

## Principal Investigator

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## General Information

### Key Personnel (in addition to PI):

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**Are external grants or funds being used to support this research?:** No external grants or funds are being used to support this research.

**How did you learn about the YODA Project?:** Colleague

## Conflict of Interest

[https://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_2018\\_mlvh2.pdf](https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2018_mlvh2.pdf)  
[https://yoda.yale.edu/system/files/coi\\_ak.pdf](https://yoda.yale.edu/system/files/coi_ak.pdf)

## Certification

**Certification:** All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

**Data Use Agreement Training:** As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

### Associated Trials:

1. [NCT00653952 - 30-57 - A Phase 3, Randomized, Open-Label, Comparative Study of CAELYX® versus Paclitaxel HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy](#)
2. [30-49 - A Phase 3, Randomized, Open-Label, Comparative Study of DOXIL/CAELYX® versus Topotecan HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy](#)

**What type of data are you looking for?:** Individual Participant-Level Data, which includes Full CSR and all supporting documentation

## Research Proposal

### Project Title

Predicting Individual Treatment Effects for Doxil/Caelyx in Malignant Ovarian Cancer

#### Narrative Summary:

Research protocols that are used to test cancer treatments typically focus on estimating average treatment response. More than half of RCTs (randomized control trials) in oncology fail to show expected effects. This might be, at least partially, a result of RCTs' focus on average effects rather than individual effects. This proposal is based on the premise that individual differences in the effects of oncology treatments are to be expected and that medically relevant predictions of individual response may often be obtained using the full constellation of available data. We propose to demonstrate a method for obtaining predicted individual treatment effects (PITEs) in an oncology RCT.

#### Scientific Abstract:

**Background:** While personalized medicine has been shown to have great promise for the treatment of cancers, new statistical approaches which have promise for finding a greater individual differences in the effects of treatment have yet to be widely implemented.

**Objective.** This study will utilize the predicted individual treatment effect (PITE) framework to test for evidence of individual differences in the effects of Doxil for the treatment of ovarian cancer and to examine the predictors which contribute most to observed differences.

**Study Design.** This is a secondary data analysis of the Doxil clinical trial.

**Participants.** All subjects included in the primary analyses for the clinical trial will be included.

**Main Outcome.** The primary outcome will be progression free survival.

**Analyses.** We propose to utilize the predicted individual treatment effect (PITE) framework in which available baseline covariates are utilized to predict the treatment effect for each individual. We will conduct a permutation test to evaluate whether there is overall evidence for individual differences in treatment effects. If so, we will describe the range of differential effects, conduct cross validation analyses, and assess variable importance to provide information about the primary contributors to the individual differences in the effects of the intervention.

#### Brief Project Background and Statement of Project Significance:

Randomized controlled trials (RCTs) are typically designed to assess the average causal effect of a treatment.(1,2) Implicit in this approach is the assumption that the estimated treatment effect is reasonable for at least most individuals in the population. One of the challenges in oncology is the vast amount of heterogeneity within and between types of cancers, heterogeneity between individuals, and even heterogeneity between tumor sites within the same patient.(3) Thus, the very nature of cancer casts doubt on the appropriateness of assessing only the average effects of treatment. This is the rationale behind the ideological movement toward personalized medicine and targeted therapies.(4)

Precision medicine can be greatly facilitated by statistical methods for evaluating heterogeneity in treatment effects. We note that in oncology the control condition is likely to be standard care or an alternative treatment arm rather than a no-treatment control. The PITE approach allows predicting treatment effects for patients that have not originally been part of the clinical trial. The PITE approach is a significant contribution because it results in predictions of the effect of the intervention for any individual for whom the covariates can be measured.

We have developed and is in the process of evaluating a test for the presence of any individual differences in the treatment effect given all available covariates. This permutation based test(5) evaluates whether the variance (individual differences) of the PITE observed in a given RCT is greater than would be expected due to chance. This test for heterogeneity in treatment effects is a significant contribution to oncology as it provides a tool to assess the

presence of individual differences in treatment effects in any RCT. It has been found that more than half of RCTs in oncology fail to show the expected effects(6), a possible reason for this is that while a given treatment benefits some individuals, it does not have a greater effect than standard care on average, and may do worse for some other individuals. The PITE approach with its test for individual differences in treatment effects and patient level predictions has implications for treatments that do not show benefits on average, it can be used to test for evidence that the intervention benefits some patients and it allows them to be identified.

We have utilized the PITE approach to test for heterogeneity in treatment effects and predict individual response to treatment for both binary and continuous outcomes.(7) We propose to use applied data and simulations to better understand what survival models can be effectively used for PITE and the conditions under which those models will be successful. We will also extend this work to use methods for predicting survival outcomes from the machine learning literature which can better deal with a large number of predictors. This non-trivial extension of the PITE approach to predicting individual differences in the effects of treatments on survival time will be highly significant for the application of PITEs to oncology.

### **Specific Aims of the Project:**

- Extend the PITE approach for use with trials in which survival is the primary outcome. The PITE framework has limited utility in cancer research until it can be shown to be effective at predicting treatment effects on individual survival.
- Develop an approach using PITE to obtain predictions of individual treatment effects & predictive intervals under each arm in a multi-arm trial. This aim increases the utility of PITEs by obtaining individual predictions & predictive intervals for multiple interventions.
- Establish & demonstrate a procedure for selecting a statistical model to estimate PITE in oncology trials. The overarching goal is to develop tests of heterogeneity and then to obtain predictions useful to oncologists and their patients.

### **What is the purpose of the analysis being proposed? Please select all that apply.**

Develop or refine statistical methods

Research on clinical prediction or risk prediction

## **Research Methods**

### **Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

All subjects included in the primary analyses for the clinical trial will be included. Our analyses rely on having as many observations as possible. If baseline outcome data are missing, we will perform multiple imputation.

### **Main Outcome Measure and how it will be categorized/defined for your study:**

The endpoints to be analyzed in this research are the same as in the trial: survival time, survival, tumor size (if available), and safety.

### **Main Predictor/Independent Variable and how it will be categorized/defined for your study:**

We plan to use all baseline covariates available.

### **Statistical Analysis Plan:**

The primary purpose of this study is to demonstrate the PITE method using the DOXIL/CAELYX trial. This method has been previously published and additional methodological papers on the PITE method with application to amyotrophic lateral sclerosis (ALS) are currently under review. For the proposed study we will implement the PITE approach using a beta R package being developed by our team. The effect of interest in this study is individual predictions of treatment effects, our analyses will include: 1) an assessment of significant variation in the effects of pegylated liposomal doxorubicin in the requested RCT data using a permutation test which compares the variability of the estimated PITEs to chance variability (the distribution of which is derived using random permutations of treatment status); 2) given that there is significant variability of treatment effects, we will estimate the predicted treatment effect for each individual in the original trial, a major outcome of the study is the description of the type of

individual differences predicted by the PITE approach; 3) finally, we will estimate predictive intervals for the PITEs and describe both the individual level predictions as well as the differences in precision across individuals. These steps are described in more detail below.

Our analyses begin by testing for evidence of significant variability in PITEs across individuals in the requested RCT data. Because the permutation test for assessing variability in PITE is a model based test, it requires PITE estimates to assess significant variability in PITE. The PITE approach is a general framework for estimating individual variability designed to work with any predictive algorithm or model. Thus, our first task is determining the predictive method to use to estimate PITE. This trial includes a moderate number of baseline covariates and some evidence of differential treatment effects. Because there are a moderate number of covariates and most are categorical, we expect that a linear model with 2-way interactions specified within both treatment and control conditions (functionally this is a 3-way interaction because all variables interact with treatment) may be the most efficient model. However, we will also consider Bayesian Additive Regression Trees and LASSO models with interactions. Simulations in which the baseline covariates and treatment status are utilized with outcome data generated different types of heterogeneity in treatment effects will be used to determine which predictive method to use.

Once the predictive model or algorithm to be used to generate PITEs has been identified, PITEs are estimated: 1) generate a predictive algorithm for the outcome under both treatment and control conditions; 2) obtain predictions for each individual of their outcome under each condition; 3) PITE is the difference between the two predictive models. Once PITEs are obtained, the first question, whether there is significant variability in the PITEs, is assessed by comparing the observed variability of the PITEs to the distribution of variability in PITEs given that treatment is unrelated to all predictors and outcomes (this distribution is obtained by permuting treatment status many times and obtaining PITE estimates for each). Given significant variability in PITE estimates, the observed distribution of PITEs will be described, answering the second aim of this study. Finally, we will apply previously derived methods (currently under review) to assess the variability of the PITEs. Both the PITE estimates and the predictive intervals will be described in the resulting research reports.

Although a research team has been involved in developing the PITE approach, (7) analysis of these data will be conducted exclusively by team members at the University of New Mexico. No other team members will be involved at this stage. Further, we have not secured access to other oncology data sources and have dropped this from the proposal.

Software Used:

R

#### **Project Timeline:**

Project start date: August 15, 2019

Analysis completion date: February 15, 2020 – Because the proposed analyses are quite time consuming and some decisions may need to be guided by simulations we anticipate this taking 6 months.

Draft of manuscript: May 15, 2020

Submit manuscript for publication: June 15, 2020

Results returned to YODA: July 15, 2020

#### **Dissemination Plan:**

We anticipate that the results we be published as a demonstration of the PITE method in journals that focus on applied statistics in medicine. One such journal might be *Statistics in Medicine*. If the results are particularly telling, we would want to submit a paper for publication in an oncology journal, emphasizing the practical implications for physician diagnostic practices and patient decision-making.

#### **Bibliography:**

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7. Lamont A, Lyons MD, Jaki T, et al. Identification of predicted individual treatment effects in randomized clinical trials. *Stat Methods Med Res.* March 2016:962280215623981. doi:10.1177/0962280215623981.

**Supplementary Material:**

<https://yoda.yale.edu/sites/default/files/lamont2018.pdf>