

## 【Grant-in-Aid for Scientific Research (S)】

### Integrated Disciplines (Informatics)



**Title of Project : Comprehensive research on statistical methodologies and their applications for development of personalized medicine**

Shigeyuki Matsui  
(Nagoya University, Graduate School of Medicine, Professor)

Research Project Number : 16H06299 Researcher Number : 80305854

Research Area : Statistical science

Keyword : genomic data analysis, personalized medicine, design and analysis of clinical studies

#### 【Purpose and Background of the Research】

Recent advances in biotechnology have accelerated the development of personalized medicine, which uses patient-specific molecular characteristics to optimize diagnosis and treatment. In oncology, for example, molecularly targeted therapies have become the mainstay, often yielding better outcomes than conventional chemotherapies. Such treatments frequently involve substantial inter-patient variation in clinical effects. Consequently, traditional approaches to efficacy assessment based on average benefit across the patient population are often inappropriate, elevating the risk of overtreatment or loss of therapeutic opportunities.

To promote personalized medicine, we must seek new paradigms for the development of diagnostics (Dx) that are capable of identifying patient-specific drug responses (e.g., molecular biomarkers).

#### Phase 1: Development of Dx

- Hierarchical modeling and empirical Bayes, merged with machine learning
- Modeling multi-omics/genetic heterogeneity in disease classification
- Biomarker screening in exploratory clinical trials/observational studies

#### Phase 2: Validation of Dx

- Assessment of predictive accuracy of omics-based predictors
- Study design for external validation
- Internal validation within exploratory clinical trials/observational studies

#### Phase 3: Testing of efficacy/safety of Rx based on Dx

- Enrichment, marker-stratified, and other approaches
- Adaptive designs, bias correction in estimating treatment efficacy
- Applicability of the prospective-retrospective approach

#### Phase 4: Evaluation of clinical utility/decision-making tools

- Meta-analysis of Rx/Dx
- Risk-benefit assessment of Rx/Dx
- Decision-making tools for treatment selection on individual patients

#### 【Research Methods】

The development of personalized medicine is divided into four phases, as shown below.

We will create new interventional and observational clinical study designs, as well as statistical methods and tools for data analysis, to assist at each of these stages.

Specifically, we will focus on case studies of a variety of cancers, rheumatoid arthritis (autoimmune disease), diabetes mellitus, and other types of disorders. Interdisciplinary collaborations will play key roles in this wide-ranging project. The work builds on a coordinated network of biostatisticians, statistical scientists, and physicians/biomedical researchers.

#### 【Expected Research Achievements and Scientific Significance】

The novel statistical methods that will be generated over the course of this project will help to achieve a paradigm shift in clinical development. We expect that the methodologies that we create during this project will significantly increase the likelihood of successfully bringing personalized medicine to clinical practice.

In relation to biostatistics and clinical epidemiology, our efforts will help establish “personalized evidence-based medicine” (pEBM), a new therapeutic framework that takes advantage of individualized diagnostic assessment. pEBM will improve the therapeutic risk-benefit profile and help reduce health care costs to society.

From the perspective of statistical science, this project will open a new methodological arena in which statistical or causal inference will meet predictive analysis. Heretofore, these topics have been addressed independently of each other.

#### 【Publications Relevant to the Project】

- Matsui S, Buyse M, Simon R. (2015). Design and Analysis of Clinical Trials for Predictive Medicine. Chapman & Hall/CRC Press.
- Matsui S, Simon R, et al. (2012). Developing and validating continuous genomic signatures in randomized clinical trials for predictive medicine. Clin Cancer Res. 18, 6065-73.

【Term of Project】 FY2016-2020

【Budget Allocation】 87,500 Thousand Yen

#### 【Homepage Address and Other Contact Information】

<http://www.nagoya-biostat.jp>