What About Randomization Tests?

- Strengths
  - Gail et al. (1996) reported nominal Type I and II error rates across a variety of conditions common to GRTs.
  - Programs for randomization tests are available.
- Weaknesses
  - The unadjusted randomization test does not offer protection against confounding (Murray et al., 2006).
  - Randomization tests provide only a point estimate and a p-value; model-based methods provide parameter estimates and standard errors.
  - Regression adjustment for covariates requires many of the same assumptions as the model-based tests.

What About Generalized Estimating Equations (GEE)?

- Methods based GEE use an empirical sandwich estimator for standard errors.
- That estimator is asymptotically robust against misspecification of the random-effects covariance matrix.
- When the degrees of freedom are limited (<40), the empirical sandwich estimator has a downward bias.
- Recent work provides corrections for that problem; several have been incorporated into SAS PROC GLIMMIX.
- Methods that employ the corrected empirical sandwich estimator may have broad application in GRTs.

What About Fixed-Effect Methods in Two Stages?

- Introduced as the first solution to the unit of analysis problem in the 1950s.
- Commonly known as the means analysis.
- Simple to do and easy to explain.
- Gives results identical to the mixed-model ANOVA/ANCOVA if both are properly implemented.
- Can be adapted to perform random coefficients or growth curve analyses.
- Can be adapted to complex designs where one-stage analyses are not possible.
- Used in several large trials, including CATCH, MHHP, REACT, CYDS, and TAAG.

What About Deleting the Unit of Assignment From the Model If It Is Not Significant?

- The df for such tests are usually limited; as such, their power is usually limited.
- Standard errors for variance components are not well estimated when the variance components are near zero.
- Even a small ICC, if ignored, can inflate the Type I error rate if the number of members per group is moderate to large.

- The prudent course is to retain all random effects associated with the study design and sampling plan.

What About Unbalanced Designs?

- Imbalance at the group-level can create analytic problems (Gail et al., 1996; Murray et al., 2006).
  - Balance at the group-level is usually easy to retain.
- Imbalance at the member level can create Type I error inflation and the risk increases with the level of imbalance.
  - Member imbalance is almost universal in GRTs.
- Johnson et al. (2015) compared 10 model-based approaches to member imbalance in GRTs.
  - A one-stage mixed model with Kenward-Roger df and unconstrained variance components performed well for $g \geq 14$.
  - A two-stage model, weighted by the inverse of the estimated theoretical variance of the group means, and with unconstrained variance components, performed well for $g \geq 6$.

What About IRGTs In Which Members Belong to More than one Group or Change Groups?

- The literature on IRGTs has focused on the simplest situation in which each member belongs to a single group and group membership does not change.
  - That pattern is not likely to hold in practice.
- Andridge (2014) has shown that failure to account for multiple group membership can result in Type I error inflation for the methods described thus far.
- Roberts (2013) has shown that multiple membership multi-level models address this problem.
  - They require data on membership time in each group, which is not routinely collected in IRGTs.