Statistica Sinica **35** (2025), 1-19
doi:https://doi.org/10.5705/ss.202022.0211

TOWARDS OPTIMAL USE OF SURROGATE MARKERS TO IMPROVE POWER

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Abstract: Motivated by increasing pressure for decision makers to shorten the time required to evaluate the efficacy of a treatment such that treatments deemed safe and effective can be made publicly available, there has been substantial recent interest in using an earlier or easier to measure surrogate marker, S, in place of the primary outcome, Y. To validate the utility of a surrogate marker in these settings, a commonly advocated measure is the proportion of treatment effect on the primary outcome that is explained by the treatment effect on the surrogate marker (PTE). Model based and model free estimators for PTE have also been developed. While this measure is very intuitive, it does not directly address the important question of how S can be used to make inference on the unavailable Y in the next phase clinical trials. In this paper, to optimally use the information of surrogate S, we provide a framework for deriving an optimal transformation of S, $g_{\text{opt}}(S)$, such that the treatment effect on $g_{\text{opt}}(S)$ maximally approximates the treatment effect on Y in a certain sense. Based on the optimally transformed surrogate, $g_{\text{opt}}(S)$, we propose PTE and a new measure to quantify surrogacy, the relative power (RP), and demonstrate how RP can be used to make decisions with S instead of Y for next phase trials. We propose nonparametric estimation procedures, derive asymptotic properties, and compare the RP measure with the PTE measure. Finite sample performance of our estimators is assessed via a simulation study. We illustrate our proposed procedures using an application to the Diabetes Prevention Program (DPP) clinical trial to evaluate the utility of hemoglobin A1c and fasting plasma glucose as surrogate markers for diabetes.

Key words and phrases: Clinical trial, nonparametric estimation, proportion of treatment effect explained, relative power, surrogate marker.

1. Introduction

Motivated by increasing pressure for decision makers to shorten the time required to evaluate the efficacy of a treatment such that treatments deemed safe and effective can be made publicly available, there has been substantial recent interest in using an earlier or easier to measure surrogate marker in place of a primary outcome. The development and testing of clinical treatments, including vaccines, often require years of research and participant follow-up. Though

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