

MediCine



SCIENCE OF LIFE

Cancer Detection's Blood Whisperer

Cost effective diagnostic tool expected to contribute immensely in early diagnosis of gastric cancer.

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INSIGHTS

Hospice or Palliative Care, What's in a Name?

Names have powerful meanings and elicit deep responses—and those responses can be decidedly negative.

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COVID-19 Vaccines and Drugs: **Medicine's Armory**

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SCIENCE OF LIFE

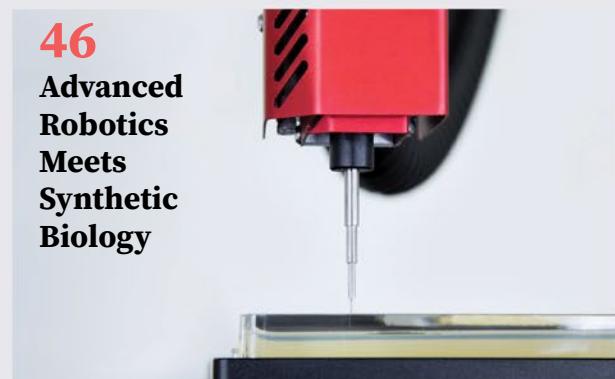
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Dean's Message

Dear Reader,

A year ago, life as we knew it was turned upside-down with the arrival of the coronavirus and the disease that it caused. More than 1.8 million people have been killed by COVID-19, and 80 million around the world were sickened, many requiring hospitalisation.

Fortunately, as 2020 drew to a close, hope dawned on the horizon with news of vaccines being approved and vaccinations commencing in various countries. In Singapore, the government has started encouraging vaccination for first responders and healthcare workers, as well as people who are exposed and vulnerable to COVID-19 even as the country moves to relax rules governing gatherings. Vigilance against the virus remains high however, though we can begin to look forward to a more normal way of life.

Here at NUS Medicine, we rode the roller coaster of events through the long months along with the rest of the country. To the credit of the School, the initial shock and bewilderment gave way quickly to acceptance and then a resolution to adapt our teaching and research work to the new realities.

I salute our staff for the way they rose to the challenge. In the face of



the unknown, colleagues adjusted routines to fit the new normal and strove to make the best out of every situation. Our scientific people contributed their expertise to the search for COVID-19 therapeutics and vaccines and organised weekly webinars to share information about the enemy. Our executives and administrators developed illustrated strips on COVID-19 for public education, while others stepped bravely and selflessly into the unknown, volunteering to serve on the frontlines during the peak of the pandemic.

But the NUS Medicine family is more than just the people who teach, learn and work here. It also comprises our donors, who through their generosity enable so much of what we do, as well as the nearly 20,000 alumni. Many of them have steadfastly supported their alma mater and contributed over the years to the School's growth and development. Some go further. The late Dr Freda Paul Malliamalar (Class of 1954) was an outstanding paediatrician and teacher. When she passed away in 2016, she bequeathed part of her estate to the NUS medical school

in support of underprivileged women medical students. Said Mr Philip Jeyaretnam, who is one of her estate's executors, "I am delighted that Dr Paul's life and career will now be honoured by this significant bequest to NUS Medicine, as she had wanted."

In a year in which so much has been lost, we only need to look carefully to see what has endured, and appreciate their priceless worth. Consider the Class of 2020. They graduated quietly, without pomp and fanfare, and were required to start work early to help lessen the pressure on our healthcare system—something they did so with distinction.

The year 2020 will, for a long time, be seared onto our memories as the year of mask-wearing, frequent handwashing, and social distancing. For the School, it will be remembered as the year of rapid adjustments, perseverance and triumph as we improvised, adapted and continued with our mission of educating and training future generations of healthcare professionals. In a year of deeply unsettling challenges posed by COVID-19, I am proud of the resounding answers that our staff and students provided to the existential questions posed by the virus.

Yours sincerely,

Yap Seng

MediCine

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Yong Loo Lin
School of Medicine

NUS Yong Loo Lin
School of Medicine
1E Kent Ridge Road
NUHS Tower Block, Level 11
Singapore 119228
Tel 6772 3737
Fax 6778 5743
Email medmedia@nus.edu.sg
Web medicine.nus.edu.sg

Follow us on

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NUS Yong Loo Lin
School of Medicine

Celebrating MEGIC at NUS Medicine Educators' Day 2020



Teachers are among the unsung heroes of the COVID-19 pandemic. They deftly adapted to the Circuit Breaker that brought traditional teaching to a screeching halt, finding alternative means to connect with and care for their students. Our educators have persevered and are continually adjusting their teaching to accommodate the necessary safety measures, innovating in order to impart their knowledge despite the continued restrictions on clinical training. Therefore, in special recognition of our educators, NUS Medicine collaborated with NUHS to organise a month-long series of events "Celebrating Education as OneNUHS" from 18 September 2020.

A special programme was dedicated to celebrating education and educators, who held webinars, Grand Round Talks and other activities. This included an introduction to medical humanities by Assistant Professor Michael Stanley-Baker and a discussion of the concept of “self-identity” by Dr Alison Tan. Professor Esuvaranathan Kesavan shared his insights on coaching in medicine, while Associate Professor Tan Chay Hoon, Associate Professor Celestial Yap and Dr Inthirani Raja Indran spoke about the impact of disruptive behaviour in healthcare.

In addition, there was a complementary series of online thematic sharing sessions on education innovation, to share inspiration and ideas to enhance medical teaching. Associate Professor Alfred Kow presented how gamification and virtual reality could be integrated to enhance the inter-professional training of patient safety. Associate Professor Nicola Ngiam showcased the use of standardised patients to effectively provide students with an alternative to real patient contact, which is especially relevant given COVID-19 restrictions. Finally, Professor Edmund Lee, Dr Soh Jian Yi, Dr Judy Sng Chia Ghee and Dr Chen Zhi Xiong contributed to a panel discussion about the use of virtual patients in training clinical reasoning skills.

NUS Medicine Educators' Day: celebrating innovation and resilience

The activities culminated in NUS Medicine Educators' Day on 23 October 2020. The focus remained on innovation, with the highlight of the event being the finals of the inaugural Medical Education Grand Innovation



14

teams worked on ideas for the inaugural Medical Education Grand Innovation Challenge, or MEGIC

Challenge (MEGIC). Similar to the Medical Grand Challenge for students, this competition is in line with the School's efforts to enhance the effectiveness of student learning through advances in pedagogy and technology.

14 teams worked to propose solutions that address unmet needs and opportunities to enhance medical education. These teams included members from different professions, disciplines and institutions, which was an encouraging sign of multidisciplinary collaboration.

Eight teams were eventually selected for the finals on Educators' Day, which was conducted entirely online. They presented their work to an esteemed panel of judges who included Vice-Provost Associate Professor Erle Lim; Professor Lakshminarayanan Samavedham, Director of the Institute for Applied Learning Sciences and Educational Technology (ALSET); and Associate Professor Lau Tang Ching, NUS Medicine Vice-Dean of Education. The judging was moderated by Dr Dujeepa Samarasekera, Director of the Centre for Medical Education (CenMED).

Invited guest Professor Lambert Schuwirth delivered a keynote address on “Developing resilience and innovation in medical education research”. Prof Schuwirth is the Strategic Professor in Medical Education at the College of Medicine and Public Health, Flinders University, Australia. He is also the Director of the Flinders University Prideaux Centre for Health Professions Education.

Prof Schuwirth discussed how the role of a teacher has evolved from one of an “enabler” to “partner” and “nurture” students. Teachers help students to “make meaning” and overcome as well as learn from adverse events. The

value proposition of medical education itself needs to be reconsidered, as one comes to consider the journey of learning and discovery instead of only concentrating on the final ‘product’.

Medical education innovation requires an understanding of key fundamental principles—human learning, assessment and medical education research itself, which is distinct from clinical research. To develop appropriate solutions, it is important to understand how society itself has changed and how preferences of students today have evolved. As such, innovation in this field includes a need to curate problems (not just solutions) and facilitate online collaborations and peer-to-peer engagement in support of learning. Despite the bleak situation in which the world now finds itself, Prof Schuwirth expressed the hope that it might spark a variety of new ideas.

The Educators' Day event concluded with a special segment in appreciation of staff who received the NUS Medicine Fortitude Award. This award was given to educators and administrators who went beyond the call of duty to enable NUS Medicine to complete the academic year and graduate the AY2019 cohort of doctors. Thanks to the tremendous effort of these award recipients during the initial months of the COVID-19 pandemic, the School was able to successfully adapt and continue teaching, assessment and other activities.

Scan for an
in-depth
look at the
innovations
under MEGIC:



The following teams won prizes at the finals of the inaugural Medical Education Grand Innovation Challenge (MEGIC).



Grand Prize

Team **Sanctum** won the **Grand Prize** for developing a prototype of a pharmacology quiz application to promote active learning and higher order thinking. This application reinforces students' knowledge of different drugs through "Drug Cards" and "Knowledge Buckets", then offers a "Question Bank" for students to apply their learning, with progress reports generated as a means of providing user data analytics for both student and faculty use.

Team members: Matthew Chew, Chua Yun Da, Gabriel Tan, Daniel Chew, Ryan Tan, David Chew, Ryan Tian, Nicole Tan, Nicholas Jin, Victoria Leong and Kim Haejin.



2nd Prize

Team **Surgical Anatomy** won the **Second Prize** for their project titled "Teaching of Normal and Abnormal Human Structure Through the Use of Surgical Videos". This collaboration between the NUS Departments of Surgery and Anatomy saw the production of guided video tutorials using surgical footage to teach anatomy, effectively integrating preclinical and clinical teaching.

Team members: Assoc Prof Dinesh Kumar Srinivasan, Dr Chong Choon Seng, Dr Ian JW Tan, Prof Hooi Shing Chuan, Caroline Zamora Bersalona and Nicholas Wong.



3rd Prize



Best Video award

Team **Medicine Learning & Teaching RoadmapApp (MLTR)** won the **Third Prize and Best Video award** for their project "Compass 2.0", which sought to make "Compass", the 1,000-page NUS Medicine curriculum document, easier to navigate by converting it into an app. In doing so, the team also aims to empower students and enhance their learning while improving tutors' oversight of their students.

Team members: Liu Ching Man, Dr Norshima Binte Nashi, Shelvi, Dr Lionel Lum, Leong Yong Shin and Chong Voon Foo.



Special Mention award

Team **MRI Safety in Healthcare** won a **Special Mention award** for their project on "Gamification as a learning tool for MRI safety", which created games to promote magnetic resonance safety for staff in the radiology department. For example, one game provides training for work using a virtual radiology department.

Game-based learning also enables the simulation of dangerous situations such as a radiology accident that places the learner in crisis mode, challenging their responses and testing their knowledge and skills.

Team members: Cheng Qianhui, Dr Yu Wai Yung, Dr Joanna Ti, Oh Hui Ping and Assoc Prof Sitoh Yih Yian.



Special Mention award

Team **VASE** also won a **Special Mention award** for their project proposing the concept of Video Assisted SElf (VASE) learning of mental health conditions. They proposed that videos could address the challenge of limited opportunities to interact with and examine real patients. Videos would also avoid potential issues related to informed consent and help boost interest and empathy towards mental health patients.

Team members: Dr Charity Low, Dr Paul Ang, Dr Kumi Mehara, Dr Eugene Chua, Dr Roy Teow and Dr Lim Choon Guan.

A Glimpse into Medical Education

From 9 to 11 December 2020, NUS Medicine hosted “NUS MED Camp”, an online exposure camp for graduating pre-university students, as part of a learning initiative organised by NUS Medicine and Harvard Medical School. The camp provided the students with valuable insight into what a future career in medicine or healthcare holds and enhanced their understanding of fundamental topics and relevant skills. Through sharing sessions, students learned to build a cache of conceptual knowledge before making decisions on their university applications.

This three-day experience was an immersive and enriching introductory programme for pre-university students who were interested in pursuing a career in healthcare, medicine or science. Student participants were selected upon the recommendation of their schools, on the basis of their academic achievements and assessed potential for the healthcare industry.

About NUS MED Camp 2020



54
participants from
19 schools



Heard from
13
speakers
across 8 disciplines
and 2 institutions

By providing a taste of the inner workings of the healthcare sector, especially in the context of the current pandemic, NUS Medicine hoped to inspire these bright young minds to pursue a future in the sector. From pharmacology to anatomy and patient care, each avenue of science and medicine was explored through a series of talks conducted by a panel of professionals. As part of the experience, participants got a chance to speak with passionate and knowledgeable faculty members, besides learning from a series of interactive modules and taking part in virtual tours of research facilities. Students also benefitted from in-depth discussions during sharing sessions and case study reviews. The camp touched on salient topics, giving students an inside look into a variety of healthcare environments, the role of integrated care hospitals in the healthcare ecosystem, and the benefits of patient-centric care as part of Singapore's holistic approach towards healthcare delivery.

“There’s so much about medicine that more than meets the eye. It’s not just about the technical knowledge or the ethics, but also involves a great deal of human interaction and handling emotions. Learning about pharmacology is also a good way for me to understand what I have learnt in chemistry, biology and math, apply in a real context.”

*Ms Chew Wen Jing,
St. Andrew’s Junior College*



Aspiring to Inspire before Expiring

Two President's Nursing Award Winners Champion Community Nursing, Lifelong Learning

Advanced Practice Nurses Ms Tay Yee Kian and Dr Alice Chua Foong Sin received the 2020 President's Award for Nurses, in recognition of their significant contributions made to the profession and community. The alumnae of Alice Lee Centre for Nursing Studies at NUS Medicine talk about their calling and what drives them.

If you ask Ms Tay Yee Kian how she came to be a community nurse, she would tell you it was serendipity that brought her to the field. After all, she had already spent over 25 years in gerontological and acute care at the National University Hospital by 2014, the year her career took a decidedly gentle shift towards community nursing.

"Looking back, I'm quite glad that my role evolved and aligned with the Ministry of Health's direction to move care to the community and focus beyond the delivery and provision of healthcare to the essentials and fundamentals of good health," said the Assistant Director of Nursing at the National University Health System (NUHS) Regional Health System Office.

On 21 July 2020, Ms Tay became the first practising community nurse from the NUHS to be honoured with the President's Award for Nurses, the highest accolade for the profession in Singapore, given in recognition of the significant contributions outstanding nurses have made to the profession and the community.

PHOTO:
Advanced
Practice
Nurses Ms
Tay Yee Kian
(left) and
Dr Alice
Chua
Foong
Sin
(right)





Ms Tay, together with Dr Alice Chua Foong Sin, both Advanced Practice Nurses (APNs) were among five nurses who received the award this year.

Dr Chua said, "The reward in nursing is unique as it offers the opportunity to make a difference in the lives of others. I started my career in paediatric oncology and transitioned to adult oncology. My satisfaction comes from being able to help our patients. Their appreciation has kept me going for many years."

"As a nurse, I'm always challenged by different situations and individuals because our patients come from all walks of life. They have shaped me both professionally and personally."

Spearheading community nursing in western Singapore

Ms Tay recalled that during her years as a gerontological nurse, she saw how elderly patients tended to be unwell soon after discharge from the hospital due to inadequate care at home.

"Many of these patients needed readmission soon enough. That made me think of the need for us to move into the community to help care for these patients during the critical transition period," she said.

Ms Tay got her chance to do exactly that in 2014 when she joined the Regional Health System Office of the NUHS, to help set up a community nursing unit for the western region of Singapore.

She leads a team of over 50 nurses and care coordinators who look after patients referred to the unit by the acute hospitals within the NUHS cluster, as well as those from a predictive list of patients with a history of readmissions.

"Our services run the gamut from good health promotion practices and disease prevention campaigns to pre-frail and end-of-life care. Community nursing is evolving and APNs contribute in the timely management of patients with the ability to order tests, establish differential diagnoses and prescribe or titrate certain medications," she said.

"The Master of Nursing programme at NUS Nursing prepared me well, especially in physical assessment and pharmacology. With Singapore's ageing population, APNs have the ability to practice not only in clinical care, but also in educating caregivers to reduce the chances of their loved ones returning to the hospital."

Ms Tay Yee Kian



Ms Tay on a visit to a patient enrolled in the award-winning NUHS CareHub programme, which ensures that enrolled patients continue to receive the necessary coordinated, multidisciplinary care after their discharge.

As a nurse consultant, Ms Tay is also often asked to contribute to the care planning for patients with highly complex medical conditions. She also makes sure care standards are established and maintained.

"The Master of Nursing programme at NUS Nursing prepared me well, especially in physical assessment and pharmacology. With Singapore's ageing population, APNs have the ability to practice not only in clinical care, but also in educating caregivers to reduce the chances of their loved ones returning to the hospital," said Ms Tay.



One community project that she is especially proud of is the award-winning NUHS CareHub programme, a nurse-led model of care which has reduced patients' hospital stay by two days.

The post-discharge transitional care programme ensures that enrolled patients, often at high risk of readmission, can continue to receive the necessary coordinated, multidisciplinary care at home.

Among the services it provides are a personalised care plan for the patient after a discussion with the patient's family and caregivers, follow-up telephone calls to check on the patient's condition, and clinician consultations and rehabilitation services as needed.

On her receiving the President's Award, Ms Tay said it is proof that community nursing is growing in significance in Singapore.

"I am deeply blessed and honoured to receive this award. It is not just for myself, but also for the community team. There is an increasing need for community nurses. Many patients need us to be there with them in their homes to help them manage their care."

Upping standards of cancer care

Dr Chua, an APN specialising in head and neck cancer, is a pioneer nurse and Assistant Director of Nursing at the National Cancer Centre Singapore (NCCS).

She joined the Centre when it was established in 1999. Since then, the accomplished lifelong learner has been unrelenting in her pursuit of knowledge and skills in oncology nursing through postgraduate studies and overseas fellowships. She received her Doctor of Nursing Practice degree from Duke University School of Nursing in 2019, following a Master of Nursing from NUS Nursing in 2008.

"I think it's important to stay on top of current trends and practice through continued research and education, especially in a constantly changing healthcare landscape," she told The Straits Times in a recent interview.

As the APN and nursing lead at the SingHealth Duke-NUS Head and Neck Centre's Allied Health Professional Clinic, Dr Chua manages patients with head and neck cancers throughout the trajectory of their disease. She found her niche in this sub-speciality as patients with such cancers experience significant side effects such as the inability to talk or swallow, pain and disfigurement. "Due to the nature of head and neck cancers, I noticed many clinical gaps that I could fill to facilitate a smoother treatment journey for the patients," she said.

Dr Chua runs concurrent head and neck consultations with surgical oncologists, in which she independently manages patients, reviews new cases and discusses management plans with the doctors.

"We have developed a multidisciplinary pre-operative clinic where we come together with different allied health professionals to assess the patient before the surgery, so that we can better understand the needs of the patient, what to anticipate and counsel the patient on, as well as facilitate a smooth post-surgery recovery process."

Dr Alice Chua Foong Sin

"We have developed a multidisciplinary pre-operative clinic where we come together with different allied health professionals to assess the patient before the surgery, so that we can better understand the needs of the patient, what to anticipate and counsel the patient on, as well as facilitate a smooth post-surgery recovery process," she said.

Dr Chua is also planning to run a survivorship clinic for patients with non-complicated head and neck cancers.

She reckons that 60% of her time is spent in clinical work while the rest is divided between administrative functions as well as research projects and providing education and guidance to nurses and allied health professionals.

To date, she has conducted six research studies as the principal investigator on topics centred on the care and quality of life, assessment, treatment and management of patients with cancer.

Driving nursing to greater heights

Dr Chua is also involved in numerous education committees at the hospital, cluster and national levels focusing on the professional development of nurses. The groups include the Committee for APN Competence (CAC), where she serves as chairperson and APN

“Receiving this award is an honour for me and the team. It brings to my mind what one mentor used to say to me: ‘We have to always aspire to inspire before we expire.’ This award has really affirmed this for me.”

Dr Alice Chua Foong Sin

Centre lead mentor, and the SingHealth APN development committee as a member.

In 2018, she was appointed Deputy Director of the Nursing Allied Health Education Unit (Division of Cancer Education), where she facilitated the development of an Oncology Care Programme for nursing and allied health professionals.

“As an APN, I feel I am in a privileged position to guide, mentor and drive the nursing profession to greater heights by practising above our licence,” said Dr Chua.

As the first NCCS APN lead, she has mentored six NCCS APN interns into full-fledged APNs. She currently oversees 10 APNs and the Nurse Clinical Services.

Her aspiration after receiving the President’s Award remains centred on nursing education.

“I hope for the nursing profession to grow as a community,” she said. “Receiving this award is an honour for me and the team. It brings to my mind what one mentor used to say to me: ‘We have to always aspire to inspire before we expire.’ This award has really affirmed this for me.”

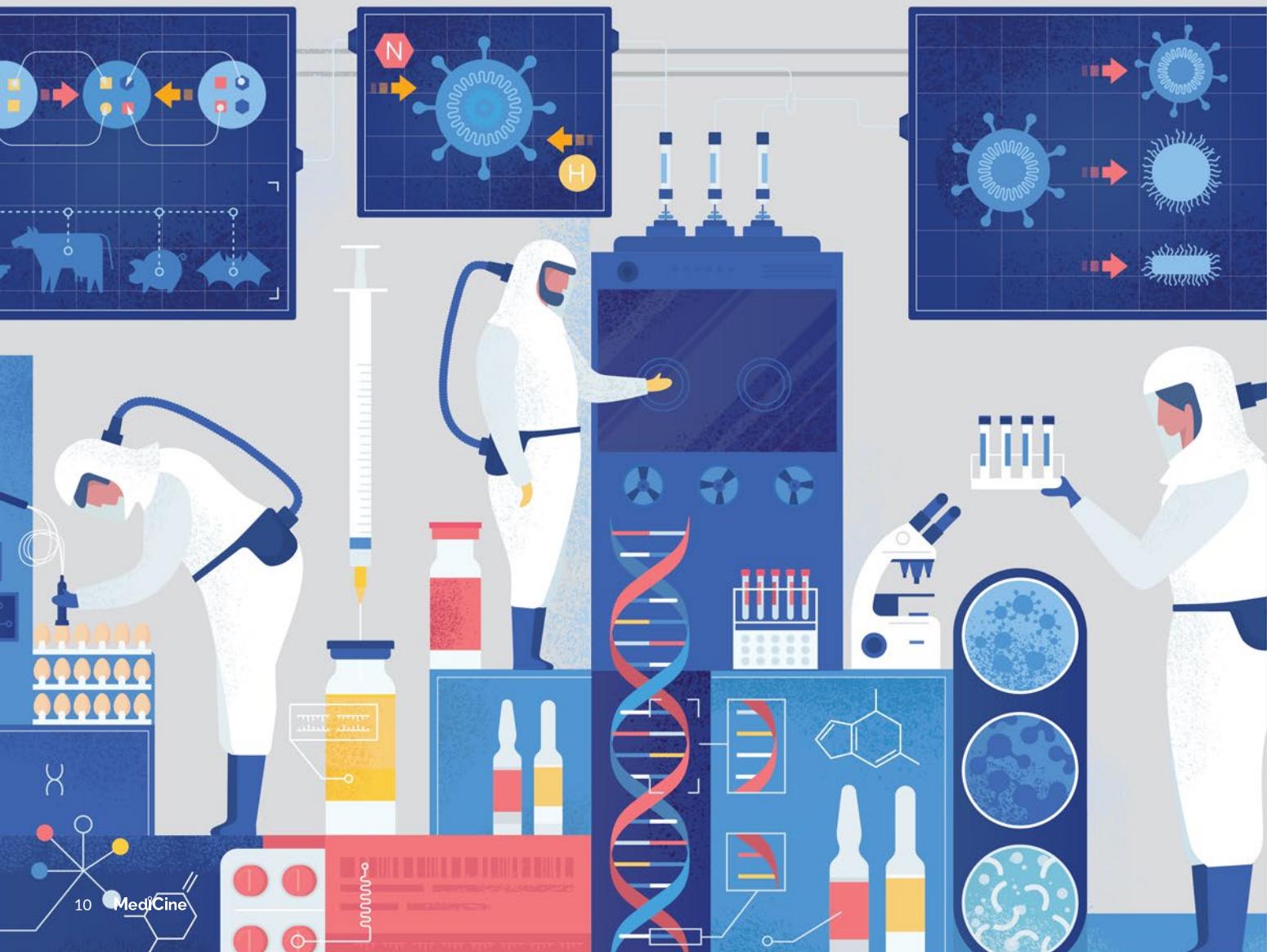
Dr Chua manages and reviews patients through concurrent consultations with surgical oncologists.



COVID-19 Vaccines and Drugs: Medicine's Armory

BY DR KHOR ING WEI

The first COVID-19 vaccine, as well as several antiviral drugs, have been granted emergency use approval in the West. While this is nothing short of amazing, challenges of manufacturing, distribution and acceptance need to be overcome before the world can begin to return to some semblance of normality.





Since August 2020, pharmaceutical companies and governments have moved swiftly to analyse clinical trial results and ramp up manufacturing of yet-unapproved COVID-19 vaccines and drugs. Widespread vaccination of populations will be crucial to protect people from becoming infected with SARS-CoV-2, while the drugs will help to prevent infection as well as treat people who are already infected.

China and Russia have approved vaccines that were developed in their respective countries, and started immunising their populations months ago¹. In December 2020, the US, UK and Canada granted emergency approval to the mRNA vaccine developed by Pfizer and BioNTech, and the first doses have been delivered to immunise healthcare workers and high-risk individuals such as nursing home residents. Singapore has approved the vaccine and plans to immunise its population by the third quarter of 2021².

Another mRNA vaccine, developed by Moderna, was approved by the US for emergency use soon after the Pfizer-BioNTech vaccine. As of 3 January 2021, the viral vector vaccine from AstraZeneca/University of Oxford has been approved for emergency use by the UK and India, while the viral vector vaccine from Johnson & Johnson may be next. This is significant because the AstraZeneca vaccine is cheaper than the Pfizer and Moderna ones (\$3-\$4 vs \$20 per dose for the Pfizer vaccine and \$25 to \$37 per dose for the Moderna vaccine; all three vaccines require two doses), and may be



13
Vaccine Candidates in clinical trials

2
Vaccine Candidates will be tested in upcoming clinical trials in 2021

easier to transport and store³. The Johnson & Johnson vaccine requires only one dose. Although these are the frontrunners in the vaccines race, it will be difficult to produce sufficient doses to vaccinate all or even most of the world's populations. The good news is that more than 20 additional vaccines are in the final stage (Phase 3) of clinical testing, with 200 more at earlier stages of development, and will help fill this gap¹. *Table 1* shows some of the vaccine candidates that are currently being evaluated in clinical trials or that are scheduled for testing in upcoming trials.

An earlier version of this article, published in August 2020, contains a description of the different types of vaccines being developed.

Besides vaccines, drugs to treat individuals who are already infected with COVID-19 are being developed and tested at a rapid pace. A few drugs, including Remdesivir from Gilead Sciences and the REGN-COV2 antibody cocktail from Regeneron Pharmaceuticals, are already being used for certain hospitalised COVID-19 patients. Other drugs are being developed to treat the excessive

inflammation that becomes the main concern in severe cases of COVID-19^{4,5}. Some of the antiviral and anti-inflammatory drugs that are currently being tested or will be tested soon in clinical trials are shown in *Table 1*.

As we move into 2021, other concerns such as manufacturing, distribution and the public's response to vaccines will take centre stage. Governments and companies have already anticipated these issues and have forged partnerships to rapidly produce millions of doses of vaccines and drugs, and deliver them under proper conditions to where they are needed. Many of the frontrunner vaccines' manufacturers have been ramping up production alongside R&D and clinical trials, with the help of funding from governments and non-profit organisations such as The Coalition for Epidemic Preparedness Innovations (CEPI).

Scan to see an earlier version of this article:

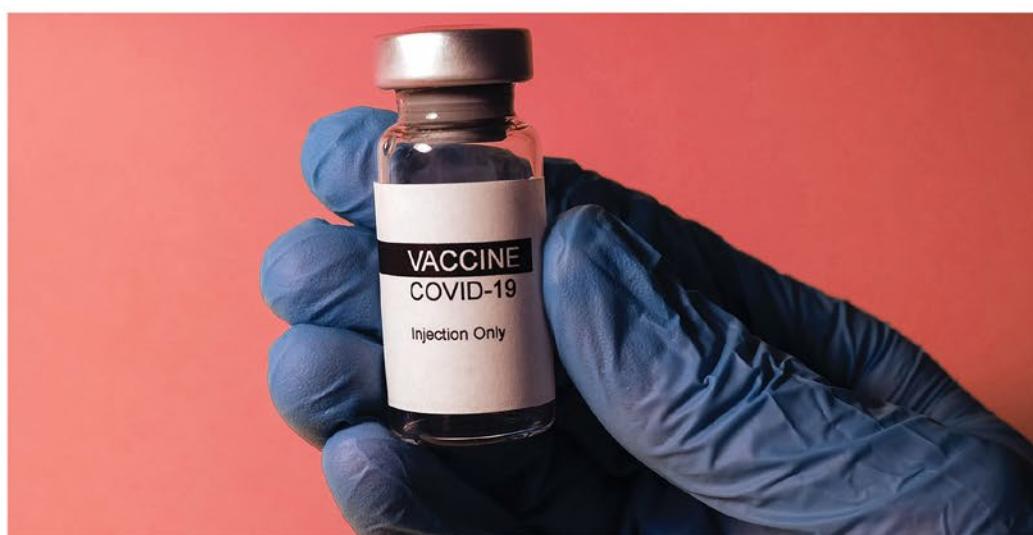


Table 1.
Some of the vaccine candidates currently being developed

In clinical trials

Whole virus vaccines

Vaccine Candidate CoronaVac	Developed By Sinovac Biotech (China)	Vaccine Candidate BBIBP-CorV	Developed By Beijing Institute of Biological Products (China)
How It Works Whole SARS-CoV-2 virus that has been inactivated so it does not replicate in the body.		How It Works Whole virus inactivated by treatment with β -propiolactone	
Stage of Development and Early Results Phase 1 and 2 clinical trials started in April 2020. More than 90% of participants showed a neutralising antibody response, and none experienced severe side effects. A Phase 3 trial started on 21 July 2020 in Brazil and 11 August 2020 in Indonesia ⁶ .			Stage of Development and Early Results Phase 1 and 2 trials showed that the vaccine induced strong neutralising antibody responses in 100% of participants aged 18 to 59, and >90% of participants aged $\geq 60^7$. No severe side effects were reported. Two 4- μg doses, given three weeks apart, gave the strongest neutralising antibody response.

Subunit vaccines

Vaccine Candidate NVX-CoV2373	Developed By Novavax (US), The Coalition for Epidemic Preparedness Innovations (CEPI), the European Commission, and the Paul Ehrlich Institute (Germany)	Vaccine Candidate SCB-2019 (S-Trimer)	Developed By Clover Biopharmaceuticals (China)
How It Works Pre-fusion S protein linked to a nanoparticle (Novavax's proprietary technology), injected together with Novavax's Matrix-M adjuvant ⁸ . Goal is to cause immune cells called antigen-presenting cells to move to injection site, stimulating neutralising antibody and T-cell responses against the virus.		How It Works Native (probably pre-fusion) S protein of SARS-CoV-2, administered together with Dynavax's FDA-approved CpG1018 adjuvant (used in an approved vaccine for Hepatitis B virus) ¹⁰ . By injecting this in the muscle, the goal is to induce neutralising antibodies against the virus.	
Doses required: 2			Stage of Development and Early Results Phase 1 trial started in late June 2020 to evaluate the safety and ability to provoke an immune response of various doses of SCB-2019.

Storage/transport conditions: 2°C to 8°C (refrigerated)

Stage of Development and Early Results

Phase 1 and 2 trials started late May 2020. Phase 3 trials of vaccine vs placebo started in the UK (September 2020) and US in subjects aged 18 to 84 years. The number of subjects in each group to develop symptomatic COVID-19 after vaccination will be determined⁹. CEPI has committed US\$388 million towards clinical trials and manufacturing.





Viral vector vaccines

Vaccine Candidate Ad5-nCoV	Developed By CanSino Biological (China) and Academy of Military Medical Sciences' Institute of Biotechnology (China)	Vaccine Candidate AZD1222 (previously known as ChAdOx1 nCoV-19)	Developed By Jenner Institute, University of Oxford (UK) and AstraZeneca (UK). AstraZeneca to manufacture and distribute vaccine.
<p>How It Works</p> <p>Entire spike protein in an adenovirus type 5 (Ad5) vector that does not replicate well in the body. By injecting this in the muscle, the goal is to induce neutralising antibodies against the virus.</p> <p>Dose required: 1</p> <p>Storage/transport conditions: 2°C to 8°C (refrigerated)</p>	<p>How It Works</p> <p>S protein in a chimpanzee adenoviral vector that does not replicate in the body. Goal is to inject into the muscle and stimulate production of neutralising antibodies and T-cells against the virus.</p> <p>Doses required: 2</p> <p>Storage/transport conditions: 2°C to 8°C (refrigerated)</p>	<p>Stage of Development and Early Results</p> <p>Phase 1 trial, evaluating safety and antibody response to three different vaccine doses, is ongoing. Results showed increases in neutralising antibodies and T-cells, with peaks at 28 days and 14 days, respectively¹¹. A few participants in high-dose group reported more severe fever, fatigue and/or muscle pain. High pre-existing levels of antibodies against adenovirus (a common virus) reduced the neutralising antibody response to the vaccine.</p> <p>Based on results of Phase 1, Phase 2 evaluated safety and immunogenicity of low and medium doses of vaccine vs placebo in 500 subjects. Preliminary results showed strong neutralising antibody responses against live SARS-CoV-2 in 47% to 51% of participants, and virus-specific T-cell responses in 88% to 91% of participants¹¹. The low dose (5×10^{10} viral particles) was as effective as the medium dose. Phase 3 clinical trials, testing Ad5-CoV against placebo, started in August and September 2020 in Pakistan, Russia and Saudi Arabia. Approved by the Central Military Commission of the People's Liberation Army in June 2020.</p>	<p>Stage of Development and Early Results</p> <p>Phase 1 and 2 trials testing safety and immunogenicity in 510 subjects started end April 2020, expected to complete in May 2021. Preliminary results showed that two doses of the vaccine provoked virus-specific T-cells and neutralising antibodies, without causing serious side effects¹³.</p> <p>Phase 2 and 3 trials are being conducted in the UK, and a Phase 3 trial is ongoing in Brazil. Preliminary results from 11,636 participants showed 90% efficacy in participants given a half dose of vaccine followed by a full dose \geq 1 month later, and 62% efficacy in participants given two full doses \geq 1 month apart¹⁴. No serious side effects have been observed thus far.</p> <p>The same team previously used this technology for MERS and obtained strong immune responses in clinical trials.</p> <p>The UK government has committed £65.5 million towards clinical trials. The US government's National Institute of Allergy and Infectious Diseases (NIAID) and Biomedical Advanced Research and Development Authority (BARDA) are also funding the Phase 3 trial.</p>

Vaccine Candidate Ad26.COV2-S (also known as JNJ-78436735)	Developed By Johnson & Johnson (US) and BARDA (US government)
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How It Works

Ad26.CoV2-S consists of proteins from SARS-CoV-2 incorporated in a viral vector that does not replicate.

Dose required: 1

Storage/transport conditions: 2°C to 8°C (refrigerated)

Stage of Development and Early Results

Phase 1 and 2 clinical trials, which started in late July 2020, has so far shown that the vaccine induced strong neutralising antibody responses and no serious side effects. A Phase 3 trial (ENSEMBLE) of up to 60,000 participants started in August 2020¹⁵. Johnson & Johnson aims to apply for Emergency Use Authorisation (EUA)—the U.S. Food and Drug Administration (FDA)'s rush approval for urgent use—in early 2021, which would make first batches of the vaccine available for high-risk people¹⁶.

Johnson & Johnson has used this virus vector platform in its approved Ebola vaccine, as well as its HIV, RSV and Zika vaccine candidates¹⁷.

Johnson & Johnson and BARDA have committed a total of US\$1 billion to this effort.

Vaccine Candidate mRNA 1273	Developed By Moderna (US) and NIAID (US government)
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How It Works

mRNA encoding the entire pre-fusion S protein of SARS-CoV-2, wrapped in a lipid nanoparticle. Goal is to inject into the muscle and stimulate a neutralising antibody response against the virus¹⁸.

Based on work with the respiratory syncytial virus which found that only the pre-fusion form of the S protein (before virus melds with the host cell membrane) provokes a strong neutralising antibody response.

Doses required: 2 (1 month apart)

Storage/transport conditions: Stable at 2°C to 8°C (refrigerated) for 30 days (according to Moderna); long-term storage at -70°C (frozen in dry ice)

Stage of Development and Early Results

Phase 1 trial with 45 subjects, evaluating safety, side effects and ability to provoke an immune response to three different vaccine doses, started in March 2020. On May 18, Moderna reported promising results in eight Phase 1 participants, showing that the vaccine induced strong immune responses and was well tolerated at low and medium doses. The high dose produced severe side effects in three participants¹⁸.

Phase 2 included only the low and medium doses. Phase 3 enrolled 30,000 participants, with almost all having received both vaccine doses. Interim results showed almost 95% efficacy for preventing COVID-19 infections vs placebo (five symptomatic COVID-19 cases in vaccine arm versus 95 cases in placebo arm)¹⁹. Appears to prevent severe disease (severe cases [11] occurred only in the placebo arm). More details about immune responses in participants should be released soon.

The US government has committed ~US\$955 million towards clinical trials and manufacturing¹⁹.

Moderna received an EUA from the FDA on 18 December 2020. It has also applied to the European Medicines Agency (EMA) and started a rolling review application with the Health Sciences Authority in Singapore for emergency use²⁰.



Vaccine Candidate BNT162b2 mRNA	Developed By BioNTech (Germany) and Pfizer (US)
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How It Works

mRNA coding for the S protein of SARS-CoV-2

Doses required: 2 (3 weeks apart)

Storage/transport conditions: -70°C (frozen in dry ice)

Stage of Development and Early Results

Phase 1 and 2 trials of mRNA vaccine BNT162 in several hundred healthy people are ongoing²¹. Preliminary results showed that BNT162 could induce neutralising antibody and T-cell responses similar to those in people recovering from COVID-19.

Phase 2 and 3 trials of more than 43,000 people (some at higher risk of COVID-19) started in end July 2020. Pfizer reported interim results, showing a 95% vaccine efficacy²².

Pfizer is developing its own -70°C cold-chain distribution to vaccination sites, where many people could be vaccinated in one day.

The UK approved the vaccine for immediate use in high-risk individuals on 2 December 2020. First vaccine to be granted EUA status by the FDA on 11 December 2020. Healthcare workers and high-risk individuals have already started to receive the vaccine.

Vaccine Candidate ARCT-021 (previously known as LUNAR-COV19)	Developed By Arcturus Therapeutics (US), Duke-NUS Medical School (Singapore), Catalent (US) and the Singapore Government . Catalent will perform large-scale manufacturing (up to 100s of millions of doses)	Vaccine Candidate CVnCoV (mRNA vaccine)	Developed By CureVac (Germany) and CEPI
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How It Works

Self-replicating mRNA vaccine coding for the S protein of SARS-CoV-2.

Stage of Development and Early Results

Duke-NUS researchers performed preclinical testing, showing that the vaccine induced strong neutralising antibody and T-cell responses. Ongoing Phase 1 and 2 clinical trials are evaluating the efficacy of a one-dose and two-dose regimen of ARCT-021²³.

The Singapore government has provided S\$220 million funding towards the vaccine's development and manufacturing, and will own the rights within Singapore²⁴.

How It Works

mRNA coding for a part of the S protein of SARS-CoV-2²⁴.

Stage of Development and Early Results

Phase 1 started end June 2020, and will evaluate safety, side effects and ability to provoke an immune response of several vaccine doses in 168 healthy subjects. Phase 2, with a target of 660 subjects (some aged >60 years) started in August 2020.

CureVac has extensive experience working with mRNA therapies and is planning to build a new production facility in the next two years. Together with its present facilities, this would enable it to manufacture several billion vaccine doses per year²⁵.

The European Commission has offered up to €80 million towards development and manufacturing.

DNA vaccines

Vaccine Candidate INO-4800	Developed By Inovio Pharmaceuticals and CEPI
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How It Works

DNA vaccine that matches the DNA sequence of the virus. Injected through the skin, followed by electroporation²⁶. Goal is for the DNA to go into the cells, and cause virus-specific antibodies and T-cells to be produced.

Doses required: 2

Storage/transport conditions: room temperature

Stage of Development and Early Results

Early results of Phase 1 trial showed antibody and T-cell responses in 94% of subjects and no serious side effects eight weeks after receiving the vaccine²⁶.

A Phase 2 and 3 trials to evaluate the efficacy of INO-4800 against placebo is expected to start soon²⁷.

Will be tested in upcoming clinical trials in 2021

Vaccine Candidate DNA vaccine	Developed By Sanofi Pasteur (France) and GlaxoSmithKline (GSK) (UK)
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How It Works

DNA vaccine that codes for a protein (antigen) that will stimulate an immune response against SARS-CoV-2, administered together with GSK's adjuvant.

Stage of Development and Early Results

Clinical trials expected to start in Q3 or Q4 2020 and available by Q3 or Q4 2021.

Repurposed vaccines

Vaccine Candidate Repurposed Bacillus Calmette-Guerin (BCG) vaccine , currently used for TB in some countries

How It Works

The BCG vaccine may stimulate the innate immune system, the body's first line of defense against invaders, which could help to prevent the SARS-CoV-2 virus from infecting cells and reproducing. Still need more evidence that it works against SARS-CoV-2.

Stage of Development and Early Results

Large trials in the US, Australia and the Netherlands are ongoing to evaluate the efficacy of BCG vaccine for respiratory illnesses including COVID-19.

One study, which looked at data until 22 April 2020, reported that countries with high rates of BCG vaccination tended to have lower COVID-19 mortality²⁸. However, another study which looked at data until August 2020 did not find a relationship between BCG vaccination rates and COVID-19 deaths²⁹.

Vaccine Candidate Clec9A-RBD ("Fusion" vaccine)	Developed By NUS Medicine (Singapore) and Monash University (Australia)
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How It Works

Consists of an antibody (stimulates the immune response more generally) fused to a protein called an antigen that stimulates a specific immune response against SARS-CoV-2³⁰. The vaccine may help to boost the weakened immune systems of elderly individuals against the virus.

Dose required: 1

Stage of Development and Early Results

Currently being tested in preclinical studies. Clinical trials expected to start end 2021.





Antiviral and anti-inflammatory drugs

While vaccines are typically used to protect healthy people from getting sick with COVID-19, antiviral drugs can be used to prevent disease in healthy people or to treat people who already have the disease. Some antiviral drugs prevent the virus from infecting cells, which is the first step in establishing an infection. Other antivirals work by binding to virus particles already present in a person, targeting the virus for destruction by the immune system. Besides antivirals, other drugs that suppress the inflammatory response are being tested in more severe COVID-19 infections, in which inflammation is a major problem. Most of the antivirals that are currently being tested or that are scheduled for testing in 2020 are antibodies or small molecules, a class of chemical compounds (*Table 2*).

One small molecule, Remdesivir, was originally developed to treat Ebola virus infection. An early report indicated that Remdesivir sped up recovery in hospitalised COVID-19 patients, prompting the FDA to grant an emergency use authorisation (EUA) to make



12
Antiviral Candidates in clinical trials

2
Antiviral Candidates will be tested in upcoming clinical trials in 2021

it available for certain high-risk COVID-19 patients. However, a large trial conducted by the World Health Organization of Remdesivir, Hydroxychloroquine, Lopinavir/Ritonavir and Interferon found that none of these therapies reduced mortality or the need for ventilation, nor did they shorten hospital stays, compared with standard care. Nonetheless, combinations of Remdesivir with other therapies remain promising options for treating COVID-19 patients.

Antibodies isolated from the blood of patients who have recovered from COVID-19 can be potent antiviral agents, useful for protecting people against infection and treating the disease in COVID-19 patients. The dual-antibody cocktail REGN-COV2, developed by Regeneron Pharmaceuticals, binds to two different sites on the viral S protein, essentially giving the drug two shots on goal. REGN-COV2 has shown strong results in reducing viral levels and reducing the need for further medical visits in COVID-19 outpatients, especially those who had not raised antibodies against the virus when treatment began. Another antibody,

AOD01, was identified from screening B-cells (the cells that produce antibodies) as part of a Singapore whole-of-government effort, involving scientists at the DSO National Laboratories and NUS Medicine, as well as collaborators at the Ministry of Defence, Ministry of Health and the Economic Development Board. AOD01 had one of the highest neutralising activities against SARS-CoV-2 reported to date in cell culture (the ability to block the virus from infecting cells). A clinical trial of AOD01 is expected to start soon.

Another candidate, APN01, is neither an antibody or a small molecule. Instead, it is a protein that mimics the receptor used by SARS-CoV-2 to enter cells in the body. The hope is that APN01 will bind to the virus, thus preventing the virus from binding to its receptor and infecting cells. Results from clinical trials are expected next year.

Some of these drugs are repurposed existing drugs, which have already been tested in clinical trials and approved by regulatory authorities for another disease.



Table 2.

Some of the antiviral drug candidates currently being developed

In clinical trials

Mimic of virus receptor

Vaccine Candidate APN01	Developed By Apeiron Biologics (Austria)	Vaccine Candidate Actemra® / Roactemra® (tocilizumab) (Original indication: rheumatoid arthritis; cytokine storm side effect of CAR-T therapy)	Developed By Roche (Switzerland) and BARDA (US government)
How It Works Mimic of the human angiotensin converting enzyme 2 (rhACE2), the protein receptor that the virus uses to get into cells ³¹ . Goal is for rhACE2 to bind the virus, preventing it from binding to the ACE2 receptor on cells. APN01 also reduces harmful inflammation in lungs and prevents acute respiratory distress syndrome.		How It Works Inhibits function of Interleukin-6 (IL-6), an important protein in the inflammatory response. Goal is to reduce excess inflammation in severe COVID-19 ³² .	
Stage of Development and Early Results Phase 2 testing of APN01 vs placebo in 200 patients is ongoing. Skipped Phase 1 and went directly into Phase 2 testing after regulatory approval in April ³¹ .		Stage of Development and Early Results A clinical trial in France showed a reduction in deaths or life support interventions, vs a control group ³² .	
		Safety and efficacy of the drug plus standard of care being tested in a Phase 3 trial (COVACTA), vs placebo plus standard of care, in patients hospitalised with severe COVID-19. Actemra reduced the risk of death by 29% ³³ . However, another trial showed no difference in clinical worsening with Actemra vs standard of care ³⁴ .	
		Another Phase 3 trial (REMDACTA) testing the efficacy and safety of the drug plus Remdesivir (see below) vs placebo plus Remdesivir in patients hospitalised with severe COVID-19 started on 28 May 2020 ³⁵ .	
Vaccine Candidate REGN-COV2	Developed By Regeneron Pharmaceuticals (US)	Vaccine Candidate Bamlanivimab (LY3819253 or LY-CoV555) , human monoclonal antibody specific for SARS-CoV-2	Developed By AbCellera Biologics (Canada), Eli Lilly (US), and the Vaccine Research Center, NIAID (US)
How It Works Cocktail of two antibodies (casirivimab and imdevimab) that bind to the S protein of SARS-CoV-2.		How It Works Starting with 500 antibodies obtained from the blood of one patient who had recovered from COVID-19, AbCellera used its platform to select a few top antibody candidates and is now testing one (LY3819253).	
Stage of Development and Early Results Results from a Phase 1 trial showed that REGN-COV2 is likely safe. Phase 2 and 3 trials showed that REGN-COV2 reduced by 10-fold the amount of virus and 57% the need for further medical visits in COVID-19 outpatients ³⁶ . Patients who did not have antibodies against the virus (had not raised an immune response) at the start of the trial responded better than those with antibodies.		Stage of Development and Early Results Phase 1 trial of patients hospitalised with severe COVID-19 ³⁸ and Phase 2 trial of patients with mild or moderate COVID-19 ³⁹ are ongoing. Interim results from the Phase 2 trial suggested that Bamlanivimab could reduce number of hospitalisations, however, findings were not definitive.	
Based on these strong results, the FDA issued an EUA for REGN-COV2 on 21 November 2020, for COVID-19 patients at high risk for progression to severe disease ³⁷ .		In May 2020 , AbCellera received CAD\$175.6 million in support from the Government of Canada towards developing antibody therapies against COVID-19. In November 2020, the FDA granted the drug an EUA for mild-to-moderate COVID-19 patients at high risk for progressing to severe disease ⁴⁰ .	



Antibodies

Vaccine Candidate VIR-7831 and VIR-7832 , human monoclonal antibodies targeting ACE2 receptor of SARS-CoV-2	Developed By Vir Biotechnology (US), NIAID (US), GSK (UK), WuXi Biologics (China), Biogen (US)	Vaccine Candidate Remdesivir	Developed By Gilead Sciences (US) and NIAID (US government)
How It Works		How It Works	
Derived from an antibody obtained from the blood of a patient who had recovered from SARS. The antibody targets ACE2, the receptor used by the virus to enter cells, and could neutralise SARS-CoV-2 in cell culture ⁴¹ .		RNA polymerase inhibitor (blocks RNA polymerase enzyme that virus needs to replicate). Shown to inhibit SARS-CoV-2 in cell culture; case studies have also reported some improvement in patients with severe COVID-19 ⁴⁵ .	
Stage of Development and Early Results		Stage of Development and Early Results	
Phase 2 and 3 trials (without a Phase 1 trial) of VIR-7831 started in August 2020, and Phase 1b and 2a trials of VIR-7832 are expected soon. Results from the VIR-7831 trial could be announced in January 2021 ⁴² .		Gilead is conducting two Phase 3 "SIMPLE" trials (one for severe and one for moderate COVID-19), of five-day and 10-day Remdesivir treatment regimens plus standard of care, vs standard of care alone. The NIAID is conducting a Phase 2 trial of 1,059 hospitalised COVID-19 patients with lower respiratory infection. Independently, the WHO is conducting a large international trial ("Solidarity") of 12,000 hospitalised COVID-19 patients to evaluate Remdesivir and other drugs. Conflicting results have emerged from the SIMPLE and NIAID trials vs the Solidarity trial.	
How It Works		How It Works	
Antibody specific for C5a, a component of the complement system that is involved in inflammation. This may be useful in treating more severe COVID-19 disease ⁴¹ .		Early results from the first SIMPLE trial in severe COVID-19 patients showed similar time to clinical improvement for patients on the five-day and 10-day treatments (>50% recovered by Day 14). Most patients did not have severe side effects ⁴⁶ .	
Stage of Development and Early Results		Stage of Development and Early Results	
Results from a small exploratory Phase 2 study of 30 patients showed that IFX-1-treated patients had a 35% to 50% lower death rate than patients who did not get IFX-1, but the study was too small to make definitive conclusions ⁴³ .		Results from the second SIMPLE trial in patients with moderate COVID-19 showed that five-day treatment plus standard of care led to 65% higher rate of clinical improvement at Day 11 vs standard of care alone ⁴⁷ .	
How It Works		How It Works	
Larger Phase 2 and 3 trials of 390 COVID-19 patients with severe pneumonia are ongoing, and are expected to complete in August 2021 ⁴⁴ .		The NIAID trial showed that patients on Remdesivir recovered more quickly than those on placebo (10 vs 15 days), and had 27% lower mortality at month 1 ⁴⁸ . On 1 May 2020, Remdesivir received EUA from the FDA for use in select hospitalised COVID-19 patients.	
Stage of Development and Early Results		Stage of Development and Early Results	
However, preliminary results (released in October 2020) from the WHO's Solidarity trial indicated that Remdesivir had no effect on mortality, need for ventilation and length of hospital stay ⁴⁹ .		Singapore's Involvement	
Singapore's National Centre for Infectious Disease (NCID) is one of the centres for the two SIMPLE Gilead clinical trials and the NIAID trial, with 90 Singaporean patients with severe COVID-19 enrolled.		The Director of the Infectious Disease Research and Training Office of the National Centre for Infectious Diseases at Tan Tock Seng Hospital, Singapore, Dr David Lye, is the second author on the New England Journal of Medicine paper about the results of the first SIMPLE trial.	



Mimic of virus receptor

Vaccine Candidate Lopinavir and Ritonavir (Kaletra®) (original indication: HIV infection)	Developed By Abbvie (US)
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How It Works

Combination of two protease inhibitors that block the HIV protease, an enzyme that HIV needs to infect cells. Rationale is that the drug combination could also block the protease of SARS-CoV-2.

Stage of Development and Early Results

Currently tested in more than 20 trials (according to Clinicaltrials.gov) to treat COVID-19 or to prevent disease in people who have come into close contact with a confirmed case.

Clinical trial in patients with severe COVID-19 at a hospital in Wuhan, China showed no benefit of combination over standard of care⁵⁰.

Singapore's Involvement

A study led by Prof Dean Ho at NUS, using an AI platform (IDentif.AI), identified the combination of Remdesivir with Lopinavir and Ritonavir as an optimal therapy, 6.5 times more potent than Remdesivir alone. Published in a preprint paper (not peer-reviewed)⁵¹.

IDentif.AI also predicted that lopinavir and Ritonavir, as well as Hydroxychloroquine and Azithromycin would not be effective. The WHO Solidarity trial showed no effect with lopinavir and Ritonavir or Hydroxychloroquine in COVID-19, but did not evaluate combinations of these therapies with other therapies⁴⁹.

Vaccine Candidate Dexamethasone (original indications: allergies, skin conditions, gastrointestinal disorders, rheumatic disorders, endocrine disorders, etc.)	Developed By Multiple companies manufacture this generic drug
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How It Works

Dexamethasone is a steroid that reduces inflammation. Goal is to combat lung inflammation in severe COVID-19 disease, to prevent progression to respiratory failure and death.

Stage of Development and Early Results

The RECOVERY trial of hospitalised COVID-19 patients compared 4,321 patients on standard care vs 2,104 patients on standard care plus Dexamethasone. Results from this trial showed that Dexamethasone reduced deaths most effectively (by 35%) in the most severe patients, who required mechanical ventilation⁵². It was less effective in less severe patients, who required oxygen support only (reduced deaths by 20%), and not effective in the least severe patients who did not require respiratory support.





Vaccine Candidate Camostat mesylate (original indication: chronic pancreatitis)	Developed By Clinical trial performed by Yale University
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How It Works

Inhibits the TMPRSS2 protease, which is required for the SARS-CoV-2 virus to infect cells.

Stage of Development and Early Results

Phase 2a trial of 114 people with early-stage COVID-19 (within two days of diagnosis). Efficacy for reducing viral load (number of virus particles) and lessening COVID-19 symptoms will be evaluated at two, seven and 14 days after starting seven-day treatment regimen⁵³.

A small study evaluating the efficacy of camostat mesylate in 11 patients with severe COVID-19 showed that it improved disease severity and reduced inflammation⁵⁴.

Vaccine Candidate Favipiravir (Avigan®) (original indication: influenza)	Developed By Tayoma Chemical , a subsidiary of Fujifilm
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How It Works

Inhibits RNA polymerase of virus, thus preventing viral replication.

Stage of Development and Early Results

Interim clinical trial results reported on 20 May 2020 did not show efficacy against COVID-19⁵⁵. Stanford Medicine is testing the drug in 120 newly diagnosed COVID-19 outpatients to see if it reduces virus shedding.

Will be tested in upcoming clinical trials in 2021

Vaccine Candidate COVI-SHIELD antibody cocktail/ COVI-GUARD antibody	Developed By Sorrento Therapeutics, Mount Sinai Health System, University of Texas Medical Branch (all US-based)	Vaccine Candidate AOD01 , human monoclonal antibody that neutralises SARS-CoV-2	Developed By DSO National Laboratories and NUS Yong Loo Lin School of Medicine (Singapore)
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How It Works

Cocktail of three antibodies will include Sorrento's star SARS-CoV-2 neutralising antibody, STI-1499, reportedly able to stop 100% of infections by the virus⁵⁶.

Stage of Development and Early Results

Phase 1 trial of COVI-GUARD (STI-1499 alone) started in July 2020⁵⁴. Trials of COVI-SHIELD are expected to start soon.

How It Works

One of five human monoclonal antibodies isolated from the blood of patients who recovered from COVID-19, using a high-throughput screening method that the team developed. The ability of the antibodies to block SARS-CoV-2 from infecting cells is the highest reported to date⁵⁸.

Stage of Development and Early Results

Clinical trials of AOD01 projected to start in the upcoming months⁵⁸.

Singapore's Involvement

Only COVID-19 therapy to be wholly developed in Singapore.

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You Can't Always Teach an Old Drug New Tricks: Lessons from WHO's COVID-19 Drug Trial

BY PROFESSOR PAUL TAMBYAH, CLINICAL PROGRAMME LEAD, INFECTIOUS DISEASES TRANSLATIONAL RESEARCH PROGRAMME AND ASSOCIATE PROFESSOR MIKAEL HARTMANN, SENIOR CONSULTANT AND HEAD, GENERAL SURGERY, NATIONAL UNIVERSITY HOSPITAL

The COVID-19 pandemic is unprecedented in terms of its impact on the world.

While other pandemics have been more deadly such as the plague, cholera and great influenza pandemic, these all occurred before the modern era of antimicrobials. With the development of penicillin and other antibiotics for bacterial infections, a range of drugs for tuberculosis and malaria and even highly active antiviral agents for the human immunodeficiency virus (HIV) and hepatitis C (HCV), many previously deadly infectious diseases are no longer a death sentence.

From the start of the pandemic, doctors and scientists have been looking very hard for drugs which can be used to treat and prevent SARS-CoV-2 infection. Public health interventions such as quarantine

and contact tracing were and still are widely used to prevent infection. However, once infection occurs, there was only supportive care including ICU care, oxygen and other standard medical treatments but no specific targeted options against either the virus or the host immune response. Since developing new virus specific drugs from scratch takes years (probably about 10 to 15 years on average) to move from discovery to patients, the only option initially was to consider existing licensed medicines that may also be effective in treating COVID-19 patients. This process is known as repurposing of drugs. It is not a new process and in fact, one of the most effective cardiac drugs used to treat heart attacks is aspirin which was initially developed as a fever and pain medicine from the bark of the willow tree.

When any treatment is used for a disease, especially for a brand new disease such as COVID-19, it is important to know whether the treatment works or not. This is particularly important for drugs which may have side effects which are potentially harmful to patients. The reality however, is that when the patient is in front of us, we do not have the luxury of time to wait for the results of studies published in medical journals. We tend to want our patients to get better so we use whatever drugs are available that may have some benefit. After a while, we accumulate enough data from the patients we have treated to analyse the outcomes in observational studies to report whether the drugs have any benefit at all. There have been multiple observational studies published since the early days of the COVID-19 pandemic and many have hit the headlines. These headlines have often caused controversy and paradoxically may have confused the public.





When any treatment is used for a disease, especially for a brand new disease such as COVID-19, it is important to know whether the treatment works or not. This is particularly important for drugs which may have side effects which are potentially harmful to patients.

The reason for this is that these observational studies tend to be biased and unreliable. Treatment outcomes and confounding issues may not be standardised, sometimes patients who are only moderately ill are more likely to receive certain drugs while patients who are looked after by certain physicians may receive no treatment at all based on the preferences or beliefs of the individual patients. The solution to this then is the randomised clinical trial (RCT). These clinical trials have been conducted in clinical medicine including infectious diseases for many years. In the 1960s and 70s, the definitive treatment for tuberculosis was established through the UK Medical Research Council (MRC) trials conducted in many centres including Singapore. Randomisation ensures that patients in all treatment groups are roughly comparable and the only difference is in the treatment assigned to the group. This reduces the bias found in observational studies and allows us to determine if the effect is due to the study drug itself. RCTs also have standardised end points (such as length of hospitalisation, need for oxygen or death) which ensures that the results from the different treatment arms can be accurately compared.

Multiple small randomised clinical trials have been published of the various treatments for SARS-CoV-2

initially from China and then later on from all over the world. These studies have been funded either by the drug companies who developed the drugs or national health authorities from the US, UK and China. Due to differences in study design (such as when the drugs were started), drug dosing regimens and end points, the results were often contradictory and the confusion from the observational studies was only slightly reduced.



WHO Solidarity Trial

(started on March 22)

Hydroxychloroquine
- Discontinued on June 18

Lopinavir-Ritonavir
- Discontinued on July 4

Interferon
- Discontinued on October 16

Enter the World Health Organization (WHO) Solidarity Trial. In a remarkably short time the WHO Solidarity Therapeutics Trial, randomised 11,266 adults admitted to 405 hospitals in 30 countries including from Albania to South Africa. The trial design was remarkably simple—once the patients gave informed consent to participate in the trial, they were randomised online to one of up to five treatments depending on local availability of the drugs—Remdesivir, Hydroxychloroquine, Lopinavir-Ritonavir, Interferon (initially in combination with Lopinavir-Ritonavir)—and standard of care. There were no forms to fill up but the doctors in charge of the patients just had to return to the online system to report the outcomes—how long the patients were hospitalised and whether they had any serious adverse effects or died. An ‘adaptive trial design’ was used for the study which allowed investigators to drop any of the arms if it did not work in interim analyses.

The trial started on 22 March 2020—Hydroxychloroquine was discontinued for futility on 18 June 2020, Lopinavir-Ritonavir on 4 July 2020 and Interferon on 16 October 2020. An interim analysis of the patients enrolled up to 4 October 2020 was published recently as a pre-print (i.e. before peer review). These results indicate that Remdesivir, Hydroxychloroquine, Lopinavir-Ritonavir and Interferon regimens appeared to have no effect compared with standard of care on 28-day mortality of COVID-19 among hospitalised patients.

These results are quite different from the optimistic reports from studies conducted by Gilead and the US National Institutes of Health on Remdesivir—a drug initially developed to treat Ebola. There are several possible reasons for this. First, the primary end point of the Solidarity Trial is death—this is very objective—you are either dead or alive! For many of the other trials, end points have included duration of hospitalisation or time to clinical improvement both of which could be affected by other factors although the randomisation would reduce the risk of bias somewhat. It is thus possible that Remdesivir may speed up recovery in those who are going to recover but have no impact on overall survival. The same has been true of RCTs of other antivirals such as Oseltamivir for influenza.

RCTs of treatment with Hydroxychloroquine and Lopinavir-Ritonavir have not shown significant benefits. Although a small study of 127 patients in Hong Kong hospitals showed some benefit of the combination of Lopinavir-Ritonavir and Interferon, there were no deaths in that study.

While it is disappointing to note the results of the WHO Solidarity Trial, it is not all gloom as the Recovery Trial in the UK reported meaningful benefit in mortality using Dexamethasone in ICU patients but not in those not requiring oxygen therapy. This study did report an unusual and alarmingly high ICU mortality which may hamper its generalisability to other parts of the world outside the UK. The other drugs in the Recovery Trial Hydroxychloroquine (which has been published in pre-print) and Lopinavir-Ritonavir (not published but reported) also have no significant benefits similar to the WHO Solidarity Trial. This is important as reproducibility is one of the key tenets in science.

Many people are confused about the data from scientific research on SARS-CoV-2 which often appears on TV before it has gone through rigorous scientific peer review. That is partly due to the commercialisation of science and medicine in the modern era. Richard Feynman described the scientific method very well (although he was talking more about physics) when he said that first, we make a guess or come up with a hypothesis. Then we design the experiment and see if our guess or hypothesis is right. Feynman said “If it disagrees with experiment, it’s wrong. In that simple statement is the key to science. It doesn’t make any difference how beautiful your guess is, it doesn’t matter how smart you are, who made the guess, or what his name is... If it disagrees with experiment, it’s wrong. That’s all there is to it.”¹

Thus when large RCTs which are the best designed experiments in clinical medicine are published, we can change



the way we treat our patients. Sometimes it is painful as we have to give up our beliefs based on good observational studies especially when multiple large well-designed trials show the same thing. Historical examples of this problem are many, for example Vitamin A and E had in large cohort studies been shown to reduce the risk of lung cancer, however when finally a large RCT was done not only did it not work but instead the vitamins increased the risk of death in the participants. (Similar findings were observed in studies of high dose chemotherapy with stem cell transplants for advanced breast cancer where four RCTs showed no benefit compared with standard chemotherapy despite observational studies appearing to show some improvements in survival of these women).

Once again, while the results of the WHO Solidarity Trial are disappointing for clinicians who treat patients with COVID-19, there are still a number of trials underway with repurposed drugs to prevent the disease and also new drugs are in development to try to treat those infected. The WHO Solidarity Trial is really unique in that it enrolled so many patients from middle income countries who are often not included in large research trials. Also, its simple study design with minimal paperwork, online reporting and an objective meaningful end point (death!) are a model for future studies of other infectious and even non-communicable diseases in the future. Ultimately, the people benefit when we have objective data from science to guide our treatment and prophylaxis of the diseases which affect our well-being.

1. <https://fs.blog/2009/12/mental-model-scientific-method/>.

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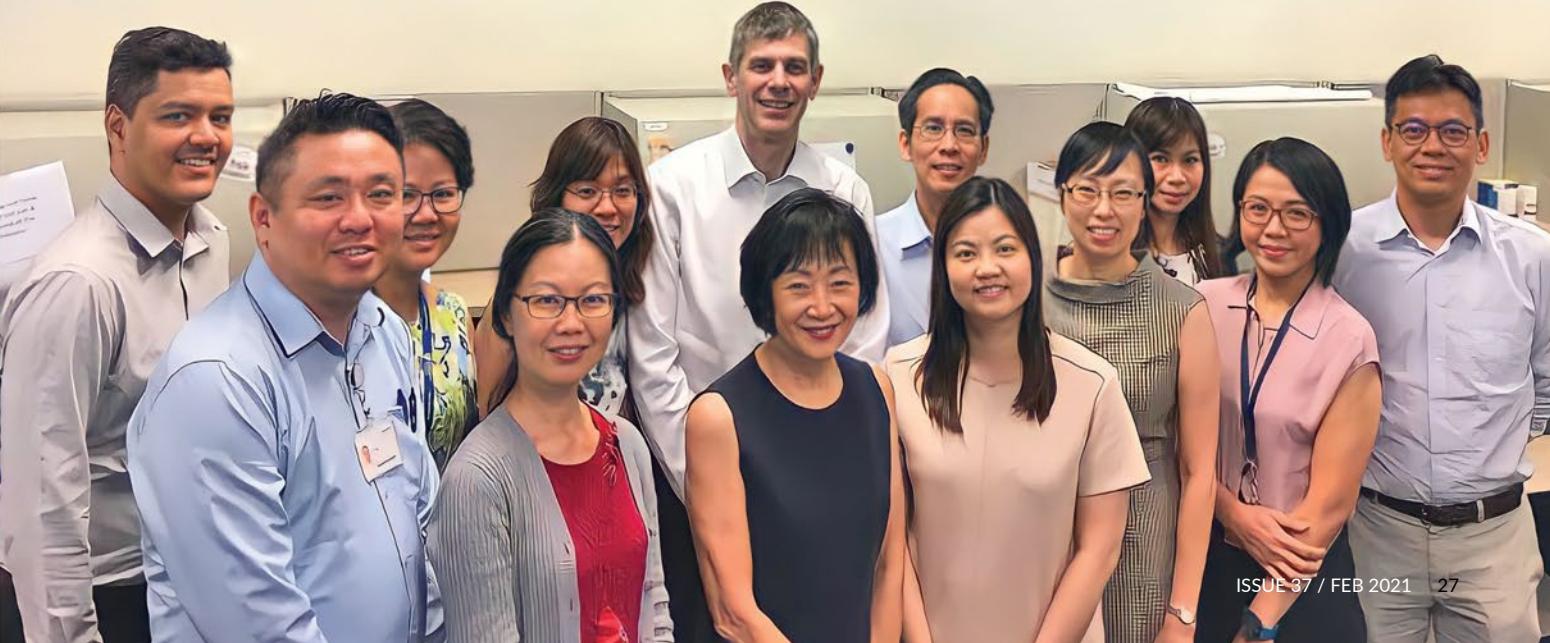
New Kid on the Block: Department of Family Medicine in Primary Care Research

BY DR GOH LAY HOON, ASSISTANT PROFESSOR, DIVISION OF FAMILY MEDICINE,
DEPARTMENT OF MEDICINE

The National University Health System's (NUHS) Department of Family Medicine was established on 1 February 2018. One of its six strategic goals is Quality Research that entails recruiting and expanding the research unit (PCRU) in collaboration with key partners and stakeholders to establish NUHS Family Medicine as a key contributor to innovative medical and health services research.

PHOTO:
Members from the NUHS Department of Family Medicine with Professor Andrew Farmer (4th from left back row) in April 2019*.

The Primary Care Research Unit (PCRU) was established under the guidance of Professor Doris Young, Head of the Department of Family Medicine, in February 2019. The overall strategic goal of PCRU is to achieve excellence in Family Medicine primary care research. The objectives are to build manpower capacity, research skills capability, and local and international research collaborations to develop research programmes that address national health priorities and create career tracks for clinician-scientists in Family Medicine.



From the beginning, PCRU gathered a group of multidisciplinary researchers from NUS and other primary care entities to form the PCRU advisory group. The group members are experienced researchers from NUS Saw Swee Hock School of Public Health, Alice Lee Centre for Nursing Studies, NUHS' Research Office, National University Polyclinics, National Healthcare Group Polyclinics and Agency for Integrated Care. This group brought research expertise to discuss and advise PCRU on novel research topics, research methodologies and funding sources.

Within the first year, a grid with research themes of national and

global importance and relevance in improving clinical practices and patient outcomes was drawn up to guide the research endeavours for the Department (see *Table 1*). Clinical themes of diabetes mellitus, cardiovascular disease including chronic kidney disease, cancer care, mental health and healthy longevity were mapped onto aspects addressing behavioural and implementation sciences, innovative new models of care, data analytics and disadvantaged populations. This grid also aligns to research programmes at NUS Medicine. PCRU uses the research grid to focus its energy and resources in building research programmes. The medical education research focuses on medical humanism and educational pedagogy.

The PCRU was established to build manpower capacity, research skills capability, and local and international research collaborations to develop research programmes that address national health priorities and create career tracks for clinician-scientists in Family Medicine.

Table 1.

	Diabetes/CVD	Cancer Care	Mental Health	Healthy Longevity
 Behavioural and Implementation Sciences	PACE-D patient activation and conversation study Systematic review on diabetes self-care	Follow up of breast cancer patients and caregivers	Postnatal mental health problems study	Perceptions of older people with chronic conditions about primary care study
 Innovative Primary Care Models	GP Primary Care Networks for improving DM care study		GP survey on youth mental health study	
 Digital Medicine and Data Analytics	CKD risk prediction study GP Initiative-MOHT quality improvement study	Gastric cancer mRNA study		
 Disadvantaged Populations	REVERSE-Diabetes (Gestational DM) study			



At the Department's annual strategic meeting held in January 2020, PCRU gathered existing and potential research collaborators to discuss and give further input to enhance the grid. From the meeting, PCRU derived three research strategies to be accomplished in 2020: aligning PCRU activities to its goals (capacity, capability and collaboration); identifying key projects, project leads and collaborators and sharing existing resources with its collaborators in teaching and conducting research. PCRU's research strategies were shared at the NUS Medicine Head of Departments' meeting on 6 July 2020 by Professor Doris Young.

Capacity: Building a clinician-scientist pipeline for Family Medicine research

PCRU builds its pipeline of Family Medicine researchers through targeted research training programmes for family doctors at different training levels with gradated objectives and deliverables. To date, PCRU is training 19 family doctors in research—two Junior Academic Faculty Scheme (JAFS) lecturers or FM Scholars, 13 National University Polyclinics doctors and one general practitioner—who are undertaking the College of Family Physicians Singapore's fellowship programme and four first-year Family Medicine residents. In 2020, PCRU also provided research teaching and opportunities for about 20 NUS Medicine students. In 2021, the FM Scholars' programme will expand to four Scholars from two the year before and start a new research training programme for the four first-year FM residents. The Department of Family Medicine also has its first PhD candidate who has been awarded the 2019

National Medical Research Council Research Training Fellowship.

In 2020, PCRU conducted eight Research Forums featuring primary care researchers sharing their research journeys and findings to an audience which comprised about 50 primary care researchers.

Capability: Building research unit and developing research skills

By 2020, PCRU has increased in strength with four research staff (one research fellow, two research associates, one research assistant and one senior research executive). The number of projects has also



12

Peer-reviewed
Papers were
published by the
Department from
2019 to 2020

grown to 11 (see *Table 1*), with grants amounting to S\$760,000 (see *Table 2*). A grant review committee was set up to improve PCRU's skills in developing and submitting successful research grant proposals. PCRU also leverages on existing NUS/NUHS research development workshops to hone its research skills.

Collaborations: Establishing impactful joint research projects and programmes

PCRU brings together local and international researchers from general practice, hospital practice, basic sciences, aged care, cancer care, biostatistics, health informatics, medical education, nutrition and psychology.

PCRU is aligned with research programmes at NUS Medicine. The medical education research focuses on medical humanism and educational pedagogy.

Table 2.

Research Project	Research Themes	Investigators
PACE-D	Diabetes, mental health	Dr Victor Loh
GP Primary Care Networks for Improving DM Care	Diabetes, innovative models of care	Dr Goh Lay Hoon
Singapore Primary Care Cancer NeTwork (SPriNT)	Primary care cancer	Prof Doris Young and A/Prof Lim Fong Seng
GP survey on Youth Mental Health	Mental health	Dr Victor Loh
Systematic review on diabetes self-care	Diabetes	Dr Tan Wee Hian and Mr Mohd Sufyan
Chronic kidney disease study using data analysis	Chronic kidney disease, data analytics	Dr Desmond Ong, Dr Goh Lay Hoon and Dr Ling Zheng Jye
Breast cancer patients and caregivers	Primary care cancer	A/Prof Lim Fong Seng and Mr Mohd Sufyan
REVERSE-Diabetes	Diabetes prevention	Prof Johan Eriksson and Prof Doris Young

International visitors

From 2019 to 2020, PCRU hosted eight primary care researchers from universities around the world. These esteemed researchers who visited were Professor Andrew Farmer from University of Oxford UK, Professor Irene Blackberry from La Trobe University Australia, Professors Jon Emery and Lena Sanci and Associate Professor Jo-Anne Manski-Nankervis from University of Melbourne Australia, Professor Cindy Lam from University of Hong Kong, Professor Samuel Wong from Chinese University of Hong Kong, Professor Claire Jackson from University of Queensland Australia and Dr Ruth Teh from University of Auckland, New Zealand. They generously shared their expertise and experience to advise and guide PCRU in its planning and work.

Asia-Pacific Academic Primary Care Group

PCRU has research training and collaborations with primary

care researchers from eight universities in the Asia-Pacific region, forming the Asia-Pacific Academic Primary Care Group (AAPCG). The universities are Singapore's Duke-NUS Medical School and NTU Lee Kong Chian School of Medicine, University of Melbourne in Australia, University of Hong Kong, and Chinese University of Hong Kong, University of Malaya, University Putra Malaysia and Fudan University in the People's Republic of China. Once a year, the group holds a workshop on research methodology and update one another on their research programmes to facilitate future collaborations.

Funding: Building strong sources of revenue to support PCRU's research efforts
PCRU is strategising to successfully obtain grants

and pool resources to sustain its research. It also intends to work towards attracting philanthropic support for its research endeavours.

Future Research Directions for PCRU

The future looks bright and exciting for PCRU, the new kid on the block in NUS/NUHS research. PCRU has started to forge its way steadily to create research opportunities for local family doctors to participate in impactful primary care research that will influence health practices and improve clinical outcomes for their patients. A 2020 PCRU Report Card outlining targets, programmes, action plans, achievements and future plans was used to document its accomplishments in 2020 and will be used to guide PCRU in attaining the Department's key research objectives for 2021.

Dr Ruth Teh's
(third from left)
visit to DFM in
January 2020*.


DEPARTMENT OF FAMILY MEDICINE PRIMARY CARE RESEARCH UNIT (PCRU)

For Dr Ruth Teh
January 2020

YONG LOO LIN SCHOOL OF MEDICINE
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* Photographs taken before implementation of COVID-19 safe distancing measures, when classes and activities moved online.

An MBBS with a Difference

NUS medical students can now take a year off to study for a postgraduate qualification before returning to complete their degree.



Undergraduate medical students at NUS Medicine now have the opportunity to study for a Master's degree in addition to their medical qualification, the MBBS.

They will be able to take one academic year off their MBBS programme to pursue another area of study, before returning to complete their medical studies. The MBBS Intercalated Year Programme (IYP) will give these medical students opportunities to learn beyond their curriculum, giving them the opportunity to pursue other disciplines and subjects. This widens students' learning experience and provides them with additional knowledge and skills that they will need as future doctors working in complex environments where multidisciplinary collaboration and interactions are common.

The IYP is a unique offering that differentiates NUS Medicine MBBS students and provides new opportunities for NUS medical graduates to expand their roles in the healthcare sector beyond clinical practice.

Besides the inaugural Master's of Science by Research programme

on offer (see box), more courses are expected to be available as the programme matures. NUS Medicine is exploring a Master's in Public Health with the NUS Saw Swee Hock School of Public Health for the IYP. More details will be made available in due time.

With the objective of training more doctors who are trans-disciplinary in their outlook, there are plans for additional courses in data analytics, design thinking, implementation science, health economics, innovation and entrepreneurship to be set up in the coming years.

"We are excited to offer this new programme to enhance our students' learning experience with us. Hopefully as the programme grows, we will be able to offer more of such growth opportunities to a greater number of students," said Associate Professor Lau Tang Ching, Vice-Dean for Undergraduate Education at NUS Medicine.

NUS Medicine Dean, Professor Chong Yap Seng said that the demands within the practice of medicine are constantly evolving, but are more pronounced in this generation. "We want to provide our students not only with the technical knowledge they need as doctors, but also with soft skills and the analytical minds needed to solve problems of the future."

What is the MBBS Intercalated Year Programme?

Undergraduate students at NUS Medicine can now take one academic year off to pursue another area of study under the MBBS IYP. The first course available is a Master's of Science by Research offered by the NUS Medicine Division of Graduate Studies. This research-oriented programme will equip up to five selected Medicine students with the competencies to spearhead and drive medical biotechnology efforts.

Students will undertake supervised research with staff members from any of the School's departments for their period of candidature.

Requirements:



take and pass coursework, which comprises two core modules and elective modules totaling 16 modular credits



submit a thesis to the Board of Examiners at the end of the year of study.



The course fees for the Master of Science (Research) will be fully sponsored by the School, with an additional stipend awarded to eligible students.

Interested applicants must possess a good academic record, in addition to the requirements of the respective programmes.

Mental Gymnastics for ‘Thinking’ Future Doctors

BY DR CHEN ZHI XIONG, ASSISTANT DEAN (EDUCATION), NUS MEDICINE

Is the ‘logical’ conclusion always the right one? Have you thought about the problems that each solution or innovation might bring? Must something be quantifiable in order to be true? If that is the case, how do we measure the impact of parents on their children?

Who can predict the next pandemic? Could a new course of a disease be projected? What will be the most pressing healthcare need in 10 years’ time? Why do patients reject certain medical devices and interventions despite the best science and design behind them?

Traditional medical and surgical competencies will no longer be sufficient to deal with the complexity of future healthcare problems, individual or global. The ability to inquire astutely, think laterally and make deft metacognitive jumps between disparate information dots will be a skill that any motivated workforce will need, to remain nimble and agile by 2022¹. COVID-19 has greatly accelerated the need to acquire this skill. In relation to this, traits like complex information processing and problem-solving, reasoning and ideation, systems analysis and evaluation, cognitive adaptability and social-cultural-emotional intelligence are of particular importance¹. Against the backdrop of a

Did You Know?

iHealthtech researchers come from multidisciplinary backgrounds—from engineering to medicine and other science specialties—to work collaboratively on health technology to address current critical clinical needs in the areas of precision medicine, smart sensors and artificial intelligence (AI), mental health and ageing, and microbiome.

iHealthtech seeks to:



Identify
critical clinical
unmet needs
and challenges



Innovate
health
solutions and
technologies



Incubate
to bring health
technologies from
bench to bedside



Impact
patients, doctors
and society

sector with traditionally low adaptability and agility like healthcare, the need to acquire this skill among the healthcare workforce becomes even more critical².

In response, the NUS Medicine conceptualised and developed the Inquiry & Thinking Pathway. This is an initiative that aims to inspire students to be curious while accustomising them to various thinking methods and reasoning approaches that challenge their existing worldviews and instil a love for inquiry.

Broadly, the pathway is divided into three themes—Purpose, Paradigm and Process. Piloted at an inaugural summer school, this pathway saw Phase II, III

and IV students participating from March to July 2020.

Phase II students went through an intensive two-week programme where they had 17 faculty members taking them through topics such as complexity and systems thinking, evidence-based medicine, moral dilemmas, evolving disease patterns, paradigms and methodologies and how to ask good questions. During these two weeks, participants went on a virtual tour of Institute for Health Innovation & Technology (iHealthtech), discussed difficult topics, and worked in teams to develop a project proposal in tandem, using the skills and techniques they learned, to answer a question of interest relating to health and medicine.



Top:
A Summer School that 'Zoom'ed by in two weeks.

Bottom:
Our iHealthtech guide 'e-inspiring' our students.

From the horse's mouth



Li Yuqian (Phase II, Class of 2024)

"The Inquiry & Thinking Pathway Summer School was a great opportunity for us to learn what research is all about and the different types of research that are ongoing. We came into this programme with an open mind and we took away more insights than we expected. The professors conducting each segment of the lecture series were extremely willing to share about their experiences in the research field and it was amazing to see how these professors were able to manage intensive research together with their clinical work."

The goal at the end of this two-week programme was for every group to draft a proposal and present it to a panel of professors. Thus, we were introduced to a variety of databases that we were previously unaware of. For example, we discovered PubMed and were surprised by how easy it is to retrieve research papers from the large database. More importantly, we realised that many professors started off their research based on the fact that they noticed a problem in the current approach and were actively seeking a solution to better the lives of their patients. This in itself is extremely inspiring.

As the summer school occurred in the middle of our vacation, many of us had other various commitments. Personally, it wasn't an easy two weeks trying to juggle COVID-19 management work at my MOH internship, introduce incoming Phase I students to the School during MediCamp and keep up with the curriculum in the summer school. Despite being very exhausted at the end of it, I felt a great sense of accomplishment.

Overall, we are extremely thankful to the professors who took time out of their busy schedules to share their passion with us and guide us in our process of crafting a good research proposal. It was a meaningful two weeks well-spent and hopefully, the juniors will get the opportunity to participate in this summer school."



Sebastiaan Zhiyong Blok (Phase II, Class of 2024)

"The Inquiry & Thinking Pathway Summer School was a fantastic experience that supplied me with a coherent research framework, priming me to develop myself as an all-rounded thinker and inquirer. Modules taught me to ask the right questions, given the modern academic milieu. Especially insightful were the lessons that steered me in the pursuit of purpose in academia: why do we perform research, and how do we ask the appropriate questions? Additionally, I was equipped with the basic skills in seeing through research: how do we go about answering these questions?

The summer school has incited in me a great desire to continue on my inchoate journey as a keen observer, who doesn't hesitate to scrutinise the world around him. It is truly a worthwhile experience, and opens doors as a researcher. Moreover, it is a wonderful opportunity to spend time with friends, and build lasting friendships. Frantically chasing deadlines late into the night (and early morning) with friends develops a sense of camaraderie; this is especially so if you end up producing a research proposal which has real potential to come to fruition. Thank you Yang Hui and Beverly for making my summer school such an awesome experience!"

1. Future of Jobs Survey 2018, World Economic Forum.
2. McKinsey Global Institute workforce skills executive survey, March 2018; McKinsey Global Institute analysis.

Artificial Intelligence Enables Single-Patient Clinical Trials

NUS Medicine's Institute for Digital Medicine pilots novel N-of-1 (single subject) trial designs to improve patient outcomes with rapid and economical solutions.

The stuff of science fiction not so long ago, artificial intelligence (AI) is now powering a dynamic new range of customised, single-patient trials that are proving to be more effective than traditional, templated clinical treatments.

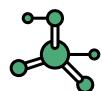
The trials led by the Institute for Digital Medicine at NUS Medicine and involving teams drawn from backgrounds as diverse as engineering, healthcare economics, behavioural sciences, computing, public health, and public policy, are helping to improve patient outcomes through rapid and economical solutions.

These outcomes are being achieved by the use of AI to integrate groundbreaking advances in medicine and digital technology. The aim—to drive revolutionary trial design protocols and targeted healthcare solutions that deliver faster, and more effective clinical interventions. The Institute (also known as WisDM) has thus far pioneered a way to pinpoint effective drug mixes against COVID-19, and developed digital therapies to address cognitive decline for post-brain radiation therapy and other oncology patients as well as other ageing and illness-related challenges.

Digital drug development for COVID-19

Through an interactive digital platform called IDentif.AI (Optimising Infectious Disease Combination Therapy with Artificial Intelligence), which leverages AI to calculate the most effective combination of drugs and doses, the NUS Medicine researchers have found that the most optimal drug combination regimen against COVID-19 comprises Remdesivir, Lopinavir and Ritonavir.

The IDentif.AI platform looked at a pool of 12 drugs that were selected based on their status of being under evaluation in multiple clinical trials. IDentif.AI differs from conventional AI approaches, and does not rely on using pre-existing data to train algorithms and predict treatment regimens. Instead, it designs experiments using different permutations of drugs and doses to crowdsource the live virus to determine the combinations that optimise antiviral activity. At the heart of IDentif.AI is a powerful, AI-discovered relationship between drugs and doses to efficacy and safety using a quadratic algebraic algorithm. This allows for the optimal combination, which resides among more than 530,000



530,000

possible combinations tested in **100+** experiments over **2 weeks** to arrive at **1** optimal combination

possible combinations to be identified with only a few hundred experiments within two weeks. Through the platform's ability to leverage unforeseen drug interactions within each combination, optimised recommendations for the drugs and corresponding doses were then suggested. Results from the IDentif.AI platform have been observed independently from a team of international collaborators on another strain of SARS-CoV-2, and two study protocols have been cleared to enable clinical studies should they be needed.

Professor Dean Ho, Director of WisDM, said, "We need rapid and economical solutions, and the IDentif.AI allows for digital drug development for COVID-19. Even as the world continues to race towards vaccines, leveraging on AI can potentially open up a new pathway to accelerate the search for an accessible and optimised intervention that may help take the strain off healthcare systems."

At the heart of IDentif.AI is a powerful, AI-discovered relationship between drugs and doses to efficacy and safety using a quadratic algebraic algorithm.

Novel trial designs for digital oncology

Through another AI-derived technology platform, CURATE.AI which provides actionable N-of-1 (i.e. single patient) combination therapy for the entire duration of patient care, trials are customised based on individual profiles, to develop drug therapies and interventions that achieve better outcomes for patients. Dynamically adjusting drug doses, CURATE.AI sustains the optimisation of combination therapy as patient responses are recorded.

In a previous pilot clinical study conducted in collaboration with a US-based hospital, a patient with advanced prostate cancer was recommended a 50% reduction in dose of an investigational inhibitor drug for increased efficacy. The patient subsequently resumed an active lifestyle as the lower dose also proved to be more

Findings have led to a clinical pilot trial that is currently recruiting patients.

tolerable. Another patient in Singapore with advanced cancer who was prescribed a reduced dose of Nab-Paclitaxel saw his lung tumour shrink while also maintaining a stoppage in progression of the cancer. This has further allowed the patient to continue treatment for a much longer duration compared to most patients who are being given this drug. These findings have led to a clinical pilot trial that is currently recruiting patients¹.

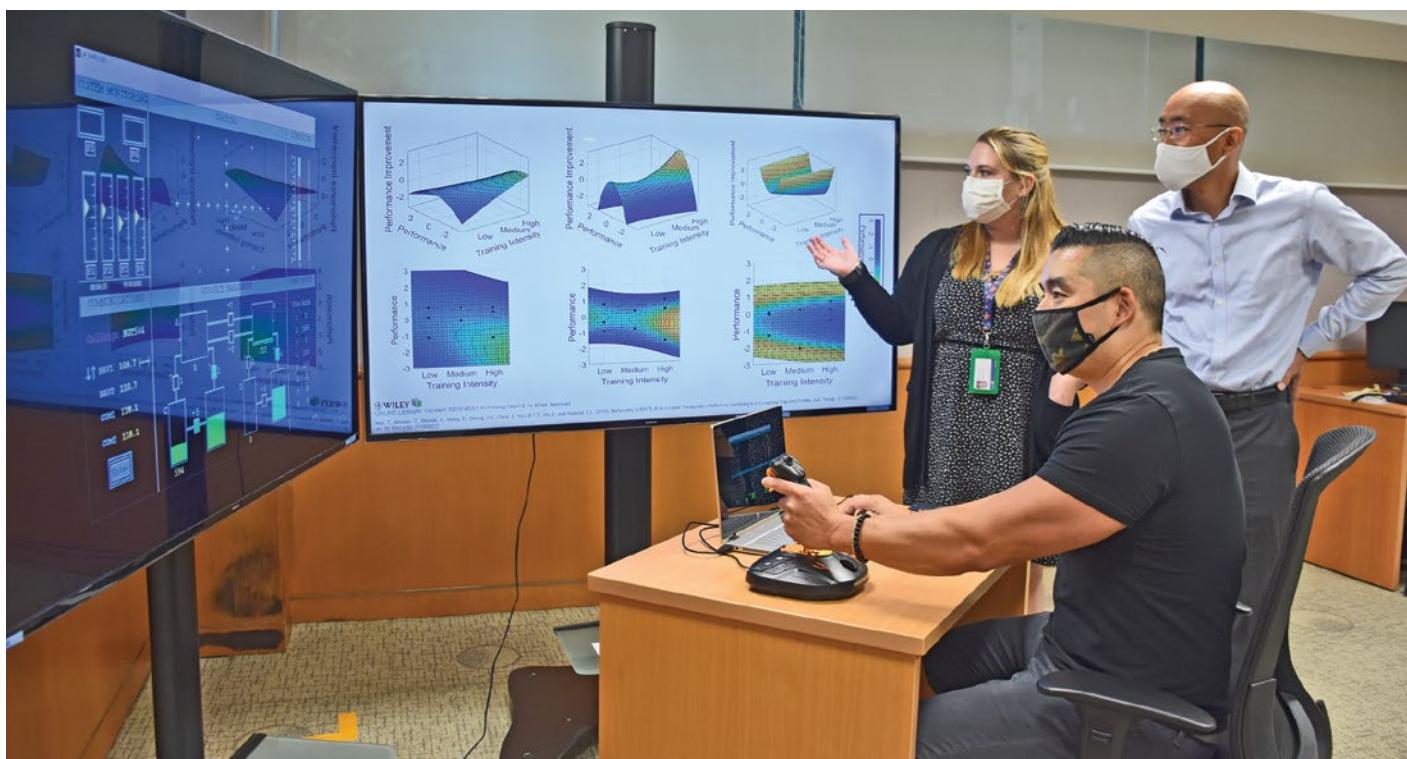
Assistant Professor Raghav Sundar from the Department of Medicine and WisDM at NUS Medicine, and Consultant with the Department of



AI-derived technology platforms and programmes
IDentif.AI
CURATE.AI

Prof Dean Ho
(at the desk) and his team.

Haematology-Oncology at the National University Cancer Institute, Singapore (NCIS) said, "In the current clinical context, the doses of chemotherapy drugs given in combination can be further optimised. Drug dosing in cancer treatments are typically based on the degree of side effects experienced by the patient. With CURATE.AI, each patient's recommended dose is calibrated using clinical data generated from their individual response to treatment. This may redefine how we care for patients and leverage digital medicine to treat cancers."



Medicine without the pill

In another expanded study using CURATE.AI, the team leveraged software as therapy to address ageing and illness-related challenges in cognitive and physical performance, such as diabetes, cognitive decline and Alzheimer's disease. Using the subject's own input data (e.g. training intensity, current performance level) and output data (e.g. degree of improvement), a personalised three-dimensional (3D) profile can be constructed to identify how different subjects perform under different intensities.

"Conventional learning approaches involve training on the same intensity or a paced increase in difficulty. However, these training regimes do not often result in the optimal outcome in every subject. In the context of digital therapy, CURATE.AI can create individualised profiles so that training may eventually be customised to improve performance," said Prof Ho.

Moving forward, the team has received funding and clearance for a clinical study to assess a digital therapeutic addressing cognitive decline in patients who have received radiation therapy to the brain. This study design will pair CURATE.AI with dynamically changing intensities of the software to provide diagnostic information regarding each patient's responses. These responses will in turn be used to personalise treatment. It is envisioned that this study will eventually lead to a therapy that can be remotely deployed in patient's homes.

"The biggest tragedy that can happen with a one-size-fits-all approach is that we lose against the disease. We believe the future of healthcare lies in AI, and using N-of-1 trial designs allows us more time to innovate, so that we don't miss out on what is truly necessary to bring about better patient outcomes."

Prof Dean Ho, Director of the Institute for Digital Medicine

Digital medicine for good

Beyond clinical diagnosis, the WisDM team aims to leverage AI and digital solutions to build sustainable and cost-neutral methods and treatments that can be deployed by all communities globally. Challenging the status quo early, their work centres on precision testing enabled by N-of-1 trial designs that have proven more effective than standardised clinical trial methods.

"The biggest tragedy that can happen with a one-size-fits-all approach is that we lose against the disease. We believe the future of healthcare lies in AI, and using N-of-1 trial designs allows us more time to innovate, so that we don't miss out on what is truly necessary to bring about better patient outcomes," Prof Ho added.

Delivering research aligned to national priorities

WisDM is one of nine new Translational Research Programmes (TRPs) at NUS

Medicine aimed at creating a strong and coherent scientific base to deliver impactful and meaningful research outcomes for the School and Singapore's health system. Besides digital medicine, the other areas are Cancer, Cardiovascular Disease, Healthy Longevity, Human Potential, Immunology, Infectious Diseases, Precision Medicine and Synthetic Biology. These nine key focus areas, which are multidisciplinary, and health and disease-based will create greater synergies and collaboration between basic scientists and clinician scientists, strengthen programmatic research and deliver research outcomes to address clinically relevant issues and applications that are aligned to national priorities.



Watch video
about the
research here:

1. More information can be found at: <https://clinicaltrials.gov/ct2/show/NCT04522284>.



The Nurse Will See You Now, Online

Nurse-clinicians, enabled by technology, provide care for recovering heart attack patients through telehealth—a system that can be as good as cardiologists' face-to-face consultations.

Recovering heart attack patients can be well cared for by highly trained experienced nurses, whose quality of care equals or even exceeds those provided by cardiologists.

These are the findings of a study involving 301 patients in three healthcare institutions in Singapore. Led by Associate Professor Mark Chan, Deputy Director of the Cardiovascular Disease Translational Research Programme, NUS Medicine and Senior Consultant at the National University Heart Centre, Singapore, the study showed that the nurse practitioners, equipped and supported by an array of digital health monitoring tools, were able to remotely monitor and assess the patients' health

daily as well as hold weekly consultations with them. Where necessary, the nurses also adjusted the patients' medication doses, providing a level of care that Assoc Prof Chan and the team found was not usually available from busy cardiologists running heavy clinics.

The Need: Continuous monitoring and frequent personalised care instead of low intensity episodic care

Heart attacks are common in Singapore where 10,000 new heart attacks occur each year. In a heart attack, or acute myocardial infarction, arteries supplying heart muscle are abruptly blocked, causing heart muscle to die very quickly. Death of heart muscle can be rapidly fatal and even among heart attack survivors,



The study involved
301
patients in three
hospitals in
Singapore.

dead heart muscle can cause a lifetime of suffering by leading to heart failure.

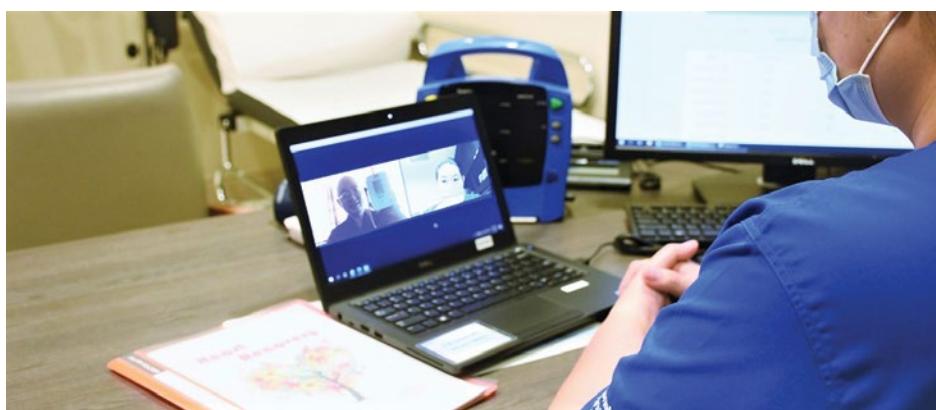
The pre-hospital and in-hospital management of heart attacks in Singapore is considered among the best in the world, with our public hospitals offering 24/7 emergency angioplasty treatment to open up blocked arteries in double-quick time. However, challenges remain in the care of heart attack patients after they leave the hospital. Ideally, heart attack patients should be reviewed early after discharge as the early post-discharge period is when they are most vulnerable to complications from the heart attack. It is also the most opportune window to adjust their medications for rapid healing of heart muscle.

The Problem: Delay in post-discharge follow-up

Yet, the reality is that cardiologists in most healthcare systems around the world are unable to see heart attack patients within a month of discharge. The primary reason for this delay in post-discharge follow-up is due to the logistic challenge of accommodating frequent in-person visits at specialist outpatient clinics in the hospital. The traditional mode of cardiologists seeing their patients infrequently in face-to-face visits, sometimes lasting as briefly as several minutes, is about to change and pave way for telehealth services.

More attentive care from nurse clinicians enabled by technology

Enter the allied health clinician, often a nurse practitioner or pharmacist with specialised training, who is increasingly taking over many patient-care



roles. Armed with an array of digital health tools that enable these allied health clinicians to monitor and communicate with patients remotely, heart attack patients can now have timely yet more leisurely outpatient follow-up with adjustment of their medications during the critical early period of heart muscle recovery.

These were the findings of the clinical trial of remote follow-up and medication adjustment by allied health clinicians for 301 heart attack patients from three healthcare institutions—National University Heart Centre, Singapore, Tan Tock Seng Hospital and the National Heart Centre Singapore in the IMproving reModeling in Acute myoCardial infarction Using Live and Asynchronous TElemedicine (IMMACULATE) trial.

Through the use of remote monitoring devices, the allied health clinicians—experienced, senior nurses with master and doctorate degrees in advanced nursing care—were able to monitor the patients' blood pressure and heart rate daily and consult weekly with the patients, a level of care that has never been possible in the traditional model of face-to-face care with busy cardiologists. The trial was a randomised controlled trial, which means patients were equally assigned to the allied health clinician-led remote management versus traditional face-to-face care by cardiologists; randomised trials remain the gold standard for testing the efficacy of new treatment strategies as it balances out all other differences between the patient groups being compared. The trial, which has just been published in the prestigious medical journal, *JAMA Cardiology*, showed that allied health clinician-led remote management using digital health tools was as safe as in-person care by cardiologists.

“Technology has also removed many of the barriers posed by traditional models of care; Artificial Intelligence now gives an ‘Iron Man’ suit to the allied health practitioner and digital tools now enable interactions across both space and time beyond traditional in-person episodic care...”

Assoc Prof Mark Chan, Department of Medicine

Moreover, patients assigned to remote allied healthcare showed a trend towards more optimal doses of key medications than cardiologist-led care.

Assoc Prof Chan, principal investigator of the IMMACULATE trial, explained that the trial results should reassure patients that nurses and pharmacists, can deliver as good if not better care than cardiologists. Assoc Prof Chan, a cardiologist himself who looks after heart attack patients, said, “Time and again, research has shown that allied health colleagues with the right training do as well and sometimes better than cardiologists, at least when taking care of conditions that are of lower complexity and pathway-driven. The reasons for this are diverse but include, perhaps, greater willingness to follow evidence-based clinical protocols and perhaps greater empathy. Certainly, research has repeatedly shown that fewer variations in practice often lead to better patient outcomes for common conditions.”

He continued, “Technology has also removed many of the barriers posed by traditional models of care; Artificial Intelligence now gives an ‘Iron Man’ suit to the allied health practitioner and digital tools now enable interactions across both space and time beyond traditional in-person episodic care. Limitations of course exist with this model of

allied health-led technology enabled care: first, large initial investments in training are needed to upskill the allied health providers, second, the reliance on technology will always bring along data security risks, a trade-off for convenience, and third, clinical pathways probably work for only approximately 50% of conditions in cardiovascular practice. There are still many patients with complex cardiovascular diseases and multiple co-morbidities that will require highly-specialised in-person ‘bespoke’ care by an experienced cardiologist; assigning the less complex patients to unskilled allied health practitioners then frees up specialist cardiologist to focus on the highly complex patients.”

Assoc Prof Chan and the same team of investigators spanning all three healthcare clusters are now embarking on a far more ambitious trial of 6,000 heart attack patients in partnership with the Ministry of Health (MOH), MOH Office for Healthcare Transformation (MOHT), Health Promotion Board (HPB), Institute for Digital Medicine (WisDM) and Integrated Health Information System (IHIS), in which more advanced digital tools are paired with wireless devices and wearables to enhance patients well-being. Called “Acute Myocardial Infarction: Allied Health-Oriented, Patient-Centred Technology-Enabled (AMI-HOPE)” care, the much larger study will be completed in 2023 and the results known in 2024.

Cancer Detection's Blood Whisperer: Scientists Develop Blood Test for Gastric Cancer

Cost effective option compared with existing diagnostic tools expected to contribute immensely in early diagnosis of gastric cancer.

After eight years of discovery research, product development and clinical validation involving 5,248 subjects from Singapore and South Korea, a team of clinicians and scientists from Singapore has developed a non-invasive blood-based diagnostic test for gastric cancer (also known as stomach cancer). The

test can potentially be used as a cost effective screening test for the early detection of gastric cancer.

Gastric cancer is the third leading cause of cancer deaths worldwide according to World Health Organization (WHO) statistics. In Singapore, it is the fifth and sixth cause of cancer deaths in males and

A few of the researchers behind the development of the test kit.*
↓

females respectively, causing approximately 300 deaths every year. Gastric cancer mortality is high due to late presentation. Endoscopy is currently the standard diagnostic test for gastric cancer. However, it is perceived as invasive and expensive, hence many patients are reluctant to undergo endoscopy even if they have gastric symptoms.



“The majority of gastric cancer patients are diagnosed at advanced stages, for which the five-year survival rate is lower than 5%. Early detection is thus the key to reducing death from gastric cancer.”

Prof Jimmy So, Head and Senior Consultant with the NUH Division of General Surgery (Upper Gastrointestinal Surgery)

Led by Professor Jimmy So, Head and Senior Consultant with the National University Hospital's (NUH) Division of General Surgery (Upper Gastrointestinal Surgery), Professor Yeoh Khay Guan, Senior Consultant with the NUH Division of Gastroenterology and Hepatology, and Associate Professor Too Heng-Phon from the NUS Medicine Department of Biochemistry, the team included clinicians and scientists from the National University Health System (NUHS) the Bioprocessing Technology Institute (BTI) of the Agency for Science, Technology and Research (A*STAR), national platform Diagnostics Development (DxD) Hub, and MiRXES Pte Ltd, a Singapore headquartered molecular diagnostic company spun off from A*STAR's BTI.

The team started this project in 2012 by first examining 578 microRNA¹ candidates in 682 patients. They discovered a panel of 12-microRNA biomarkers that can differentiate gastric cancer patients from normal patients with an accuracy over 92%. Based on this panel

of 12-microRNA biomarkers, the team created a clinical assay (or test kit) which was manufactured to clinical standards. From 2013 to 2018, the team validated this blood panel in a multicentre cohort involving more than 5,000 subjects from Singapore², making this study the most extensive evaluation of circulating microRNAs as biomarkers for gastric cancer detection to date, worldwide.

“The majority of gastric cancer patients are diagnosed at advanced stages, for which the five-year survival rate is lower than 5%. Early detection is thus the key to reducing death from gastric cancer. To bring about a meaningful fall in the gastric cancer mortality rate, an effective strategy that would detect gastric cancer early so as to enable prompt intervention is required. This non-invasive blood test is a breakthrough in gastric cancer diagnosis and it may potentially be used as an effective screening test for the early diagnosis of gastric cancer,” explained Prof So, who is also Head and Senior Consultant with the Division of Surgical Oncology, National University Cancer Institute, Singapore.

Outperforms conventional blood-based biomarkers

The performance of this test was confirmed with endoscopies and biopsies and was shown to detect gastric cancer with high sensitivity across age groups, genders, ethnicities and tumour stages. The test is able to detect 87% of all gastric cancers, including 87.5% of patients with stage I cancers.

In addition, the results showed that this blood-based test was more accurate than any of the existing conventional blood-based biomarker tests for gastric cancer detection. The findings were published in *Gut*, a leading international medical journal in October 2020³.

Cost-effective risk assessment tool for gastric cancer before endoscopy

Based on a cost-effectiveness analysis to explore the economic and health impact of using the test in a hypothetical national screening programme in Singapore, the team has found that it may be a cost-effective screening tool for gastric cancer in high-risk groups⁴ as it costs much less⁵ than endoscopy.



approximately
300
gastric cancer deaths in Singapore every year



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This test thus provides an alternative solution for those who would like a better understanding of their risk of contracting gastric cancer in evaluating their need for endoscopy. Results from this test would help to identify patients who are at high risk of stomach cancer to undergo endoscopy, thereby reducing the reliance on endoscopy⁶.



"With further health technology assessment to demonstrate the effectiveness of this assay as a screening tool in the Singapore population, we are hopeful that the assay will be implemented as a screening test for gastric cancer when used in combination with follow-up endoscopy for high-risk patients," shared Prof So.

Assoc Prof Too however emphasised that, "The test does not replace endoscopic evaluation. We believe this assay provides an option for patients who might not be keen on initial endoscopic screening and adds to the current cancer detection tool armamentarium, just as the stool DNA test is an option for colon cancer screening. Furthermore, the convenience and non-invasiveness of this test allows the public to have access to better healthcare."

Future plans

The research team is planning to evaluate the feasibility of utilising this test in the primary care setting to identify people who are at risk of contracting stomach cancer. Additionally, further research on improving the usability of test kit is also currently underway.

This non-invasive blood-based assay was co-developed with MiRXES Pte Ltd and the DxD Hub, which led the assay optimisation, analytical verification and clinical validation of the product. The assay has been commercialised as GASTROClear™ and has successfully attained European CE mark⁷ in 2017 and gained the Health Sciences Authority's approval in 2019. MiRXES is also conducting local clinical studies to seek regulatory approval of GASTROClear™ in China and Japan, which have

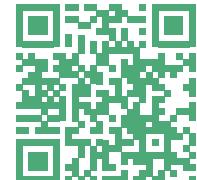


Members of the SGCC team. Front row: Prof Patrick Tan from Duke-NUS Medical School, Prof Yeoh Khay Guan, Prof Yoshiaki Ito. Back row: Dr Yong Wei Peng, Adj Prof Melissa Teo from the National Cancer Centre, Singapore, and Prof Jimmy So.*

the highest numbers of new stomach cancer cases per year globally. The test takes about three hours to run in a clinical lab and the test report can be delivered to the patient's doctor within a week.

The research was supported by Singapore Ministry of Health's National Medical Research Council under its Bedside & Bench grant (NMRC/ BnB/0014b/2014), the Translational and Clinical Research grant (TCR/009-NUHS/2013), and the Technology Development Grants from A*STAR. The

study was supported by the Singapore Gastric Cancer Consortium (SGCC), a national translational research group comprising clinicians and scientists working in stomach cancer research from academic medical centres, universities, hospitals and research institutes across Singapore.



Scan to hear more from the researchers:

1. MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression post-transcriptionally. Aberrant expression of miRNAs has been linked to the development of many diseases, including cancer. Cell-free miRNAs have been shown to circulate stably in serum and plasma, and dysregulation of their expressions correlate with cancer onset and progression, making them attractive biomarker candidates.
 2. Patients were between the ages of 40 and 90 years, who were scheduled to undergo gastroscopy based on standard clinical indications at National University Hospital and Tan Tock Seng Hospital in Singapore from 2013 to 2016.
 3. <https://gut.bmjjournals.org/content/gutjnl/early/2020/10/07/gutjnl-2020-322065.full.pdf>.
 4. 50 years and above male Singaporean Chinese with previous infection with Helicobacter Pylori (HP).
 5. Cost varies according to different healthcare providers. In public hospitals for example, the cost is estimated to be less than S\$200.
 6. Patients with positive 12-microRNA test results will be recommended to undergo endoscopy.
 7. This signifies that the product has been assessed to meet high safety, health and environmental protection requirements.
- * Photographs taken before implementation of COVID-19 safe distancing measures, when classes and activities moved online.

A

HOSPICE

OR

PALLIATIVE

CARE

What's in a Name?

BY DR NOREEN CHAN, HEAD AND SENIOR CONSULTANT, DIVISION OF PALLIATIVE CARE, NATIONAL UNIVERSITY CANCER INSTITUTE, SINGAPORE

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A well-meaning colleague once asked me: "Can you call yourself something other than Palliative Care?". It is just a name, but names have powerful meanings and elicit deep responses, and when it comes to hospice and palliative care, those responses can be decidedly negative.

The Palliative community gets its fair share of bouquets and brickbats, and one frequent jibe is we cannot even decide what to call ourselves. Hospice or Palliative or both? What's the difference? Naming practice varies from country to country (more about that later), and has been influenced by how palliative care developed, and linguistic and cultural mores.

International bodies like the APHN and WHPCA—the Asia

Pacific Hospice Palliative Care Network and Worldwide Hospice Palliative Care Alliance—include both terms. In Singapore, the convention is that "hospice" refers to community-based organisations, and "palliative" to the specialty practice and hospital-based departments and services. We consider the approach to be similar and often use the term interchangeably, but that is not the case in many countries.

In the United States of America for example, "hospice" describes a specific model of care that is Medicare-funded, largely home-based, and requires a doctor to certify that a patient has 90 or fewer days to live. It also requires the cessation of disease-directed treatment, for example, no further chemotherapy for cancer. Therefore, the idea of a

hospice in the USA is very much associated with end of life care, so much so that proponents of palliative care have taken pains to distinguish themselves from hospice care.

It gets even more confusing when one considers that different Chinese-speaking dominions have their own terms as shown in the box below.



China
姑息治疗

(this is the term adopted by the World Health Organization)



Hong Kong
临终关怀



Taiwan
安宁照顾



Singapore
慈怀疗护

Some of these terms have unfortunate meanings, for example 姑息 suggests “withering”, or “do nothing”; and 临终 means “near the end”.

Of course, it will be clear by now that a lot of this is a reaction—and a very normal human one—to the association of words like “hospice” with illness, dying and death.

But first, a brief history lesson on the origins of the terms...

Hospice versus Palliative

The term Hospice derives from *hospitium*, and the same Latin root, *hospes*, gave rise to words like hospital, hotel, hostel and hospitality. The earliest hospitals in Middle Ages Europe were run by religious orders and offered refuge to travellers, some of whom were pilgrims who had travelled long distances under arduous conditions.

The monks and nuns provided food and lodging, protection and whatever care they could, and this spirit of charitable whole-person care was a strong influence in the development of the hospice services in many countries, including Singapore.

Palliative derives from the terms *pallium* and *palliare*, meaning “to cloak”. To understand the origin of this term, we must go back 50 years to 1970's Canada, where a urology cancer surgeon named Balfour Mount attended a discussion on Elizabeth Kubler-Ross' seminal book “On Death and Dying”, and after visiting St Christopher's Hospice in London, returned to the Royal Victoria Hospital in Montreal to set up the first palliative care ward.

He coined the term “palliative care” and is considered the father of the discipline in

Canada. Why was a new term needed? This was because in Francophone regions, the term hospice was closely associated with charity poorhouses, where the destitute and indigent would go. It is somewhat ironical then, that over the decades, palliative care or *soins palliatif* has acquired some negative associations of its own.

A rose by any other name?

So what can we do about ‘branding’ hospice and palliative care so that it is more acceptable? One way is to call it something else. Studies across different countries have shown that patients find the term “supportive care” more acceptable, and an oft-quoted 2011 paper from MD Anderson Cancer Center described how changing the name of the service from Palliative to Supportive Care, resulted in an increase in referrals.

Other services have followed suit and changed the name totally, or to “Supportive and Palliative Care”. I must admit to being in two minds about this. If we are not careful, the ‘bad press’ and misunderstanding about palliative care would eventually affect supportive care too, and how often can we go hunting for more palatable-sounding names? Surely the more sustainable response is to educate people about what palliative care is and is not, and ensure that we really do what we say we do.

What is our ‘brand’?

The meanings of words and the ideas associated with them can, and do, change over time. Take the word “apathy”, which in ancient Greek times, meant “free of passions” or “free of suffering”, what we would today understand as equanimity. But nowadays, apathy is likened to indifference and has a much more negative connotation.

Palliative care is always going to have a hard time selling itself because of those inescapable negative associations, but the elephant in the room is not going away by calling it something else. My preferred approach is not to avoid the term, but to broaden its meaning and relevance beyond end-of-life care. If the meanings of words can evolve, that is an opportunity to promote better understanding.

Recognising and responding to suffering is something we all should be doing. Promoting well-being, especially for the sickest and most vulnerable, should be something *everyone* does—you, me, all healthcare providers, families, governments, whole communities. If we support this notion, then palliative care can be viewed as an enabler, preparing everyone to care, championing “quality of life for every age and every stage”. Enabler: now here's a name that connotes hope.

In Singapore, the convention is that “hospice” refers to community-based organisations, and “palliative” to the specialty practice and hospital-based departments and services. We consider the approach to be similar and often use the term interchangeably.

Please Call Me By My True Names

By Thich Nhat Hanh¹

Don't say that I will depart tomorrow—even today I am still arriving.

Look deeply: every second I am arriving to be a bud on a Spring branch,
to be a tiny bird, with still-fragile wings, learning to sing in my new nest,
to be a caterpillar in the heart of a flower,
to be a jewel hiding itself in a stone.

I still arrive, in order to laugh and to cry, to fear and to hope.
The rhythm of my heart is the birth and death of all that is alive.

I am a mayfly metamorphosing on the surface of the river.
And I am the bird that swoops down to swallow the mayfly.

I am a frog swimming happily in the clear water of a pond.
And I am the grass-snake that silently feeds itself on the frog.

I am the child in Uganda, all skin and bones, my legs as thin as bamboo
sticks. And I am the arms merchant, selling deadly weapons to Uganda.

I am the twelve-year-old girl, refugee on a small boat, who throws
herself into the ocean after being raped by a sea pirate.

And I am also the pirate, my heart not yet capable of
seeing and loving.

I am a member of the politburo, with plenty of power in my hands.
And I am the man who has to pay his "debt of blood" to my people
dying slowly in a forced-labor camp.

My joy is like Spring, so warm it makes flowers bloom all over the Earth.
My pain is like a river of tears, so vast it fills the four oceans.

Please call me by my true names, so I can hear all my cries and laughter
at once, so I can see that my joy and pain are one.

Please call me by my true names, so I can wake up and the door of my
heart could be left open, the door of compassion.

1. From <https://www.mindfulnessbell.org/archive/2015/06/poem-please-call-me-by-my-true-names>.

Epigenetics Opens Door to New World of Medicine

BY PROFESSOR ROGER FOO, SHEIKH ZAYED BIN SULTAN AL NAHYAN PROFESSOR IN MEDICINE AND SENIOR GROUP LEADER AT THE GENOME INSTITUTE OF SINGAPORE, AND DR ANENE-NZELU GEORGE, RESEARCH ASSISTANT PROFESSOR, CARDIOVASCULAR RESEARCH INSTITUTE, NATIONAL UNIVERSITY HEART CENTRE SINGAPORE

The term “epigenetics” used to conjure up memories of only what we have read about in the Dutch winter famine¹, or studies on the Developmental Origins of Health and Disease². But research has come a long way with the dissecting of epigenetic molecular mechanisms. With the growing discovery of epigenetic factors that drive cell fates or control cellular gene expression, we are seeing their real value as medicines spring from the identification of these epigenetic mechanisms. It is an exciting time to witness the threshold as new medicines now “cure”, rather than the conventional ones that simply slow down the course of disease.

As the world woke to yet another day of a relentless barrage of COVID-related news, a group of North American clinician-scientists released (with little fanfare?) the results of a landmark human clinical trial on gene therapy for Beta-Thalassemia and Sickle-Cell Disease³. Some have called this “molecular surgery”, because it is a permanent change that actually cures the disease. The work showed that the scourge of life-threatening blood disorders, which plagues millions of lives worldwide, can be achieved through CRISPR-editing of a gene “enhancer” active only in blood cells. Gene enhancers are the epigenetic switches in our genome.

Problematic transcription factor crisply edited CRISPR is becoming a household name, accompanying the publicity boost from recent Nobel laureates, Jennifer Doudna and Emmanuelle Charpentier, who were celebrated for their pioneering work on CRISPR gene editing. This technology can be targeted to protein-coding genes, which comprises only 2% of the human genome, and can also be targeted to epigenetic switches, found in the rest of the 98%, and which drive gene expression and cell behaviour.

Patients who suffer the blood disorders lack the healthy version of haemoglobin in their red blood cells and cannot carry oxygen effectively. These haemoglobin proteins appear in the first six months of life to replace fetal-haemoglobin, which performs the same role, but at the fetal stage (when the baby is still in the womb). Scientists realised that the switch from fetal to adult-haemoglobin is controlled by a transcription factor. By suppressing this transcription factor, it becomes possible to retain high levels of healthy fetal-haemoglobin, thence overcoming the issue of the lack of adult-haemoglobin.

More intricately, the scientists identified the enhancer region of the transcription factor gene, which is specifically active only in blood cells, and responsible for regulating the abundance of this transcription factor. Now,

CRISPR gene editing can be targeted to protein-coding genes, which comprises only 2% of the human genome, and can also be targeted to epigenetic switches, found in the rest of the 98%, and which drive gene expression and cell behaviour.

by CRISPR editing, targeted to this enhancer region—one of our eponymous ‘epigenetic switches’—we have the molecular surgery that turns off the expression of the transcription factor, allows for sustained production of fetal-haemoglobin, and provides the cure so that red blood cells now have sufficient oxygen-carrying function.

This work is a brilliant example of how molecular insights, built upon molecular technologies, may bring an end to human suffering. We are now finally reaping the benefits from the human genome sequencing project accomplished about 20 years ago. Together with CRISPR technology, the future for gene therapy is promising. Epigenetics is no longer just observations or phenomena yet to be understood. We are taking firm strides into the new world of medicines that set out to cure.

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2. <https://pubmed.ncbi.nlm.nih.gov/27609592/>.
3. <https://www.nejm.org/doi/full/10.1056/NEJMoa2031054>.

PHOTO:
Singer-PIXL
maintains
picking accuracy
and repeatability
across uneven
agar surfaces.

Advanced Robotics Meets Synthetic Biology

BY DR ROOPA RAJASHEKAR, RESEARCH FELLOW, DEPARTMENT OF BIOCHEMISTRY AND NUS SYNTHETIC BIOLOGY FOR CLINICAL AND TRANSLATIONAL INNOVATION

Synthetic biology is the marriage between science and engineering to design and build biological parts and cutting-edge devices to help fuel bio-based economies. This motivation to accelerate innovation in synthetic biology between academia and industry resulted in the establishment of the Singapore Consortium for Synthetic Biology (SINERGY), hosted by NUS. One successful outcome of the collaboration between academia and industry is the development of a high-precision, automated high throughput colony picker, Singer-PIXL.

Singer-PIXL was born out of a collaboration between Singer Instruments, a UK-based technology leader in automation and robotic instruments for the life sciences industry, and Singapore BioFoundry, Singapore's first and only biofoundry which houses state-of-the-art robotic systems and is hosted by NUS Synthetic Biology for Clinical and Translational Innovation (SynCTI).

Screening of large libraries of microbial strains is a common task in synthetic biology. While screening is traditionally performed manually, handpicking thousands of colonies is not only impractical and tedious but also inefficient and costly. Despite the huge advantages of robotic colony picking systems, these platforms have not been widely adopted largely due to issues such as inconsistency, low throughput and cross-contamination.

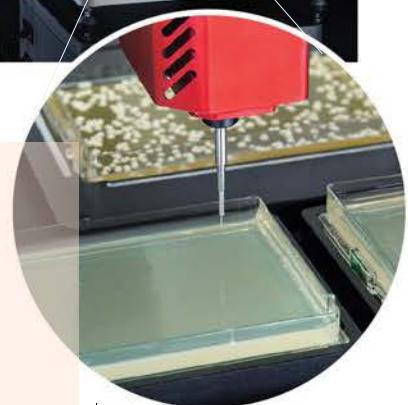
This is a problem that was waiting to be solved. In 2017, Singer Instruments and NUS SynCTI signed a research collaboration agreement to conceive and develop a new advanced and automated high-throughput colony picker, following the Design-Build-Test-Learn mantra of BioFoundry.

From here, Singer's scientists and engineers worked closely with NUS SynCTI researchers to design and test Singer-PIXL, developing the next-generation colony picker Singer-PIXL, which evolved to become a high-precision colony picker. To maximise its reach and utility, Singer-PIXL was housed at the BioFoundry for proximity to researchers, who could use the instruments and provide constant feedback to design and learning.

Singer-PIXL went from design to automation within two years. Its improved functionality in design and automation is a result of input and feedback from researchers at NUS SynCTI. With this new design and capabilities, it has found wide acceptance in the synthetic biology community for its high precision and efficiency.

This collaboration has proven to be a good model and blueprint for the

development of future advanced robotics. Through initiatives like SINERGY, which nurture corporate-academia partnerships and enhance interaction between researchers and engineers, new technologies for automation and robotic screening platforms are developed. Within SINERGY, a number of synergistic public-private sector partnerships are in the works. This bodes well for the future of synthetic biology.



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Changing the game of precision picking, sterility and ease-of-use.



User-friendly software interface

Singer-PIXL uses a touchscreen interface to guide users through the workflow to set up protocols for picking the right colonies in minutes. It is also incredibly simple to operate for end users, typically allowing them to master 90% of software functionality within 10 minutes of introduction.



Pinpoint picking technology

This meticulously developed technology is high on reliability and sterility. Compared to existing models of colony pickers which use metal pins that must be sterilised each time and run the risk of cross-contamination, Singer-PIXL uses a polymer-based PickupLine that is freshly cut, to generate sterile ends as pin heads to transfer microbial colonies. After the colony picking is completed, the 'tip' is snipped off and disposed to prevent cross contamination. Another advantage of the pinpoint technology is that it can cope with any variation in agar height automatically, to ensure that every single colony on the plate is picked and transferred without damage to the agar plates. The motors are accurate to 50 microns and the picking profiles are adjustable to optimise for even the most tenacious colonies.



Reliability

Singer-PIXL automates colony recognition, colony selection, imaging, and picking to and from various source and destination plates, ranging from petri dishes to multi-well plates. It adapts to protocols and is capable of tracing and exporting every plate, colony and parameter. Singer-PIXL accepts 90mm and 150mm petri dishes, as well as rectangular plates. It also pins onto agar or into liquid, including 96- and 384-well PCR and microtiter plates. It allows users to pick colonies based on both visible light and fluorescence imaging as it possesses six SpectraStar channels, namely blue, cyan, green, white light and two wavelengths of ultraviolet.

Telemedicine Is Here to Stay

Updates from the CENTRES Telemedicine Workshop

BY MATHAVI SENGUTTUAN, RESEARCH ASSOCIATE, PHD STUDENT,
AND TRACY DUNBROOK, INSTRUCTOR, FROM THE CENTRES
PROGRAMME AT THE CENTRE FOR BIOMEDICAL ETHICS

As communication remains largely virtual in the wake of the COVID-19 pandemic, uncertainty over how much longer this 'new normal' will last continues for the medical community. But with the passage of time, we are embracing technology that seeks to make our professional and social interactions more convenient and engaging, above and beyond safe-distancing mandates. Healthcare is no stranger to these developments.



In Singapore, many healthcare providers have shifted to tele-platforms, particularly since the Circuit Breaker period from April to June 2020. People are increasingly turning to telemedicine providers and apps like WhiteCoat, Speedoc, Doctor Anywhere, etc., through which designated local doctors can be contacted within a few minutes¹. Consequently, several challenges have arisen, particularly regarding efforts to match the quality of care that has been provided through traditional modes of healthcare delivery. The National

Telemedicine Guidelines 2015 (NTG)², as well as the SMC Ethical Code and Ethical Guidelines (ECEG) require healthcare professionals to provide the same standard of care delivered by in-person consults³. Further concerns about how to practise telemedicine ethically include the maintenance of privacy and confidentiality, access and justice issues, obtaining consent to telemedicine sessions, concerns about liability and ensuring beneficence through maintaining a requisite standard of care.



Our Speakers at CENTRES Telemedicine Workshop

Associate Professor Chan Mei Yoke

Chairperson, Hospital Ethics Committee and Senior Consultant, KK Women's and Children's Hospital

Ms Rebecca Chew

Deputy Managing Partner, Rajah & Tann Singapore

Associate Professor Chin Jing Jih

Chairman of the Medical Board and Senior Consultant, Tan Tock Seng Hospital

Associate Professor Raymond Chua

Group Director, Health Regulation Group, Ministry of Health

Associate Professor James Low

Senior Consultant, Geriatric Medicine and Palliative Care, Khoo Teck Puat Hospital

In response to these concerns, on the 26 and 27 November 2020, the Clinical Ethics Network + Research Ethics Support (CENTRES) programme based at the Centre for Biomedical Ethics (CBME) organised a fully virtual, two-day Telemedicine Workshop. Nearly 250 participants, primarily doctors, nurses, healthcare administrators and academics, gathered over four sessions to deliberate on issues and concerns over ethical telemedicine delivery.

On Day 1, an expert panel comprising Associate Professor Chan Mei Yoke, Chairperson, Hospital Ethics Committee and Senior Consultant, KK Women's and Children's Hospital; Ms Rebecca Chew, Deputy Managing Partner, Rajah & Tann Singapore; Associate Professor Chin Jing Jih, Chairman of the Medical Board and Senior Consultant, Tan Tock Seng Hospital; and Associate Professor Raymond Chua, Group Director, Health Regulation Group, Ministry of Health (MOH) explored potential solutions to these challenges⁴, followed by small group discussions with the participants. Day 2 offered Senior Consultant, Geriatric Medicine and Palliative Care, Khoo Teck Puat Hospital Associate Professor James Low's insights into practical and ethical challenges faced during teleconsultations in nursing homes and specialist outpatient settings⁵. Breakout discussions with participants on cases highlighting ethical issues that healthcare professionals may face during telehealth interactions with patients ended the workshop. The information shared by the experts and the robust discussions with participants charted a path forward towards better patient care in telemedicine.

Privacy and confidentiality in telemedicine

Maintaining the privacy and confidentiality of both patients as well as practitioners is an ethical necessity in patient care. Given the inherent limitations and risks of technologies used in healthcare delivery, providers have a critical duty to implement safety features, utilise reliable platforms and meet cybersecurity standards, in order to avoid hacks and data leaks.

As Assoc Prof Chin noted during the panel session, practitioner responsibility in ensuring privacy of the patient, especially in multi-member households where others might inadvertently or intentionally listen in, is equivalent to that of in-person consultations. This duty extends to requesting that patients participate in the consultation in a suitable environment, one that is quiet, and free from disturbances.

Deciding who should participate in a session is also important. A patient may want to include family members or caregivers. Practitioners may want to include others as well. For example, in consultations with minors, they should be accompanied by chaperones, especially in sensitive physical examinations when practitioners of the opposite sex are involved. Assoc Prof Chan recommended that in such cases another representative from the practitioner's end should also be present, in order to increase patient comfort.



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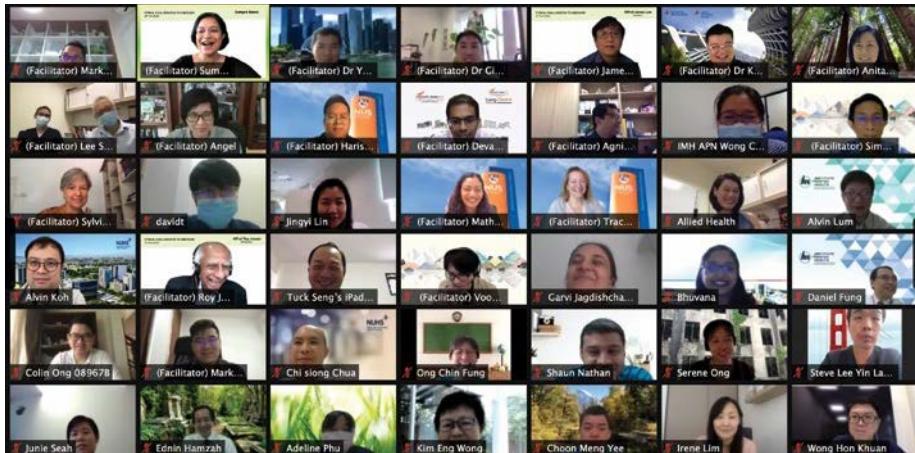
In light of apprehensions about the ease with which teleconsultations can be covertly recorded, Ms Chew suggested that practitioners also look at this issue from the patients' perspective. Recording consultations, which is not necessarily exclusive to telemedicine, may help patients remember and process the medical advice they receive during a session⁶. Some participants expressed concern about their pictures or surroundings potentially being manipulated by patients, more so than the act of recording. While there is no legal barrier at present against recording consultations, the panel members agreed that the patient should obtain permission from the practitioner before going forward, as a matter of courtesy and in order to maintain trust in the patient-practitioner relationship.

Consenting to teleconsultations

Methods used to obtain informed consent from patients for teleconsultations have invited ample scrutiny⁷. From boilerplate end-user agreements in telehealth-specific platforms to simple verbal agreement over telephonic/Zoom conversations, the validity of consent for remote medical appointments is being called into question. Conceptually, the standards for consent to a telemedicine appointment are no different from those required in face-to-face consultations⁸. But the risks and shortcomings associated with teleconsultations might not be adequately grasped through non-traditional methods, especially by patients with limited capabilities and resources. The onus is thus on practitioners to assess the suitability of patients for telemedicine⁹, and so is the obligation to advocate for the patient, and ensure that they adequately understand the content in wordy standardised agreements related to the use of telemedicine platforms. As the choice of platform is critical, practitioners need to conduct due diligence before engaging patients in telemedicine encounters, including carefully reviewing the terms and conditions of eligible platforms, as well as avoiding unreliable platforms. As the panel members concurred, the goals and limitations of the teleconsultation must be comprehensibly shared with the patient as well.

Justice: Access to telemedicine

Patient access to telehealth remains a fundamental ethical concern. Regardless of the ubiquity of technology, effective universal access to the internet and the devices necessary for its use continues to be difficult to achieve. Elderly patients often struggle to obtain the necessary devices, as well as the tech literacy required for telemedicine. Older persons residing in geriatric care and



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Workshop participants.

nursing homes, and the staff taking care of them often rely on teleconsultations with attending physicians. Assoc Prof Low has implemented a comprehensive system for Khoo Teck Puat Hospital under the GeriCare@North programmes. On Day 2 of the workshop¹⁰, he presented a detailed overview of the processes and protocols in place for these telemedicine initiatives. Partnering facilities are funded and provided with the requisite telemedicine hardware and software, as well as training opportunities and courses to upskill nurses and other professionals in accordance with the mandate under the NTG¹¹. This initiative has resulted in greater access to care opportunities for the elderly when in-person consults are impractical.

On a general note, providers arguably have an ethical responsibility to facilitate access to technology as an issue of justice¹². The obligation to provide access is not direct and has to be extrapolated from the text of the Guidelines. The NTG and the ECEG require that patients who have access to, but need to control some elements of the equipment, should be sufficiently trained to do so¹³. Enhancing the health literacy of the patients and caregivers, and improving health-seeking behaviour through

tele-platforms can be equally important in ensuring quality of care in telemedicine. The applicability of a doctors' duty to 'charge a fair and reasonable fee for services rendered'¹⁴ is relevant to telemedicine as well. However, the lack of personal feel or three-dimensional presence, its resultant impact on communication, and the shortage of literature on the cost-effectiveness of telemedicine make it difficult to ascertain the ethical validity of charging fees on par with in-person consultations. At the same time, MOH requires that the standard of care in a telemedicine session meet that of an in-person consult, and as in a clinic consult, the time commitment of the medical professional is the same. Considering these factors as well as the infrastructural and overhead expenses of setting up and maintaining tele-platforms and screening patients for these services may justify charging similar fees for telemedicine. Nevertheless, as patients and caregivers may feel that there is a significant difference between an in-person and a virtual medical appointment keeping them sufficiently informed about the details of the fee structure, insurance options and justification for costs is vital¹⁵.



Regulatory perspectives

In response to questions raised by participants during the panel, Assoc Prof Chua offered several perspectives into the regulatory aspects of practising telemedicine in Singapore, from involvement with the Licensing Experimentation and Adaptation Programme (LEAP). Inaugurated by the MOH in 2018, LEAP serves as a regulatory sandbox due to the lack of current legislation governing the space beyond the NTG, to understand the landscape of telemedicine, formulate, and review licensing and regulatory requirements, and provide e-training for providers¹⁶. As more providers join the sandbox, their insightful experiences are informing the creation of additional standards for privacy, cybersecurity, charges, etc. that could potentially be implemented in the new Healthcare Services Act. For example, the Singapore Standard for Supply and Delivery of Medicines, developed in collaboration with the Pharmaceutical Society of Singapore (PSS) and the Singapore Standards Council, expands the ambit of existing PSS guidelines to include

delivery of medication beyond the brick and mortar premises of medical clinics/services¹⁷. Access is further enabled through the convenience of having medication delivered to the preferred location after a telemedicine/in-person consultation, and the standards can ensure that this is done in a safe manner. Replication of standards in other aspects of telemedicine is likely to alleviate some of the abovementioned concerns as well.

Telemedicine as the way forward in promoting patient-professional relationship

Telemedicine might not be appropriate for some patient-practitioner interactions. The necessity of physical examination, the importance of face-to-face communication and personal touch, difficulties when engaging in sensitive conversations or breaking bad news, and any uncertainties in delivering the requisite standard of care can make a telemedicine session unsuitable in a particular case. Yet, the convenience, efficiency, and opportunities to access

healthcare for patients cannot be underestimated. Nor can the necessity of telemedicine during the pandemic be undervalued. As the NTG affirms, telecare is better than no care at all, when elderly and other isolated patients are precluded from accessing in-person care¹⁸. By accepting that telemedicine will continue to exist and is likely to grow, it could create a positive impact on the patient-practitioner relationship¹⁹. Practitioners will be able to conduct follow-up sessions, review test results and medication use and remain in touch with patients more often and conveniently than ever before. Patients may be able to communicate their concerns in a timely and effective manner. Telemedicine is also making medicine re-examine and reevaluate existing communication with patients and various aspects of practice in an effort to deliver an acceptable standard of care through virtual modalities. Telemedicine is part of medicine's future, and in addressing our concerns about it now, we can improve overall healthcare delivery.

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A Medical Student Comes Home

BY JACQUELINE LIEW, PHASE II MEDICAL STUDENT

Phase II medical student, Jacqueline Liew, reflects on her journey studying medicine and achieving her personal dream of studying at NUS Medicine, after a short detour.



PHOTO:
Day trip to
Rottnest
Island.



As a rather sheltered 13-year-old, I embarked on a community service trip to Vietnam. At the orphanage, children lay sick on the floor with no access to healthcare. Befriending the children at the orphanage and witnessing their living conditions first-hand struck a chord in my heart. This ignited my aspiration to become a doctor—to be a friend, a listening ear, and a helping hand to those in need.

After my GCE A-Level examination, I applied to NUS Medicine but failed to gain entry. Devastated, I spent the next few months making sure that my heart was in the right place and that studying medicine was the choice for me. For a year, I volunteered at an organisation that provides affordable healthcare for migrant workers in Singapore. After spending a gap year volunteering and working odd jobs, I was still sure that I wanted to pursue medicine, so I made the difficult and costly decision of moving to Australia to study.

While there was a lot of adjusting to do, I had an amazing time at the University of Western Australia (UWA). Studying abroad forced me into independence and self-reliance. I experienced a new way of life, a new system of education, and a new environment. To immerse myself in the university culture, I joined a choir, The Winthrop Singers, and the Western Australian Medical Students' Society where I managed Red Party's Red Aware Week—a fundraiser and campaign that raises awareness for HIV/AIDS.

It was not uncommon to spend weekends having brunch at local cafes, driving through the bushlands, hiking and relaxing at the beaches. I spent weekday mornings taking long runs in the neighbourhood park to soak in the scenery before starting my day at the university or at my part-time job. The sunsets were also particularly breathtaking.

Jacqueline (first row, fourth from the right) after a performance with the Winthrop Singers.



Despite enjoying my time in Perth, I always counted down to the days until my next flight back to Singapore.

This year, in the heat of the COVID-19 pandemic, I was given the choice to return to Singapore to continue studying remotely. I jumped at the opportunity to return home to spend time with my family and friends in Singapore. Towards the end of the first semester of my third year, I received news that NUS Medicine had opened up spaces for transfer students. Hopeful, but with conservative expectations, I applied for the second time. Every stage of the application process was nerve-racking—from writing my application essay in the midst of my final examinations, to the interview. When I got news of an offer to NUS Medicine, I was delighted. I had finally achieved my long-time dream of entering the NUS Yong Loo Lin School of Medicine.

While the academic rigour is as intense, clinical exposure comes in a lot earlier at NUS. Thankfully, I had very helpful peers who helped me adapt to the new environment.

I also joined the junior committee of SIGNapse, a sign language interest group at NUS that aims to bridge the communication gap between the deaf and hard of hearing community, and the university community.

Living and studying in the place I call home is something I really cherish, especially after having been away for so long. Though I've entered the School at an odd time, with many classes being held online, it has been exciting nonetheless. I am so thankful for the opportunities I have been granted, and I look forward to the rest of my studies and my career ahead.



Inspiring Health For All



**Yong Loo Lin
School of Medicine**

NUS Yong Loo Lin
School of Medicine
1E Kent Ridge Road
NUHS Tower Block, Level 11
Singapore 119228

Tel 6772 3737
Fax 6778 5743
Email medmedia@nus.edu.sg
Web medicine.nus.edu.sg

@NUSMedicine

@NUS Medicine

NUS Yong Loo Lin
School of Medicine