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Study designs in biomarker research

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ABSTRACT

In order to advances in technology, nowadays science is facing to a large variety of biomarkers. Issues of selecting appropriate study design for biomarkers, facing with a large number of biomarkers, multiple biomarkers, and usefulness of a new biomarker the today is more complicated. Current study is an overview of the issues discussed in studies of biomarkers.

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Introduction

Biomarkers as biological disease signs play important role not only in diagnosis of disease but also in understanding disease process and even in cure process. In recent years along with advances in technology, recognizing new biomarkers has been subject of many studies. Moreover, because of possible classification errors, authors have considered to select powerful biomarkers. Difficulty in selection process and variety of biomarkers power in diagnosis, suggest authors to consider study designs for biomarkers more carefully. Since each design can use for any biomarker, the subject of study deign depends only on purpose of study. In many studies, different research methods have addressed also for the classification of biomarkers, biomarker power, biomarker misclassification, and the discovery of new biomarkers for disease diagnosis.

Biomarkers

What is biomarker? A biomarker is a sign or an indicator of disease, and it can be answer to question that physician asks. NCI dictionary in the definition of cancer terms define biomarker as: "A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. biomarker may be used to see how well the body responds to a treatment for a disease or condition, Also called molecular marker and signature molecule [1]."

Moreover, biomarker is defined by the Biomarkers Definitions Working Group as "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [2]."

Biomarkers should have some features, they

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should easily measure and biomarker activity should remain almost constant in patients. In addition, an ideal biomarker should show the intensity and severity of the disease in the entire region of biomarker expression. Diagnosis biomarkers should be associated with the specific disease and not be related to any other situation.

Furthermore, an ideal biomarker should have suitable sensitivity and specificity, and must have high predictive power. Unfortunately, such ideal biomarkeris difficult to find,therefore, some researchers suggest the combination of different biomarkers for enhance their power.

Biomarker Classification

In many different studies biomarkers have classified in base of different reasons. The subjects that biomarkers have been intended can summarize as: Diagnosis, Screening, Risk prediction, Treatment selection and Monitoring. One can clarify these captions as follows: In a disease process first of all, absence or presence of disease should investigate (Diagnosis), how disease process is progressing (Screening), what is the risk of disease (Risk prediction), which design should be selected for treatment (Treatment selection) and during therapy how is disease status (Monitoring). According to these intended uses of biomarkers, researchers have classified biomarkers by these usages or by merging some of them.

Therefore, for example in Oncology Clinical Trials 2010 three types of biomarkers have introduced:

-Prognostic biomarkers are a biological measure of whether the patient will respond to a particular drug endpoint.

-Predictive biomarkers: Biological markers that predict the speed of the progression of the underlying disease.

-Surrogate and Pharmacodynamic biomarkers, when the change in biomarker is the controlled parameter , in other words, it is an endpoint and if it is use for drug activity or optimize dose, the biomarker is Pharmacodynamic Biomarker. In evaluating effectiveness of a specific treatment, surrogate biomarkers take place of a clinical endpoint in clinical trials [3, 4].

A researcher measures biomarkers once before treatment or several times before, during and after treatment, measurement once before treatment results prognostic and predictive biomarkers, whereas measurement in other way can result every three type of biomarkers.

In another classification way, two type of biomarkers is defined: exposure biomarkers, and disease biomarkers. Exposure biomarkers are used in risk prediction and disease biomarkers are used in screening and diagnosis and monitoring of disease progression [5].

Biomarker Based Trials and Designs

Researchers in choice of design should consider to what they know about trial,what are the treatment and biomarker effects? They should know about type of trial (discovery or confirmation)? If trial will be done again, and what is the type I and type II errors in terms of biomarkers?

Gosho *et al.* [6] had a comprehensive study on biomarker study designs as follows:

- Standard Randomized Clinical Trial (RCT) Design
- Biomarker by Treatment Interaction Design
- Biomarker - Strategy Design
- Enrichment Design and Hybrid Design
- Adaptive Signature Design
- Biomarker - Adaptive Threshold Design
- Adaptive Accrual Design
- Bayesian Adaptive Design

Factually, selected design is so variable in order to researcher, available facilities and sources. Interested readers can have access comprehensive information about above mentioned designs by Gosho *et al.* [6].

Standard Randomized Clinical Trial (RCT) Design

In clinical studies, Randomized Controlled Trials (RCTs) can use to identify new biomarkers. In this design patients divide in order to levels of biomarkers (especially in two level: biomarker positive, biomarker negative), and after randomization take test or standard treatment. This is similar to conducting two independent RCTs to compare different treatments.

Biomarker by Treatment Interaction Design

In this design we use the biomarker status for approve a treatment effect, than we use the biomarker as a stratification factor. Biomarker positive and biomarker negative groups after randomization take standard and test treatments. This process is similar to implementing RCT in both biomarker positive and biomarker negative arms [7].

Biomarker - Strategy Design

Biomarker - Strategy design allocate patients in classification; biomarker based strategy or non-biomarker strategy. In biomarker based strategy arm, patient takes test or standard treatment due to the biomarker result (positive or negative). In other arm, non-biomarker based strategy patient can take only standard treatment or maybe either due to randomization [8].

Enrichment Design and Hybrid Design

Studies that are limited to patients who are most likely to be affected by the use of the experimental drug are "target design" or "enrichment design". In these designs, the researcher uses a validated diagnostic test limitation of eligibility in comparing test group and control group [9]. In this design before screening we have a step for patients that are selected for the study based biomarker status. First, all patients divide to groups based on biomarker status and only the wanted status is will considered, in a binary biomarker, patients with biomarker positive status will considered and others take out of study (Enrichment design) or maybe they take standard treatment (Hybrid design). In both two designs patients with biomarker positive status after randomization take test treatment or standard treatment [10].

Adaptive Signature Design

In adaptive signature design, the researcher has not got a test or signature that identifies patients. Firstly, patients randomly allocate for test and standard treatments, the researcher perform a statistical test for comparing the difference at α1 significance level. If there was a significant difference and the test treatment is better, then the analysis is finished. If there is not, the second stage starts. In next stage comparison for test and standard treatment perform in only biomarker positive patients at α2 significance level. If there was a significance difference and the test treatment is better the analysis is done again, if there is not, researcher should accept fail in efficacy show of test treatment [6, 11].

Biomarker - Adaptive Threshold Design

Biomarker - Adaptive threshold design is developed to identify the sensitive patients to test treatment. Mainly with this design researcher can identify a cut-off point that makes comparison between test treatment and standard treatment easier. General procedure for adaptive signature and biomarker-adaptive threshold is: first, researcher does a basic RCT design, and for all patients comprise between test and standard treatment at α1 level of significance, if there were a significant evidence, therefore the RCT succeeded in showing efficacy of test treatment. If there were not a significance evidence, for biomarker positive subgroup, researcher makes comparison between test and standard treatment at α2 level of significance. In this stage if there were significance evidence, then we succeeded in showing efficacy, if not, we can result test treatment in showing efficacy is failed [12].

Adaptive Accrual Design

In this design after conducting a basic RCT between test and standard treatment, in the biomarker negative patients, researcher considers an interim analysis for comparison test and standard treatment. If interim analysis fails to show any significance difference in biomarker negative group, the comparison will restricted to biomarker positive patients. If there was unclarity, comparison for test and standard treatment will conduct between all patients and biomarker positive patients [13]. The word accrual indicates stop in occurring biomarker negative in interim analysis or continue in take them for next stage.

Bayesian Adaptive Design

The Bayesian Adaptive Design is an outcome based randomization design and it use a Bayesian hierarchical framework for assigning patients to test or standard treatment. In this design we have more than two biomarkers. Patient based on status of biomarkers are assigned to groups, for example patient with positive biomarker status for all biomarkers assigned to group 1 and etc. Then these groups based on researcher's prior knowledge or based on randomization take test or standard treatment [14].

Sources of Bias in Biomarker Performance Studies

Many of biomarker studies because of small sample size or wrong definition of resources and maybe endpoints suffer of lack of precision, they may have considerable bias, and need to use statistical methodology for minimize bias. Same of bias resources in biomarker studies are as follows:

- Selection bias: convenience sampling of available specimens
- Spectrum bias: advanced stage of disease vs.

healthy patients, enrichment with cases outside of IU population

• Verification bias: disease status not verified in all subjects by the reference standard

• Imperfect Reference Standard Bias

Ordering bias: order in which results are taken by test, comparator, and reference standard is not randomized; order in which disease and non-disease subjects are tested is not randomized. For predictive tests, test result is taken after onset of target condition.

• Missing biomarker results

• Test interpretation, integrity, and context bias: Device users / operators not masked to true disease status.

New Biomarkers

Ideal Biomarkers

A big family of biomarkers is using today. Nowadays new biomarkers in whole of biological system have introduced with developed tools. Many of these biomarkers are simple biomarkers like binary biomarkers that show presence or absence of a disease or a status in body. With introducing new biomarkers for a specific disease, researchers face with selection and evaluating of them. They also look for biomarkers that are valuable to measure. Since discovery of biomarkers in many contexts have developed in order to advance in technology over the past two decades, one can measure many biomarkers for a special disease. But generally an ideal biomarker for determining disease condition should have below features:

- Safe and easy to measure
- Cost efficient
- Modifiable with treatment
- Consistent across gender and ethnic groups

Evaluation of New Biomarkers

When there are multiple biomarkers for a disease, biomarker selection process is difficult to decision. Some researchers prefer to select biomarkers due to biomarker performance metrics, others make a combination of appropriate biomarkers. There are many biomarker performances metric due to type of biomarkers. ROC curves is one of suitable graphical metrics for evaluating a biomarker performance. It is also used for evaluating the accuracy of medical diagnostic systems.

In studies with multiple biomarkers, usefulness of diagnostic test increases by adding a new biomarker. Quantification of this usefulness can be done with standard methods including statistical significance and area under the ROC curve. Nevertheless, recent studies have introduced some new and useful indexes for the quantification [15].

The net reclassification improvement (NRI) and integrated discrimination improvement (IDI) is defined as two way for evaluate performance of diagnosing improvement by adding new biomarkers: NRI offers improvement offered by new markers by calculating NRI as probability of moving correctly to categories minus moving incorrectly based on new biomarkers or new algorithms.

In multiple biomarkers consider adding a new biomarker, one can consider changing in new probabilities of an event or new classification in disease based on the new biomarker, then we have new probabilities or new classification versus the old one.

Define upward movement (up) as a change in move to a higher category based on the new marker and downward movement (down) as a change in to lower category. The net reclassification improvement is defined as:

$$NRI=P(up \mid event)-P(down \mid event)+P(down \mid nonevent)-P(up \mid nonevent) \quad (1)$$

Second measure of assessing improvement diagnosing performance is integrated discrimination improvement (IDI). Since NRI consider to reclassification tables for patients and others(if there is an event or there is not event) then NRI quantifies movement in categories: if there is an upwards movement then the subject is an event and vice versa. The IDI does not consider at categories, IDI calculate sensitivity and specificity for full model and for model with removing new biomarker. Let IS denote integral sensitivity over all possible cut-off, and IP represent the corresponding integral of 'one minus specificity' [16]. The IDI is as follows:

$$IDI=(ISnew-ISold)-(IPnew-IPold) \quad (2)$$

Conflict of interest

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References

[1] Institute NC. "biomarker". NCI Dictionary of Cancer Terms.
[2] Colburn W, DeGruttola V, DeMets D, Downing G, Hoth D, Oates J, et al. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Biomarkers Definitions Working Group. Clin Pharmacol Ther 2001;69:89-95.
[3] Jenkins M, Flynn A, Smart T, Harbron C, Sabin T, Ratnayake J, et al. A statistician's perspective on biomarkers in drug development. Pharm Stat 2011;10:494-507.
[4] Schilsky RL, Halabi S. Oncology Clinical Trials: Successful Design, Conduct and Analysis: Demos Medical Publishing; 2009.
[5] Mayeux R. Biomarkers: potential uses and limitations. NeuroRx 2004;1:182-8.
[6] Gosho M, Nagashima K, Sato Y. Study designs and statistical analyses for biomarker research. Sensors (Basel) 2012;12:8966-86.
[7] Mandrekar SJ, Sargent DJ. Clinical trial designs for predictive biomarker validation: theoretical considerations and practical challenges. J Clin Oncol 2009;27:4027-34.
[8] Mandrekar SJ, Sargent DJ. Clinical trial designs for predictive biomarker validation: one size does not fit all. J Biopharm Stat 2009;19:530-42.
[9] Simon R. Biomarker based clinical trial design. Chin Clin Oncol 2014;3:39.
[10] Simon R, Maitournam A. Evaluating the efficiency of targeted designs for randomized clinical trials. Clin Cancer Res 2004;10:6759-63.
[11] Freidlin B, Simon R. Adaptive signature design: an adaptive clinical trial design for generating and prospectively testing a gene expression signature for sensitive patients. Clin Cancer Res 2005;11:7872-8.
[12] Jiang W, Freidlin B, Simon R. Biomarker-adaptive threshold design: a procedure for evaluating treatment with possible biomarker-defined subset effect. J Natl Cancer Inst 2007;99:1036-43.
[13] Wang SJ, O'Neill RT, Hung H. Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset. Pharm Stat 2007;6:227-44.
[14] Zhou X, Liu S, Kim ES, Herbst RS, Lee JJ. Bayesian adaptive design for targeted therapy development in lung cancer--a step toward personalized medicine. Clin Trials 2008;5:181-93.
[15] Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11-21.
[16] Pencina MJ, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157-72.