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Applying LGM and GMM Analyses in Clinical Trials

Working Example

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LEADING RESEARCH...
MEASURES THAT COUNT

Stull et al., 2011

- Three clinical trials conducted to assess to safety and efficacy of indacaterol
 - A novel, once-daily, inhaled, long-acting, β_2 -agonist for the treatment of chronic obstructive pulmonary disease
- Initial data analysis was conducted using ordinary least-squares regressions
 - Indacaterol was found to increase lung function and improve patient-reported symptoms and health status

Stull D. et al. Application of latent growth and growth mixture modeling to identify and characterize differential responders to treatment for COPD. *Contemp Clin Trials*, 2011; 32: 818-828

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Purpose

- The three trials were analysed using mixture modeling techniques to answer the following questions
 - Are there groups of individuals within treatment groups who respond differently but who are hidden when whole treatment group means are analysed using traditional techniques?
 - In what ways do individuals show a differential response? That is, are there hyperresponders? nonresponders? decliners?
 - In what ways are groups of differential responders different? That is, are there differences in characteristics of individuals who are responding versus those who are not responding?

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Clinical Trial Descriptions

- INHANCE
 - Indacaterol 150 μg and 300 μg vs. placebo and open-label tiotropium 18 μg for 6 months, randomizing patients at 1:1:1:1
- INLIGHT-2
 - Indacaterol 150 μg vs. placebo and blinded salmeterol 50 μg for 6 months, randomizing patients at 1:1:1
- INVOLVE
 - Indacaterol 300 μg and 600 μg vs. placebo and blinded formoterol 12 μg for 12 months, randomizing patients at 1:1:1:1
 - Only data from the first 6 months of INVOLVE were used to keep the analyses comparable across the 3 trials

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Assessments

- Primary analyses
 - St. George's Respiratory Questionnaire (SGRQ)
 - Validated measure of health status in diseases of chronic airflow limitation
 - Contains 3 subscales: Symptoms, Activity, Impacts
 - Symptoms subscale was used for the present analyses
 - Scored 0-100; higher scores indicate worse health status
 - Modified Medical Research Council (mMRC) dyspnea scale
 - Clinician-rated degree of participants' dyspnea (breathlessness)
 - 5-point scale based on the degree of physical activities that may lead to dyspnea

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Statistical Analyses: Latent-Growth Models

- Latent-growth models (LGMs) were used to explore responses on the SGRQ symptom subscale from baseline to 6 months across the 3 assessment points, controlling for key covariates including mMRC dyspnea
 - LGMs calculate 2 latent (or unobserved) variables for *each individual*: an intercept (variable for the first time point of the curve) and a slope (variable for changes in the scores over time)
 - Changes in scores are analyzed at the individual level, modeling individual variability in treatment response
 - The level of individual variability was examined to assess whether there may be groups of respondents with different slopes

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Statistical Analyses: Growth-Mixture Models

- Where considerable individual variability was found, growth-mixture models (GMMs) were conducted to assess the presence of latent subgroups of individuals showing a differential response within treatment groups
 - Subjects were assigned to their most likely latent class, with different numbers of classes tested to find the best model fit
 - Evaluation of empirical criteria of goodness-of-fit statistics and visual examinations were used to determine the number of classes that best fit the data

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Statistical Analyses: Post Hoc

- Post hoc comparisons were conducted to explore differences between the identified latent classes in terms of baseline characteristics
- Post hoc comparisons facilitate an investigation of the way in which, for example, treatment responders are different from nonresponders

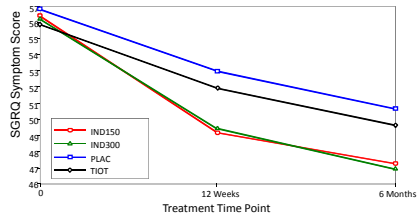
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Results: INHANCE

- LGM
 - Indacaterol 150 µg and 300 µg performed significantly better than placebo or tiotropium



NOTE: Patient age, sex, GOLD stage of COPD severity, smoking status, and baseline FEV₁ are covariates

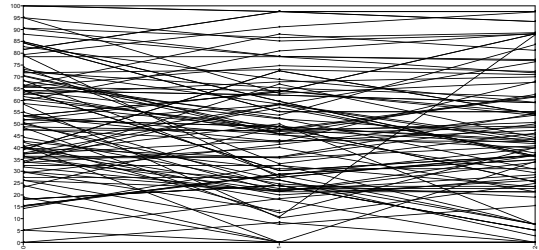
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Results: INHANCE

- Individual slopes: indacaterol 150 µg (200 randomly selected patients)



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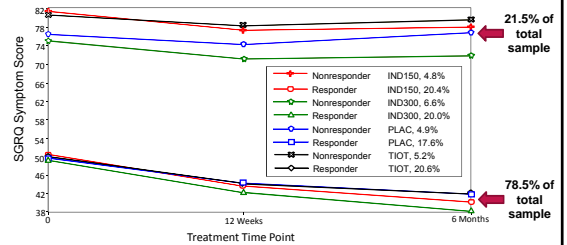


Results: INHANCE

- GMM
 - Two subsets of patients emerged in each treatment group

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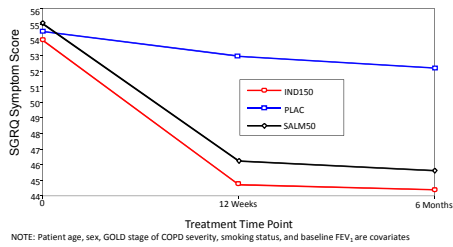
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Results: INLIGHT-2

- LGM

- Indacaterol 150 µg performed significantly better than placebo and showed noninferiority with salmeterol



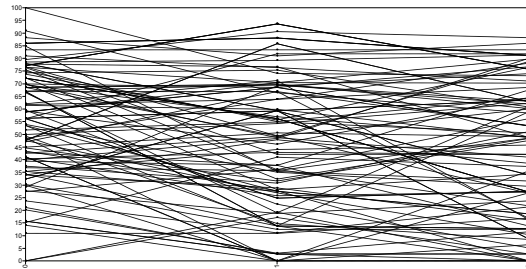
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Results: INLIGHT-2

Individual slopes: indacaterol 150 µg (200 randomly selected patients)



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Results: INLIGHT-2

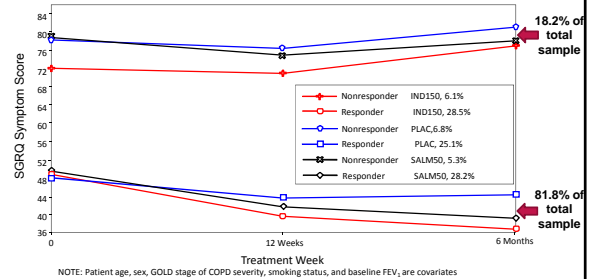
- GMM

- Two subsets of patients emerged in each treatment group

Results: INLIGHT-2

- GMM

- Two subsets of patients emerged in each treatment group



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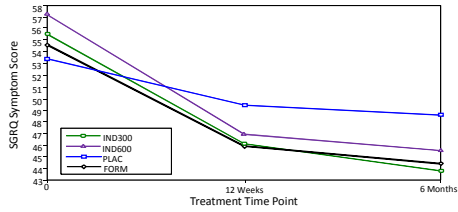
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Results: INVOLVE

- LGM

- No significant differences at 6 months between any group
- However, indacaterol 300 µg and 600 µg and formoterol had significant between slopes of change (improvement over time) than placebo



NOTE: Patient age, sex, GOLD stage of COPD severity, smoking status, and baseline FEV₁ are covariates

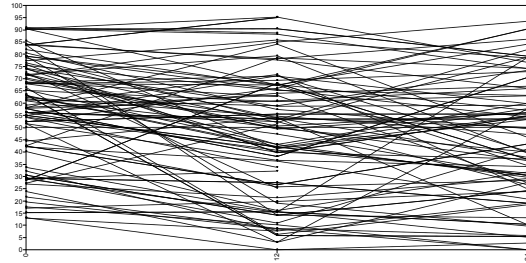
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Results: INVOLVE

- Individual slopes: indacaterol 300 (200 randomly selected patients)



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Results: INVOLVE

- GMM

- Three subsets of patients emerged in each treatment group

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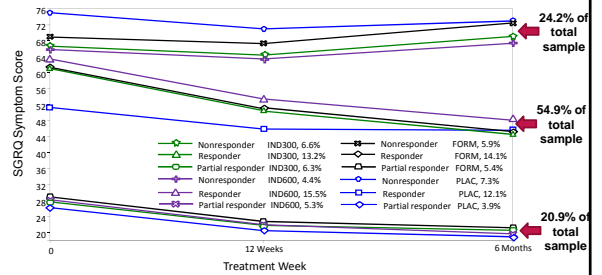
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Results: INVOLVE

- GMM

- Three subsets of patients emerged in each treatment group



NOTE: Patient age, sex, GOLD stage of COPD severity, smoking status, and baseline FEV₁ are covariates

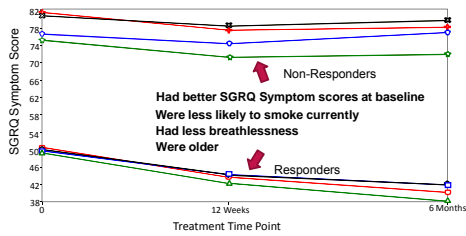
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Results: Post Hoc

- In all trials, responding patients...



...than nonresponding patients

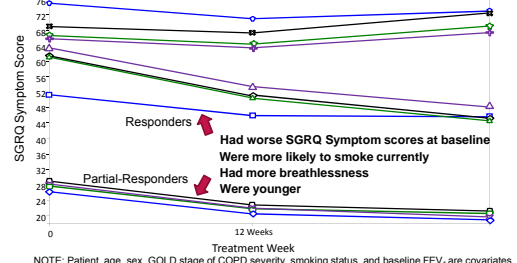
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Results: Post Hoc

- In INVOLVE, responding patients...



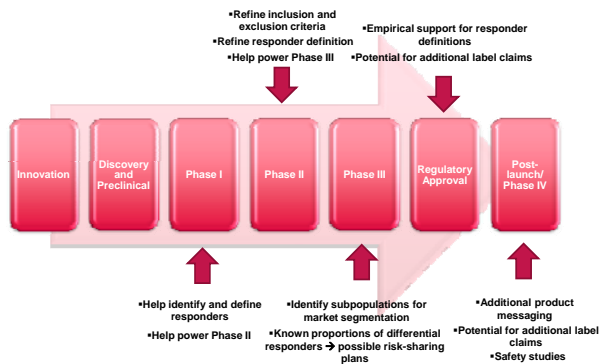
...than partially responding patients

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Overview of Potential Use in Drug Development



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Session Summary

- Clearly, heterogeneity is important when attempting to understand treatment effects
- From the patients' point of view, they want a treatment that will work
 - Maximizing treatment effectiveness and minimizing adverse events
- From the payers' point of view, they don't want to pay for treatment that won't work in individual patients
- As researchers, we can take steps to manage heterogeneity

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