Biomarker Disclosure Workgroup, Research/Analysis Subcommittee: Framework for informing disclosure

ADC meeting

May 3, 2019

AD Research/Analytical subcommittee

- **Subcommittee charge**
  - Evaluate the quality of biomarker data
  - Evaluate/quantify conclusions that can be drawn
  - Covers both symptomatic and asymptomatic subcommittees
- **Procedures**
  - Develop a systematic approach to address multiple biomarkers
  - Start with question(s) from other subcommittees, recast if needed

Overall framework

- **Identify what is needed to answer the question**
  - What are the necessary pieces?
  - Why address the problem a particular way?
  - What are we comfortable with concluding?
  - Do we need to work with a modified question?
  - What other comments do we feel are necessary?
  - Consider what else we might want to have
- **Carefully assess the following:**
  - How well is the biomarker measured
  - How suitable are the analyses, with what assumptions
  - In what population and for what time period has it been measured

APOE genotype and risk as a paradigm

- **Why start with APOE?**
  - It is the most accurately measured biomarker
  - We have more data than any other biomarker
- **Original question:**
  - What is the predictive value of a APOE genotype for short-term progression to MCI or dementia due to AD?
- **Recast question(s):**
  - What is the 5-year risk of MCI/dementia due to AD for a particular APOE genotype (e.g., e4/e4) in whites?
  - What is the lifetime (to age 85) risk of AD for a particular APOE genotype in whites?

The necessary pieces

- **How is APOE genotype measured?**
  - good: Sanger sequencing, GWAS array plus imputation, etc.
  - not so good: GWAS array without imputation, WGS at read depth 30-50x
- **What population?**
  - Most data available for whites of European descent
  - Data are more sparse for Hispanics, African Americans, other groups

The necessary pieces, part 2

- **How were individuals selected?**
  - Convenience samples (e.g., NACC) likely enriched in individuals with a family history of AD or with subtle memory loss
  - Population-based cohorts (e.g., Framingham, Rotterdam) more applicable to the general population
  - Short term risk also dependent on baseline evaluation (risk falls as screening is more stringent)
- **What analytic approach?**
  - Were subjects observed or was risk estimated, and how?
  - How was risk of death and LTFU handled?

"Answers" to questions

- **What is the 5-year risk of AD for APOE genotype ε4/ε4 in whites for a subject who is 65-70 yrs?**
  - NACC: 34.6% (20.2% – 55.2%)
  - Framingham: 9.4% (3.6%-23.5%)
  - Rotterdam: 10.4% (5.3%-19.8%)
- **What is the lifetime (to age 85) risk of AD for APOE genotype ε4/ε4 in whites?**
  - Framingham&Rotterdam: 30.8%-40.3%
  - 23 and me*, men: 51-52%
  - women: 60-68%

*Estimates from multiple sources

Comments/observations

- **Genotype effects tend to be lower from cohort studies than convenience studies**
- **Sample sizes from cohort studies are limited**
  - Few cohort studies available
  - Splitting into subgroups by multiple attributes (genotype, sex,...) yields small samples – difficult to make conclusions