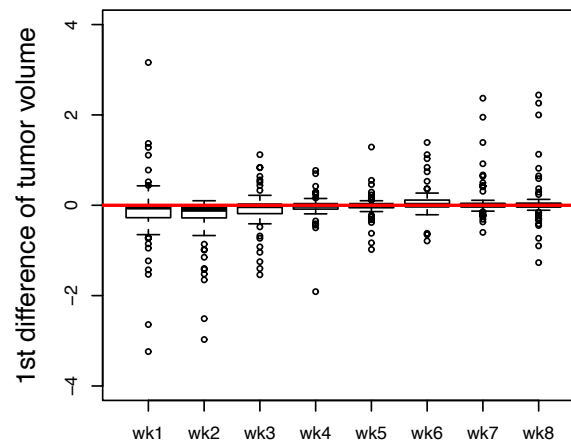
**Diet WM : 2nd diff**



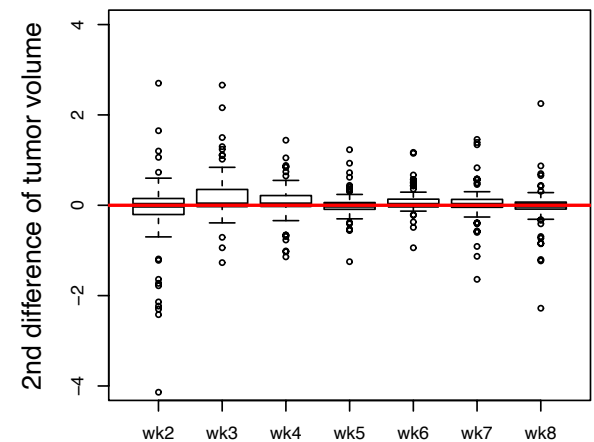
**Diet AdLib : No diff**



**Diet AdLib : 1st diff**



**Diet AdLib : 2nd diff**



# Zero-inflated Normal

- **Model:**

```
glmmTMB(voldiff2 ~ block + treatment +  
        (1|rat_ID/tumor_ID), ziformula = ~1,  
        family = gaussian())
```

Conditional model:

	Estimate	Std. Error	z value	Pr(> z )
(Intercept)	0.032407	0.030838	1.051	0.293
blockL	-0.004537	0.037118	-0.122	0.903
treatmentWM	0.025521	0.038541	0.662	0.508

Zero-inflation model:

	Estimate	Std. Error	z value	Pr(> z )
(Intercept)	-23.53	5333.77	-0.004	0.996

- WM treatment is **not** statistically significant

# Zero-inflated Gamma

(with a redefined treatment)

- Earlier evidence shows significance of WM diet as week progresses
- Question: Can we take **WM diet and week** into account **simultaneously**?
- Consider the **interaction of treatments and weeks** as a “redefined treatment” with 18 levels (9 weeks and 2 treatments)
- To test: Is the **interaction effect of week and WM** is **more significant** than week and AdLib?

# Zero-inflated Gamma (contd.)

- **Full model:**

```
glmmTMB(vol~block + Redefined_Treatment +  
        (1|rat_ID/tumor_ID), ziformula = ~1,  
        family = ziGamma(link = "log"))
```

- **H<sub>0</sub>: No interaction effect** between **WM and week** (that is, effects of 9 levels equal 0)
- **Likelihood-ratio test:** P-value 5.02e-48
- Also, as a model **AIC**, **BIC** marginally **prefers** the interaction of **WM and weeks** over the interaction of **AdLib and weeks**

# Discussion and conclusion

- Evidence of **significant diet effect** as week progressed.
- No significant treatment effect when **combined over all weeks as repeated measures**.
- The effect of week (fixed effects or otherwise) remarkably **dominates** over other effects.
- Effect of treatment (or block) is noticeable **only through week**.
- Effects of **treatment and week are deeply intertwined** and handled based on their **interaction effects** (“re-defined” treatments).
- Estimates of treatment effects are (always) **negative** indicating **negative influence** of dietary restrictions on tumor volume.
- Few number of subjects (66 rats) could be **a potential issue!**



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**THANK  
YOU**

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