Statistical Principles for Omics-based Clinical Trials

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Abstract

High-throughput techologies enable the measurement of a large number of molecular characteristics from a small tissue sample. High-dimensional molecular information (referred to as omics data) offers the possibility of predicting the future outcome of a patient (prognosis) and predicting the likely response to a specific treatment (prediction). Embedded in the vast amount of data is the hope that there exists some signal that will enable practicioners to deliver therapy personalized to the molecular profile of a tumor, thereby improving health outcomes. The challenges are to determine that the omics assays are valid and reproducible in a clinical setting, to develop a valid and optimal omics-based test that algorithmically determines the optimal treatment regime, to evaluate that test in a powerful and unbiased manner, and finally to demonstrate clinical utility: that the test under study improves clinical outcome as compared to not using the test. We review the statistical con-

siderations involved in each of these stages, specifically dealing with the challenges of high-dimensional, omics data.

Keywords. genomics; personalized medicine; predictive biomarker; statistics

1 Introduction

Omics technolgies that generate a large amount of molecular data about a cancerous tumor have the potential to provide accurate predictions of a patient's prognosis and predictions of their response to a specific treatment regime. The idea of omics-based biomarkers is that distinct tumor types can be identified using the multi-dimensional molecular data leading to treatment decisions personalized to that tumor type. An omics-based test can guide the decisions to treat or not to treat and help identify the particular therapy most likely to work. The challenge is to identify and demonstrate definitively that the use of an omics-based test improves clinical outcomes in a patient population.

An omics-based test can be used to predict a patient's prognosis, which is their expected clinical outcome. A test that provides accurate predictions of prognosis, regardless of treatment, is referred to as a prognostic biomarker. A predictive omics test is one that accurately predicts disease outcomes with the application of specific interventions. Predictive markers are therefore useful for the selection among two or more treatment options. Statistically, a prognostic test is strongly associated with clinical outcome and a predictive test modifies the association between treatment and clinical outcome (interaction). High dimensional omics data can be used to identify specific

molecular targets as potential mechnisms for drug development, however the use of omics technologies for drug development is beyond the scope of this review.

The path from development to definitively evaluating an omics-based test for prognosis or prediction of treatment response is long and arduous. Often, the end goal is to develop a test suitable for use in a clinical trial for guiding treatment. The oncology literature is full of reports that develop and/or evaluate omics-based tools for prognosis and prediction. Developing a simple test based on high-dimensional omics data can be complex and often uses novel statistical methods. Definitive evaluation of a prognostic or predictive test is costly and rife with methodological pitfalls. We aim to review such issues, giving you the resources to ask the right questions when critically weighing the evidence presented in a report of an omics-based study. Ultimately, as a practicing oncologist the question is: "Is this omics-based test something I want to use to improve patient care?".

The long road to implementing a test in a practice starts with analytical validation, that is, demonstrating that the omics-based assay accurately and reproducibly measures the molecular quantities. After the assay performance is established comes the test development and preliminary evaluation. This involves reducing the high-dimensional data into a one-dimensional quantity that will be used to make a decision. This one-dimensional quantity is often a risk score: an estimate of the probability of a speicific clinical outcome. It is necessary to establish the clinical validity of this risk score, that is, demonstrate that the risk score is independently associated with clinical outcome. Care must be taken to completely separate the development of the risk score from the

evaluation, otherwise estimates can be optimistically biased. Finally, the risk score must be translated into a binary decision, often using a threshold. It remains to demonstrate that the use of the test to make this decision improves patient outcomes.

The following sections specify questions you should ask while reading a report of an omics-based clinical study. We review the importance of such questions, and common pitfalls to watch for. If you are reporting on an omics-based trial, answers to these questions should be made clear to the reader. Formal efforts to guide reporting have been developed, such as the REMARK checklist (1), the GRIPS statement (2), and a third guideline article that lacks an acronym (3). Our review reflects these efforts through the readers' lens.

2 What is the intended clinical use?

Do: define the clinical use (4)

As with all clinical studies, the end goal is to improve patient care. Omics studies are no different, and a clear statement of the intended clinical use of the omics-test should be prominent.

3 What is the patient population of interest?

4 Is the omics assay valid?

Analytical validation of an assay involves evaluating the performance of the measurement in terms of accuracy, bias, and precision under a variety of conditions. Conditions

are things like preanalytic factors such as specimen quality, specimen collection, storage, and processing procedures, and technical aspects such as laboratory technician and batch effects from reagent lots or other assay materials. The high-dimensional nature of omics data makes it very difficult to assess each of the hundreds or thousands of outputs from a single assay. In developing a omics-based signature that only uses a subset of the components of a high-dimensional assay, one can analytically validate the final signature alone. However, prior to developing the signature, one must develop detailed standard operating procedures for specimen handling and processing to ensure a baseline level of validity.

Do: develop criteria for the rejection of poor-quality specimens. Percent tumor, necrosis, etc.

Do: filter features based on QC prior to development

Do: assess the impact of sample and specimen handling. (5–9)

Do: assess the impact of lots and batch effects. Bias, accuracy. (10,11)

Do: minimize the impact of technical aspects to greatest extent possible by developing detailed SOP.

5 What does the omics-test do?

Does the test provide a continuous score or a binary classification?

How are the features of the omics assay translated into a clinically meaningful quantity?

Compare: feature filtering based on association with outcome, regularization. (12,13)

Do: consider all available methods, model averaging. Hard to determine best method in advance.

Don't: rely on clustering to yield good predictions of outcome.

6 On what samples was the test developed?

Study design: consider retrospective (14)

Don't: confound technical factors with clinical outcomes. (15,16)

Do: maintain strict separation between development and evaluation.

Do: cross validation if you have a data-sparse setting. (17–20)

Don't: use convoluted methods leading to overfitting.

7 On what samples is the test being evaluated?

Do: define the clinical use (4)

Do: Design your study appropriately to answer the clinical question definitively (21–32)

Do: Power your trial appropriately (33,34)

Don't: do partial resubstitution

8 Are valid methods being used to evalute the test?

Bad: IDI or net reclassification (35,36)

Bad: Comparing AUCs for regression models (37)

Good: comprehensive and pre-specified approach (38)

9 Are the development and evaluation samples strictly separated?

This issue has come up in previous sections, yet this error occurs so frequently that it needs to be highlighted in its own section. The evaluation sample for the assessment of a prognostic or predictive test needs to be completely independent from the development sample. This is especially true for omics-based tests, whose developement is often complex and convoluted. Any imformation from the evaluation sample that leaks into the development sample can bias the results, making tests appear better than they truly are.

Don't: do partial resubstitution

Don't: make these mistakes (39–41)

10 Concluding remarks

Do: follow reporting criteria (1–3,42)

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