***Step*** 1. C**linical scenario:** Prognosis of cutaneous T cell lymphoma (CTCL). In early stages of CTCL, patients (Stages IA-IIA) usually do well and have slowly progressive disease, which does not require aggressive therapy associated with substantial side effects. However, about 15% of these patients have unexpected progressive course and rapid demise.

***Step 2***. **Principal goal:** To identify, among patients who are diagnosed with early stage CTCL, who should receive immediate aggressive therapy and who should receive stantard of care.

***Step 3*.** **Clinical benefit:** A biomarker progression risk model that is able to classify patients into high and low risk groups will enable personalized and more aggressive therapy for the patients at highest risk for progression.

***Step 4*. Classification performance needed:** The PI stipulates that the classifier will have clinical utility if the “number needed to treat” (*NNT*) is less than *NNTLower* = 2 in the test-positive patients, and greater than *NNTUpper* = 30 in the test-negative patients. Then 2 patients testing positive will need to receive aggressive treatment upfront in order to treat one patient who otherwise would suffer later rapid progressive CTCL, while in the test-negative patients one would have to treat an unacceptably high 30 patients to treat one patient in advance of progressive CTCL. This performance should suffice to create a clinical consensus supporting using the test for clinical decisions.

***Step 5*. Prospective study requirements**: The values *NNTLower* = 2 and *NNTUpper* = 30 correspond to the positive predictive value *PPV* = 50% = 1/*NNTLower*, and the negative predictive value *NPV* = 97% = 1 – 1/*NNTUpper*. We will be able to recruit 40 patients in this early-stage group, over 3 years, with a minimum of 2 years follow-up thereafter. If the test divides the 40 patients into roughly 25% positive and 75% negative, and the estimates match the hoped-for values 2 and 30, the confidence intervals would be 19% to 81% for *PPV*, and 83% to 100% for *NPV*, or equivalently24 1.23 to 5.35 for *NNTPos*, and 5.81 to 1180 for *NNTNeg*. The very wide confidence interval for *PPV* is due to the low sample size and low prevalence combined with the low value for *NNTPos*, which is strongly weighted towards avoiding unnecessary aggressive therapy. To obtain a more accurate and independent estimate of *PPV* , we also plan a retrospective study.

***Step 6*. Retrospective study requirements:** Combining *PPV* and *NPV* with an incidence of rapid progression of 15%, the required sensitivity (*SN*) and specificity (*SP*) are 83.3% and 85.3%, respectively (contra-Bayes Theorem). To get a sense of the accuracy of anticipated estimates in the retrospective (case/control) portion of the study, we consider anticipated results for samples sizes 22 cases (the entire complement of early stage CTCL who rapidly progressed) and 40 controls. For example, if the estimates *SN*=18/22 = 82% and *SP*=34/40=85% are observed, then the corresponding confidence intervals will be 60%–95% for *SN*, and 70%–94% for *SP*, and Bayes predictive intervals will be (1.4, 2.7) for *NNTPos* , and (16.4, 87.8) for *NNTNeg* . (These intervals derive from assuming independent Jeffreys priors for *SN* and *SP*, sampling from joint independent posteriors incorporating the anticipated results, and applying Bayes theorem).