# How to select appropriate medical real world database to meet your research question

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Recently, the importance of observational clinical studies utilizing real world data (RWD) is highlighted. In Japan, so far large scale medical databases including claims data, prescription data, and DPC data have been utilized for the clinical epidemiology and pharmacoepidemiology studies, however, outcomes evaluation has been limited due to lacking of laboratory data. Therefore, starting from 2015, we are currently developing large scale electrical medical record (EMR)-derived database in Japan for the clinical epidemiology studies. We also focus on the development of the health checkup databases of newborn, infant, and children population, under the contract with more than 140 Japanese local city governments. These activities and the future opportunities for clinical research and preventive medicine will be discussed.

# Clinical epidemiological and pharmacoepidemiological studies using the Diagnosis Procedure Combination database.

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With respect to study design, randomized control trials (RCT) are considered the gold standard in assessing the efficacy and safety for different medications. However, in addition to the issues of appropriateness, ethics, feasibility, time and costs in RCTs, the generalizability of the findings is argued because of the highly selected group of patients included in RCTs. Real-world studies using a large database, which consists of routinely collected clinical data, are complementary to RCTs in the sense that the patient populations are much more generalizable, and are becoming more common. Using the Diagnosis Procedure Combination (DPC) database, which is a nationwide database and covers approximately 50% of the acute-care inpatients in Japan, we conducted a retrospective cohort study evaluating the efficacy of several drugs including Japanese herbal Kampo medicine. Propensity score utilizing methods were adopted in these studies. Examples of our studies using the DPC database will be presented and the advantages and limitations of the studies will be discussed.

# Descriptive epidemiology of prescriptions of drugs listed in Screening Tool for Older Person's appropriate Prescriptions in Japanese (STOPP-J) in older adults: results from National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB)

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National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) is the largest insurance claim database in Japan. The aim of NDB is to analyze health care services provided by health insurance in Japan based on the Act on Assurance of Medical Care for Elderly People (2008). At the end of 2014, approximately 90% of all the health insurance claims were stored in NDB. In the present study, we described the proportion of prescription of drugs listed in Screening Tool for Older Person's appropriate Prescriptions in Japanese (STOPP-J) as those that require careful administration in older adults, using the data from NDB. Participation was limited to those who were aged equal to or more than 75 years and received any medical care provided by health insurance during the 2010-2014 period. Results suggest that more than 60% of the subjects had experiences to be regularly prescribed at least one of the drugs listed in STOPP-J. Although the prescriptions which examined in the present study do not mean inappropriate medications, further considerations for types of drugs might be required when doctors prescribe some drugs for older patients in actual clinical settings.

# Challenge to the future life with Real World Data

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The Health, Care and Educational Information Evaluation Promotion Organization (HCEI) has established a database centered on electronic medical records in collaboration with 180 medical institutions since 2015. As a characteristic of this database, it contains not only data of DPC and receipt already, but also test results and death data. As a result, we can conduct outcome research to measure the effects of drugs and treatments.
Our database is not dependent on vendors and register in the database about 19 million patients. Based on JLAC10, it has standardized 1000 kinds of inspections (with unit / sample classification), and it becomes a useful database for post marketing surveillance etc.
In addition, we have also started a project to collect data in the registry and the data extraction in the randomized controlled trial conducted by the academic society, and we are promoting efforts to eliminate the load of data extraction in the hospitals. Since effective utilization of medical data is a major cornerstone for drug discovery or quality improvement of medical treatment, we would like to continue to develop the database for the promotion of primary and secondary use of medical information and to save future lives.

# Pharmacological research development based on medical big data (disease name, Lab tests, medication, etc.) of 2 million patients at Nihon University Hospital for 15 years

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Nihon University, having been striving for the further improvement of medical progress and medical services, is engaged in research concerning the utilization of information from daily clinical practice, and in 2004 has constructed the clinical data warehouse (CDW) known as "Nihon University School of Medicine's Clinical Data Management System" (NUSM's CDMS) As of March 2019 for 15years, this system stores over 2.43 million patient profiles, medical history data for 1.27 mil. patients (24 mil. records), drug prescription data of 690,000 patients (40 mil. records), injection medicine prescription data of 270,000 patients (17.5 mil. records), and clinical test data of 800,000 patients (440 mil. records). This system possesses a sufficient amount of information for highly reliable statistical analysis. We have announced to international journals our research thus far that utilizes this abundance of information, which includes studies of the additional effects in hypertensive drugs (add-on effects), and of the side-effects that occur in the combined use of antithrombotic drugs. NUSM's CDMS is a healthcare database based on information from daily clinical practice and furthermore constructed on the premise of use in research, already at a sufficiently practical level. In observational studies using NUSM'S CDMS, the drug effects, or so-called "effectiveness", in actual clinical settings, which cannot be understood through randomized clinical trials (RCTs) carried out in limited environments, are able to be verified and helpful evidence provided.

# Pharmacological study by bidirectional approach between bench and bedside: novel evidence from risk factor analysis in cancer patients undergoing chemotherapy

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Chemotherapy-induced peripheral neuropathy (CIPN), a potentially dose-limiting toxicity, impairs the quality of life in cancer patients, whereas there are no effective countermeasures for prevention or treatment of CIPN. Our fundamental studies have demonstrated the critical role of HMGB1, a DAMP molecule, in the development of CIPN following treatment with paclitaxel, vincristine, oxaliplatin, etc. in rodents, and indicated that anti-HMGB1-neutralizing antibodies and thrombomodulin alfa capable of inactivating HMGB1 are useful in inhibiting the development of CIPN. Our retrospective cohort studies in cancer patients undergoing chemotherapy have shown that hepatocellular damage is associated with increased severity of CIPN following oxaliplatin treatment, and that women with breast cancer over menopause age have a higher risk for the incidence of CIPN following paclitaxel treatment. Our animal experiments conducted on the basis of those clinical findings have revealed that experimentally induced hepatocellular damage and ovariectomy aggravate the CIPN caused by oxaliplatin and paclitaxel, respectively, in an HMGB1-dependent manner. Collectively, bidirectional studies between bench and bedside unveil previously unknown risk factors for the incidence and/or increased severity of CIPN, in which HMGB1 might play an essential role.

# Approach to drug discovery integrating large-scale medical information databases with clinical and basic research

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In recent years, large-scale medical information databases for diseases and their related side effects have been used to accurately assess the effects and side effects of clinically used drugs. Integration of basic and clinical research with medical information databases can enable various analyses based on real-world data. We used this approach to improve the quality of cancer treatment by developing drugs to reduce the side effects caused by anticancer drugs. Focusing on acute kidney injury (AKI) caused by cisplatin (CDDP), we found that several existing drugs suppress the occurrence of CDDP-induced AKI in the FAERS (FDA Adverse Event Reporting System). *In vitro* and *in vivo* experiments revealed that administration of candidate drugs extracted by FAERS analysis significantly suppressed CDDP-induced AKI. These results suggest that the existing pharmaceutical products selected using FAERS could prevent CDDP-induced AKI. Effective use of medical data is a major cornerstone for drug discovery and improvement of the quality of life for patients with cancer. This novel strategy will provide a means to expand the possibilities of drug delivery and to elucidate mechanisms of unknown diseases.

# The impact of hypothesis and prediction in data-driven pharmacological studies

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Recent pharmacological studies have been developed based on the finding of new disease-related gene, which is accompanied with the production of gene-manipulated disease model animals and high-affinity ligands for the target protein. However, emergence of the gene-based strategy has led to the rapid deprivation of drug target molecules. To overcome this situation, we have been trying to utilize clinical big data to explore a novel and unexpected hypothesis of drug-drug interaction that leads to the drug repositioning. Here, we introduce our data-driven approach in which adverse self-reports, JMDC claims database and University hospital health records are analyzed and compared to find and validate new drug targets. We also present our recent effort to predict the binding affinity of theoretically any chemical ligands to a target protein by deep learning of chemical structures and their measured affinity to the target with graph convolutional neural network. The hypothesis and prediction provided by data-driven approaches will impact on the style of pharmacological study.