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Estimating penetrance of rare genetic mutation using ascertained families

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Unbiased estimation of age-specific cumulative-risk, or penetrance, of a disease associated with rare high-risk genetic variants, such as BRCA1/2 mutations, is vital for genetic counseling. For efficiency, such studies are typically done using ascertained high-risk families that are more likely to carry the mutations of interest than subjects in the general population. This talk will review some of the methodological challenges and recent developments for application of multivariate survival analysis methods for analysis of ascertained families with partial genetic information. In particular, contrasts between the usefulness of marginally- or conditionally-specified models will be drawn. The problem of estimation of residual familial aggregation, which could be a bi-product of such analyses, would be also discussed. Data from the Washington Ashkenazi Study will be used for illustrations. The area is likely to receive more attention in the near future as next generation sequencing are expected to identify novel high-risk rare variants for a variety of diseases and disorders.

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