'Mahoro' speeds up Keio's DNA sequencing system, PleSSision-Exome.

A NEW WHOLE-EXOME SEQUENCING PLATFORM MAKES THE CASE FOR BROADER PRECISION CANCER CARE

KEIO UNIVERSITY is leading one of Japan's largest precision oncology projects using a new whole-exome sequencing platform.

Genetic testing platform PleSSision-Exome, a DNA sequencing system that covers more than 19,000 different genes, could help expand personalized cancer medicine in Japan. Developed by Hiroshi Nishihara, a pathologist who heads the Genomics Unit at Keio Cancer Center, it's the first clinically available assay of its kind in Japan and involves the analysis of the entire exome, the protein-coding portion of the genome.

In 2019, Japan's healthcare system made its first major step towards financially supporting personalized cancer care when the country's health insurance system agreed to cover the cost of two tests that analyse multiple genes for cancer-associated mutations, enhancing the ability of doctors to tailor treatments to the specific genomic profile of a patient's cancer.

However, these tests are not a panacea and don't cover all cancer genes. Additionally, doctors are constrained by restrictions on testing before patients have failed standard chemotherapy, and further by prohibitions on off-label drug use. Consequently, only 1–2% of cancer patients in Japan ever undergo genetic testing.

To support an expansion of personalized medicine for cancer, under the leadership of Yuko Kitagawa, a director general at Keio University Hospital, Keio clinicians are now spearheading one of the largest precision oncology trials ever conducted in Japan.

CLINICIANS ARE RECRUITING FOR A CLINICAL TRIAL IN WHICH PARTICIPANTS WILL HAVE THEIR TUMOUR EXOMES FULLY SEQUENCED

Clinicians at hospitals across the country, including Keio University Hospital, are recruiting thousands of patients for the clinical trial, in which participants will have their tumour exomes sequenced using PleSSision-Exome.

The plan is to match patients to targeted treatments or immunotherapies, based on the molecular markers present in the tumour, and then track how individuals fare as a result of this genomically informed approach. "Our project can build up a huge, real-world database for the Japanese cancer research community," says Nishihara.

He hopes the study will help to provide the scientific evidence needed for the government to continue expanding precision oncology in Japan and make a case for PleSSision-Exome's use, which is not yet covered by Japan's National Health Insurance.

The PleSSision-Exome platform involves some human input from expert diagnosis, but much of the technical work is automated. To facilitate high-throughput analysis on multiple tumour specimens at once, sample preparation is performed by 'Mahoro', a robot codeveloped by Japan's National Institute of Advanced Science and Technology and the Yaskawa Electric Corporation. The DRAGEN supercomputer system from Mitsubishi Space Software then completes much of the bioinformatic interpretation of the genetic data.

Importantly, all the sequencing, analytics and therapeutic recommendations happen at the time of an initial diagnostic biopsy, when targeted drugs have their greatest therapeutic potential, rather than after patients have already exhausted other treatment options.

In a series of case studies, Nishihara and his colleagues have already shown PleSSision-Exome's potential. One middle-aged woman with breast cancer, for example, had no actionable DNA alterations, as gauged by a standard gene panel test. But a mutation found by full exome sequencing revealed that she would probably do well on palbociclib, a drug approved in Japan in 2017. An older man with prostate cancer had similarly run out of therapeutic options until PleSSision-Exome testing suggested a recently approved drug called olaparib might match his tumour. He subsequently received the drug as part of a clinical trial protocol.

"It's very exciting," Nishihara says of the platform's clinical potential. Now, he will work to turn anecdotes into quantitative evidence, which will be added to an open source platform, the Japanese RealWorld Cancer Database.

Drug repositioning studies

Keio Cancer Center is also partnering with basic scientists at the university to create and test *ex vivo* tumour models as part of personalized drug screening studies.

"A combination of genetic testing, stem cell cultures, robot technologies and drug repositioning will allow us to develop new strategies for cancers that don't respond to first-line treatments," explains Hideyuki Saya, a cancer biologist at Keio University School of Medicine.

Nishihara has teamed up with Saya to create tumour organoids — miniature lab-grown cellular models — from patients enrolled in his clinical study. The idea is to mimic the complex architecture of a person's cancer and then to screen hundreds of approved drugs to see which might target the particular vulnerabilities of the tumour.

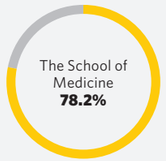
In mouse models, Saya has already found that the combination of an established arthritis drug together with a recently-approved heart disease drug is especially potent against cancer stem cells, which are hardy cells that often fuel tumour growth. But the combination doesn't work in tumours with mutations in a gene called *KEAP1*. Taking that knowledge to the clinic, Saya is now working with Nishihara to find patients, without *KEAP1* mutations and with alterations in other actionable genes, and to observe who might benefit from a drug repositioning strategy.

In his view, it is this marriage of basic biological insights and clinical genomic testing that will ultimately help Keio scientists deliver on the promise of precision cancer medicine. ■

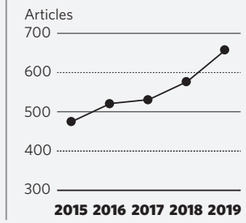
CANCER RESEARCH HUB

KEIO UNIVERSITY SCHOOL OF MEDICINE is a productive focal point for cancer research.

LIFE SCIENCE OUTPUT
The School of Medicine made up 78.2% of the university's life science output in the Nature Index from 2015 to 2018.



CANCER ARTICLES PER YEAR
in the Dimensions database



2019 ARTICLE OUTPUT IN THE NATURE INDEX
Total number (Count): 50; Share*: 13.03

* Share: Takes into account the percentage of authors from that institution and the number of affiliated institutions per article. For the calculation all authors are considered to have contributed equally to the article.

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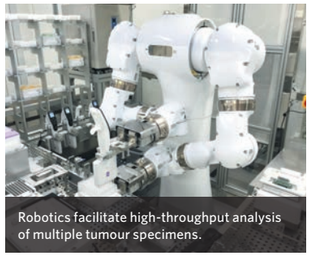
PleSSision-Exome can sequence 19,000 genes.



Robotics facilitate high-throughput analysis of multiple tumour specimens.

The Keio Cancer Center is using PleSSision-Exome to analyse the entire exome.

Keio University

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