# Statistical validation of endophenotypes using a surrogate endpoint analytic analogue

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## Abstract

Endophenotypes, which involve the same biological pathways as diseases but presumably are closer to the relevant gene action than diagnostic phenotypes, have emerged as an important concept in the genetic studies of complex diseases. In this report, we develop a formal statistical methodology for validating endophenotypes. The proposed method was motivated by the conditioning strategy used for surrogate endpoints commonly seen in clinical research. We define an endophenotype to be "a trait for which a test of null hypothesis of no genetic heritability implies the corresponding null hypothesis based on the phenotype of interest." The index, proportion of heritability explained, is used as operational criteria of validation. Usefulness of the proposed method is demonstrated through computer simulations and a study of validating the continuous performance test as an endophenotype of the schizophrenia spectrum.