Progress report 2022

Department of Biostatistics & Bioinformatics

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■　Introduction and Organization

Biostatistics is an applied statistics in the fields of medical and health sciences and contributes to these fields through developments of statistical methodologies for clinical trials and epidemiological researches. Biostatisticians who work at an organization for conducting and coordinating clinical researches (e.g., academic research organization) in hospitals and institutions are few in Japan. To this end, the Japan funding agency, Agency for Medical Research and Development (AMED), started the Support Program for Biostatiscians from 2016.

This program, with the objective of cultivating talent of excellent biostatisticians, supports the efforts of training them through collaboration between graduate schools that conduct school education, and hospitals that conduct practical training.

In FY2016, the AMED selected the Graduate School of the University of Tokyo and the Graduate school of the Kyoto University, as 2 centers for training biostatisticians, which function as core facilities, respectively. Each graduate school developed a new biostatistics course, forms a training center upon collaboration with a hospital, and performs on-the-job training (OJT).

This program improves the environment that leads to higher quality in clinical research and trials, with the collaboration of industry, academia, and the government, based upon the donations from drug companies and national research funding. Collaborative projects of industry, academia, and the government through the flow of funds in this program, are the first of their kind in Japan.

On March 1, 2017, the Department of Biostatistics and Bioinformatics was established in the Graduate School of Medicine. In the Graduate School of Interdisciplinary Information Studies in the University of Tokyo, the Biostatistics and Bioinformatics course was established on April 1, 2018. This course provides specialized education to acquire not only statistical methodologies, but also practical skills (e.g., design and analysis of clinical research, programming, reporting) for conducting clinical research. We train biostatisticians with high communication skill and ethics that can promote high quality research in collaboration with health care professionals by teaching and OJT.

Ten first-term master's students completed in March 2020, eight of whom got employment at academic medical institutions. Eight second-term master's students completed their studies in March 2021, and all of them got a job at academic medical institutions. Nine third-term

master's students completed their studies in March 2022, and eight of them got a job at academic medical institutions. Seven fourth-term master's students completed their studies in March 2023, and five of them got a job at academic medical institutions. AMED has renewed this project for more 5years since FY2021

■ Research Activities

1) Education in the Biostatistics and Bioinformatics course

In the Biostatistics and Bioinformatics course, through the following teachings, we educate a wide range of knowledge and skills required to biostatisticians. Its curriculum is made up of 28 subjects including 43 credits. For students who have taken over 40 credits, we issue a certificate along with the Master degree. Five fourth-term master's students who completed the program in March 2023 were awarded this certificate, and total of 30 master's students from the first-term were awarded the certificate. Eleven master's students as the fifth-term have enrolled in April 2022.

2) Statistical methodology and design of clinical trials and epidemiology

We study on the statistical methodologies and design for streamlining clinical trial and estimating treatment effect precisely. The research area includes Bayesian design in oncology, clinical trial design using biomarkers, adaptive design, and study on the use of Bayesian statistics in clinical trials, causal inference, and multiple comparison method.

3) Epidemiological methodology

Epidemiology deals with health or disease related incidence quantitatively in large populations, evaluates cause and effective factors, and ultimately finds the measures of prevention. It starts from epidemics (such as infectious diseases) and now its focus is on lifestyle related diseases, such as cardiovascular disorders. Also, several kinds of medical databases are developed rapidly in Japan. It is important to conduct epidemiological, pharmacoepidemiological and clinical epidemiological studies using such databases.

4) Pharmacoepidemiology

Pharmacoepidemiology is a study to investigate drug use and its effects in a population. We are engaged in research on effectiveness, risk, and cost using data obtained from hospital information system and electronic medical record.

5) Clinical Epidemiology

Clinical epidemiology is the application of the principles and methods of epidemiology to conduct clinical research studies focusing on prevention, diagnosis, prognosis, and treatment of disease. As the basic science of Evidence-based Medicine (EBM), the importance of clinical epidemiology has been increasing.

6) Medical informatics

Medical informatics is a science of studying how to use data, information and knowledge in the all medical fields, such as clinical, medical studies, education and government. Recently, the area of medical informatics is much expanding because of the progress of genomic studies or bioinformatics, and introduction of new technologies, such as virtual reality and artificial intelligence (AI).

7) Algebraic statistics

The focus of research is on developing and applying methods of algebraic statistics to specific statistical problems. In statistical inference, the computation of complicated integrals or summation sometimes makes the problem intractable. When a statistical model has algebraic structure, techniques from algebraic statistics are useful. We currently work on the topics related to Markov basis theory and the holonomic gradient method.

■ Future Directions

It has decided to continue the project for another

five years as AMED project to promote the development of biostatisticians since FY2021. Moreover, we will continuously provide one more year of post-graduate education for graduates who are employed as biostatisticians at medical institutions in academia. Also, entrance examinations should be conducted in the summer to select master's students who will enroll in the Biostatistics and Informatics Course of the Interfaculty Initiative in Information Studies and the Graduate School of Interdisciplinary Information Studies, and provide them with the education they need to become biostatisticians, as well as post-graduate education. On the other hand, public lectures on biostatistics for the general public will be provided to contribute to the enlightenment of biostatistics. In addition to the development of new clinical research designs and analysis methods, we will develop human resources capable of conducting analyses using big data such as large-scale medical databases, which are expected to increase in the field of clinical research in the future.

■ Publications
Articles (In English)

1. Facile R, Muhlbradt EE, Gong M, Li Q, Popat V, P?tavy F, Cornet R, Ruan Y, Koide D, Saito TI, Hume S, Rockhold F, Bao W, Dubman S, Jauregui Wurst B. Use of Clinical Data Interchange Standards Consortium (CDISC) Standards for Real-world Data: Expert Perspectives From a Qualitative Delphi Survey. JMIR Med Inform. 2022 Jan 27;10(1):e30363. doi: 10.2196/30363. PMID: 35084343; PMCID: PMC8832264.

2. Nishikawa A, Yoshinaga E, Nakamura M, Suzuki M, Kido K, Tsujimoto N, Ishii T, Koide D. Validation Study of Algorithms to Identify Malignant Tumors and Serious Infections in a Japanese Administrative Healthcare Database. Annals of Clinical Epidemiology. 4(1): 20-31. 2022. Doi: https://doi.org/10.37737/ace.22004

3. Watanabe K, Yoh K, Hosomi Y, Usui K, Naka G, Kishi K, Uemura K, Ohashi Y, Kunitoh H. Efficacy and safety of first-line osimertinib treatment and postprogression patterns of care in patients with epidermal growth factor receptor activating mutation-positive advanced non-small cell lung cancer (Reiwa study): study protocol of a multi-centre, real-world observational study. British Medical Journal Open 2022; 12(1):e046451.

4. Naka G, Yokoyama T, Usui K, Ishida H, Kishi K, Uemura K, Ohashi Y, Kunitoh H. Final report on plasma ctDNA T790M monitoring during EGFR-TKI treatment in patients with EGFR mutant non-small cell lung cancer(JP-CLEAR trial). Japanese Journal of Clinical Oncology, 2022, 1-5.

5. Kawahara T, Iwamoto T, Takashima I, Hanazawa R, Uemura K, Uemura Y, Mukai H, Kikawa Y, Taira N. Association of change in health-related quality of life and treatment discontinuation in metastatic breast cancer: a post hoc, exploratory analysis of two randomized clinical trials. Support Care Cancer. 2022 Oct;30(10):8367-8375. doi: 10.1007/s00520-022-07283-0. Epub 2022 Jul 20. PMID: 35857127; PMCID: PMC9512887.

6. Takeuchi Y, Iwagami M, Ono S, Michihata N, Uemura K, Yasunaga H. A post-marketing safety assessment of COVID-19 mRNA vaccination for serious adverse outcomes using administrative claims data linked with vaccination registry in a city of Japan. Vaccine. 2022;40(52):7622-7630.

7. Shoji S, Kuroda S, Uemura K, et al. Risk Factors for Severe Erectile Dysfunction after Focal Therapy with High-Intensity Focused Ultrasound for Prostate Cancer. Biomedicines. 2022;10(11):2876.

8. Ogawa M, Nakamoto K and Sei T. On the fractional moments of a truncated centered multivariate normal distribution. Comm. Statist. Simulation Comput., 51(7):3923-3942, 2022.

9. Nakachi K, Ikeda M, Konishi M, Nomura S, Katayama H, Kataoka T, Todaka A, Yanagimoto H, Morinaga S, Kobayashi S, Shimada K, Takahashi Y, Nakagohri T, Gotoh K, Kamata K, Shimizu Y, Ueno M, Ishii H, Okusaka T, Furuse J, Hepatobiliary and Pancreatic Oncology Group of the Japan Clinical Oncology G. Adjuvant S-1 compared with observation in resected biliary tract cancer (JCOG1202, ASCOT): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet. 2023. 401(10372): 195-203.

10. Nakamura Y, Okamoto W, Denda T, Nishina T, Komatsu Y, Yuki S, Yasui H, Esaki T, Sunakawa

Y, Ueno M, Shinozaki E, Matsuhashi N, Ohta T, Kato K, Ohtsubo K, Bando H, Hara H, Satoh T, Yamazaki K, Yamamoto Y, Okano N, Terazawa T, Kato T, Oki E, Tsuji A, Horita Y, Hamamoto Y, Kawazoe A, Nakajima H, Nomura S, Mitani R, Yuasa M, Akagi K and Yoshino T. Clinical Validity of Plasma-Based Genotyping for Microsatellite Instability Assessment in Advanced GI Cancers: SCRUM-Japan GOZILA Substudy. JCO Precis Oncol. 2022. 6: e2100383.

11. Morizane C, Machida N, Honma Y, Okusaka T, Boku N, Kato K, Nomura S, Hiraoka N, Sekine S, Taniguchi H, Okano N, Yamaguchi K, Sato T, Ikeda M, Mizuno N, Ozaka M, Kataoka T, Ueno M, Kitagawa Y, Terashima M, Furuse J and Japan Clinical Oncology G. Effectiveness of Etoposide and Cisplatin vs Irinotecan and Cisplatin Therapy for Patients With Advanced Neuroendocrine Carcinoma of the Digestive System: The TOPIC-NEC Phase 3 Randomized Clinical Trial. JAMA Oncol. 2022. 8(10): 1447-1455.

12. Terashima T, Morizane C, Ushiama M, Shiba S, Takahashi H, Ikeda M, Mizuno N, Tsuji K, Yasui K, Azemoto N, Satake H, Nomura S, Yachida S, Sugano K and Furuse J. Germline variants in cancer-predisposing genes in pancreatic cancer patients with a family history of cancer. Jpn J Clin Oncol. 2022. 52(10): 1105-1114.

13. Niguma K, Mamishin K, Naito Y, Nomura S, Wakabayashi M, Kusuhara S, Funasaka C, Nakao T, Fukasawa Y, Kondoh C, Harano K, Kogawa T, Matsubara N, Hosono A, Onishi T, Kawasaki T and Mukohara T. Impact of Older Age and Medico-social Factors on the Decision to Offer Adjuvant Chemotherapy to Patients With Breast Cancer. Anticancer Res. 2022. 42(7): 3743-3751.

14. Hasegawa H, Tsukada Y, Wakabayashi M, Nomura S, Sasaki T, Nishizawa Y, Ikeda K, Takeshita N, Teramura K and Ito M. Impact of near-infrared fluorescence imaging with indocyanine green on structural sequelae of anastomotic leakage after laparoscopic intersphincteric resection of malignant rectal tumors. Tech Coloproctol. 2022. 26(7): 561-570.

15. Kojima T, Kato K, Hara H, Takahashi S, Muro K, Nishina T, Wakabayashi M, Nomura S, Sato A, Ohtsu A and Doi T. Phase II study of BKM120 in patients with advanced esophageal squamous cell carcinoma (EPOC1303). Esophagus. 2022. 19(4): 702-710.

16. Aso S, Ono S, Michihata N, Uemura K, Yasunaga H. Effectiveness of vaccination on influenza-related critical illnesses in the elderly population. J Infect Chemother. 2023;S1341-321X(23)00037-5.

■ International Conference Presentation

1. Ogawa M. Estimating parameter of discrete exponential families using Markov bases under the presence of nuisance parameters. Algebraic Statistics 2022, University of Hawaii at Manoa, Honolulu, USA, May 16-20, 2022.

2. Yuki S, Sunakawa Y, Yamazaki K, Shirasu H, Taniguchi H, Masuishi T, Shiozawa M, Bando H, Nishina T, Yasui H, Ohta T, Takahashi N, Denda T, Esaki T, Kawakami H, Satake H, Takashima A, Abe Y, Nomura S, Yoshino T. Analysis of plasma angiogenesis factors on the efficacy of 1st-line (1L) chemotherapy (chemo) combined with biologics in RAS wild-type metastatic colorectal cancer (mCRC); Results from GI-SCREEN CRC Ukit study. American Society of Clinical Oncology (ASCO) Annual Meeting, 2022. Chicago, USA (June 3-7, 2022). (poster)

3. Yamakawa A, Nomura S. Recommending a timing for a stop for efficacy in group sequential trials with a survival endpoint. Abstract S1.3. 43rd Annual Conference of the International Society for Clinical Biostatistics (ISCB), Newcastle upon Tyne, UK. (August 21-25, 2022). (oral)

4. Yuki S, Sunakawa Y, Yamazaki K, Shirasu H, Taniguchi H, Masuishi T, Shiozawa M, Bando H, Nishina T, Yasui H, Ohta T, Takahashi N, Denda T, Esaki T, Kawakami H, Satake H, Takashima A, Abe Y, Nomura S, Yoshino T. Analysis of plasma angiogenesis factors on the efficacy of 2nd-line chemotherapy combined with angiogenesis inhibitors in metastatic colorectal cancer (mCRC): Results from GI-SCREEN CRC Ukit study. The annual European Society for Medical Oncology (ESMO) congress, 2022. Paris, France (Sep 9-13, 2022). (poster)

5. Izumi H, Sakamoto T, Uchibori K, Nishino K, Sakakibara-Konishi J, Nomura S, Katayama R,

Udagawa H, Shibata Y, Ikeda T, Niho S, Sakai T, Zenke Y, Nosaki K, Matsumoto S, Yoh K, Goto K. Phase I study of brigatinib plus panitumumab in patients with advanced EGFR-mutated non-small cell lung cancer resistant to osimertinib (BEBOP): early termination due to severe early onset pneumonitis by brigatinib. The annual European Society for Medical Oncology (ESMO) congress, 2022. Paris, France (Sep 9-13, 2022). (poster)

6. Okuma Y, Nomura S, Ninomiya K, Yamaguchi H, Murakami S, Kogure Y, Harada D, Okishio K, Okamoto H, Goto Y. EPONA, Efficacy of osimertinib with platinum and pemetrexed in EGFR mutant non-small cell lung cancer patients bearing CNS metastasis, and have systemic progression but stable intracranial disease on Osimertinib resistance (TORG 1938). The annual European Society for Medical Oncology (ESMO) congress, 2022. Paris, France (Sep 9-13, 2022). (poster)

7. Mitsunaga S, Ikeda M, Nomura S, Morizane C, Todaka A, Kamei K, Yanagibashi H, Mizuno N, Gotoh K, Kawamoto Y, Shirakawa H, Okano N, Nomura T, Makino I, Takahashi A, Anbo Y, Ohta K, Katayama H, Konishi M, Ueno M. Effects of gene expressions of 5-FU metabolic pathway in a phase III trial evaluating adjuvant S-1 compared to surgery alone following curative resection for biliary tract cancer (JCOG1202A1). 2023 Gastrointestinal Cancers Symposium. San Francisco, USA (Jan 19-21, 2022). (poster)