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精準醫療在婦幼的新進展暨科技部婦幼學門研究成果發表

Advancement of Precision Medicine and Achievement Presentation in the Discipline of Women's and Pediatric Medicine of Ministry of Science and Technology

時　間：111年7月16日　08:00~17:30

Time：July 16, 2022　08:00~17:30

地　點：臺北榮民總醫院 致德樓第一會議室

Place：The First Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

精準醫療在婦幼的新進展暨科技部婦幼學門研究成果發表

Advancement of Precision Medicine and Achievement Presentation in the Discipline of Women's and Pediatric Medicine of Ministry of Science and Technology

The progress of precision medicine in reproduction

精準醫學於生殖領域的進展

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The research of reproductive medicine has significantly progressed to help infertile couples to achieve pregnancy with safer and higher success rates. The basal serum anti-mullerian hormone (AMH) level is utilized effectively to predict ovarian hyperstimulation syndrome (OHSS). AMH can direct the selection of milder controlled ovarian stimulation (COS) protocols or freeze all strategy for high responders. Significant improvement of cryopreservation of oocytes and embryos is achieved by vitrification. Understanding OHSS mechanism, we can prevent OHSS by using antagonist protocol or progestin-primed ovarian stimulation (PPOS) with GnRH agonist trigger and freezing all embryos. The preimplantation genetic testing for aneuploidy (PGT-A) can be used for advanced maternal age. That may increase the implantation rate and reduce miscarriage rate. Time-lapse incubation systems are used to facilitate embryo culture and observation. It permits the embryologists to evaluate embryo development thoroughly in a dynamic fashion without taking them from the incubator. Using specific data programs, that helps the assessment of embryos according to morphokinetic changes for the ranking of embryos depending on their developmental ability. Endometrial receptivity assay (ERA) for the personalized embryo transfer of a blastocyst has been used to improve the implantation rate. The value is still controversial and need further clarification. To advance personalize medicine, precision medicine may further integrate these data including genomics, epigenomics and metabolomics as well as time-lapse imaging. Artificial intelligence (AI) and data science may play a core role in expanding the reach of precision medicine. We envisage that both precision medicine and AI will play important roles in the infertility treatment, improving outcomes but also increasing safety.

Big data in gynecologic diseases and precision medicine

大數據在婦科疾病與精準醫療

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In the past, diseases were diagnosed based on existing medical knowledge as well as physicians' experiences, and were treated according to medical guidelines. The patients who were affected by the same disease usually underwent the same treatment including medication and surgeries. However, the individual differences, such as genetic variants, body constitution, and personal response to treatment are not considered. Nowadays, new concepts and techniques have changed the world with the developments of internet of people and things, information technology, big data and next generation genome sequencing. Disease-centered therapy has been shifted to patient-centered therapy. The development of translation medicine and next generation genome sequencing facilitates the understanding of a disease from a clinical to molecular level. On the other hand, the big data helps clinicians and patients make decisions which conform to personal requirement. Therefore, the treatment of diseases has progressed from medical guidelines (one for all) to personalized medicine (all for one).

An example of the application of precision medicine in gynecologic diseases is PARP inhibitor used for maintenance therapy of advanced epithelial ovarian cancer after a debulking surgery and adjuvant chemotherapy, depending on the BRCA mutation in genetic tests. Another good examples of big data are the Taiwan Biobank, and the National Health Insurance Research Database (NHIRD), both of which recruit a large population rather than retrieve smaller samples from the target population. Thus the errors and bias from a sampling process are minimized. The application of internet of people and things and information technology makes it possible to solicit big data for trend studies and further analyses. In brief, precision medicine is an emerging approach for disease prevention and treatment that takes into account people's individual variations in genes, environment, and lifestyle. With the developments of internet, information technology, big data and genome sequencing, precision medicine can be achieved for prediction of diseases as well as making decisions.

The development on mid-urethral sling

中段尿道手術的發展

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Use of urethral slings in the treatment of incontinence started in the early 20th century. In 1990, Petros and Ulmsten described the integral theory of female urinary continence, a concept that would define the modern approach of anti-incontinence surgery. The theory proposes that a physiologic backboard is created through fixation of the middle region of the urethra to the pubic bone, via the pubourethral ligaments. Loss of this backboard, which is critical to the continence mechanism, inhibits normal urethral coaptation when the intra-abdominal pressure is increased and results in urinary incontinence. The mid urethral sling adopted the “urethral dynamic kinking” mechanism with a tension-free polypropylene tape that have been applied at the mid-urethra to cure stress incontinence.

Since the introduction of tension-free vaginal tape in 1995, multiple other commercially available types of midurethral sling have been introduced. In general, these sling types share the common characteristics of using a thin, type I synthetic mesh inserted at a midurethral level and applied without tension. The midurethral sling procedure has subsequently undergone multiple technical modifications, predominantly alterations to the technique and route used for sling insertion. Despite the variety in techniques, available evidence suggests that all sling types provide efficacious and durable outcomes. Several adverse effects have been reported that are specific to certain techniques, and include the risk of vascular, enteric or nerve injury, lower urinary tract injury, urinary retention or voiding dysfunction, and vaginal erosion. Nonetheless, the midurethral sling provides a safe surgical option overall, and represents a notable advance in the treatment of stress urinary incontinence.

The applications of artificial intelligence in reproductive medicine

人工智慧在生殖醫學的應用

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Artificial intelligence (AI) has experienced rapid advances over the past years, moving from the experimental to the practical applications in various fields. Progresses in learning algorithms and theories, the availability of big data and improvements in computing power have contributed to breakthroughs in current AI applications. Machine learning (ML) allows computers to detect patterns from large complex datasets automatically and uses these patterns to make predictions. AI is proving to be increasingly applicable to medicine, and multiple ML techniques have been used to improve the performance of assisted reproductive technology (ART).

In the clinical settings of reproductive medicine, AI would be expected to improve clinical workflow, reduce manual evaluations of quality control, and accelerate time to pregnancy. Potential applications of AI are assessing gamete quality, sperm selection, embryo grading, recommending stimulation protocols, the selection of egg donors, and alerting the need for maintenance of IVF equipment to automation. Most importantly, AI will be of the highest value in ranking of embryos toward the prediction for a live birth. Concurrently, AI would reduce the inefficiency of gametes and embryos through enhanced oocyte identification while optimizing personalized medicine through the analysis of all embryological, clinical, and genetic data. AI would improve the efficiency of oocytes and sperm contributing to forming optimal embryos. Also, AI has the promise to reduce the dosage of gonadotropins used as well as the wastage of supernumerary embryos.

In this talk, we will outline the basics of AI and ML, and address the applications of AI in reproductive medicine. The pros and cons of AI in ART are presented. We also present the preliminary outcomes of our AI project in embryo selection at Cathay General Hospital. Despite various challenges, the integration of AI and reproductive medicine raise a direction to the development of precision and individualized treatment in reproductive medicine.

Targeted maintenance therapy in gynecology

婦科之標靶性維持型治療

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Bevacizumab has been studied in combination with carboplatin and paclitaxel followed by maintenance therapy of single agent bevacizumab in the up-front treatment for advanced epithelial ovarian cancer (EOC). Compared with surveillance only, such strategy showed a modest improvement in progression-free survival. Overall, there are no objective clinical benefit on quality of life or overall survival, and this strategy should be individualized. In subgroup analysis, overall survival was improved in some patients by this strategy.

PARPi (poly ADP-ribose polymerase inhibitor) has roles in the maintenance therapy of advanced EOC after response to first line chemotherapy. Olaparib reduced the risk of disease progression or death by 70% in advanced *BRCA* mutated EOC. Olaparib plus bevacizumab received FDA approval as first line maintenance therapy whose EOC is associated with HRD, either deleterious or suspected *BRCA* mutation and/or genomic instability, and the survival benefit also extended to patients with tumors showing HRD regardless of *BRCA* status. Furthermore, regardless of the HRD status, maintenance niraparib significantly prolonged progression-free survival among advanced EOC patients who had a response to platinum-based chemotherapy.

Pazopanib has been studied for the maintenance therapy of advanced EOC. Progression-free survival was prolonged, and the effect held true regardless of *BRCA* status, although a more dramatic benefit was seen among *BRCA1/2* carriers.

HER2/neu is overexpressed in about 30% of uterine serous carcinoma. Addition of trastuzumab to carboplatin-paclitaxel with subsequent maintenance trastuzumab in the treatment of advanced uterine serous carcinoma was well tolerated and increased progression-free survival.

Prolonged hormone therapy targeting hormone receptors may maintain the therapeutic effect in some hormone-dependent gynecologic diseases. Patients receiving dienogest after fertility-preserving surgery for endometriosis had significantly lower incidence of disease recurrence than those who were managed expectantly. Other examples are hormone therapy regimens for hormone receptor-positive uterine sarcomas.

Precision medicine in stress urinary incontinence (SUI) therapy

應力性尿失禁的精準醫療

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Stress urinary incontinence (SUI) is leakage of urine during physical activity that increases abdominal pressure, such as coughing, sneezing, laughing, or exercise. SUI is the most common type of urinary incontinence in women. SUI can happen when pelvic tissues and muscles, which support the bladder and urethra, become weak and allow the bladder "neck" to descend during bursts of physical activity. This descent can prevent the urethra from working properly to control the flow of urine. SUI can also occur when the sphincter muscle that controls the urethra weakens. Weakness may occur from pregnancy, childbirth, aging, or prior pelvic surgery. Other risk factors for SUI include chronic coughing or straining, obesity and smoking. Not every woman with SUI will need surgery. Some factors should be considered before deciding whether to undergo surgery, including the severity of the SUI symptoms and their effect on daily activities, and the desire for future pregnancy because vaginal delivery causing recurrence of SUI may result in the need of reoperation.

Non-surgical options includes pelvic floor exercises, pessary, and behavioral modification. Surgical options include surgery to decrease or prevent urine leakage can be done through the vagina or abdomen. The urethra or bladder neck is supported with either stitches alone or with tissue surgically removed from other parts of the body such as the abdominal wall or leg (fascial sling), or with material such as surgical mesh (mesh sling). Surgical mesh in the form of a "sling" (sometimes called "tape") is permanently implanted to support the urethra or bladder neck in order to correct SUI. This is commonly referred to as a "sling procedure", which includes retropubic sling and transobturator sling. There is also a "mini-sling" procedure that utilizes a shorter piece of surgical mesh, which may be done with only one incision.

Non-invasive prenatal testing for aneuploidy, copy-number variants and single-gene disorders

非侵入性產前檢測：非整倍體、拷貝數變異及單基因遺傳疾病

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The rapid development of genomic technology has made the twenty-first century the most prominent century for the scientific research in genomic medicine. Technical advances by means of next generation sequencing (NGS) technologies improve the capacity to detect and quantify genetic variants, including germline and somatic mutations and polymorphisms, across the genome. The growing number of publications and patents indicate that application of NGS-based molecular testing to assist accurate diagnosis of disease incidence, the degree of prognosis or the most appropriate treatment for individual disease is inevitable in the future trend. And it is the main spirit of "Precision Medicine". For the foreseeable future, NGS-based molecular testing will be as common as the current biochemical tests or general physical examination. The application of genomics in preventive medicine, especially in prenatal care, is particularly important. The NGS-based prenatal tests through the use of maternal blood to detect fetal chromosomal and/or sub-chromosomal abnormalities have shown the advantages over the traditional prenatal tests. Nevertheless, newborns with undiagnosed clinical symptoms indicating the demand for even higher detecting resolution. To provide a more precise and accurate healthcare solution in maternal-fetal precision medicine, we have developed a platform for noninvasive prenatal molecular diagnosis to identify pathogenic variants that lead to sporadic skeletal dysplasia. In addition, we built an automatic variant scoring system in-house to speed up turn-around time for data analysis. We plan to apply the next generation NIPT in future clinical services. Generally speaking, our goal is to turn the prenatal genetic testing to a new era of fast, comprehensive and high accuracy for next generation maternal-fetal precision medicine.

Trends in reproductive genetics: Single cell, whole genome, and less invasive

生殖遺傳的研究趨勢：單細胞、全基因、減少侵襲性

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Maternal-fetal medicine (MFM) is a major subspecialty of obstetrics and gynecology, and its progress and complexity in recent years have sky-rocketed. Many new molecular and genetic modalities for screening/diagnosis have been introduced into clinical practice, and the landscape of MFM has changed dramatically in comparison to the condition even one decade ago. Screening tests like preeclampsia risk estimation, maternal serum fetal aneuploidy screening, maternal serum screening for neural tube defects, non-invasive prenatal testing, etc. have emerged one after another with dazzling speed. Meanwhile, diagnostic tests have also evolved from karyotyping, fluorescence in situ hybridization, quantitative polymerase chain reaction, linkage analysis, and capillary-electrophoresis-based Sanger sequencing, to chromosome microarrays and next-generation sequencing (including whole-exome sequencing or even whole-genome sequencing). On the other hand, one recent seminal study in Nature also demonstrated that human placenta is the only non-malignant human tissue to have extensive chromosomal and genomic aberrations, of which such somatic mutations are prevalent in human cancers. The molecular diagnosis of maternal fetal medicine, especially reproductive genetic perspective, is therefore an interesting and important topic to explore. The future trend or the Holy Grail of reproductive genetics includes the following directions, as revealed in the lecture topic: single cell, whole genome, and less invasiveness. The integration of artificial intelligence, semiconductor technology, precision machinery technology, and next generation sequencing will be and is currently generating exciting novel advancements.

What molecular Pap testing can tell you beyond cervical cancers?

分子抹片檢測：除了子宮頸癌，還可以告訴你什麼？

Hung-Cheng Lai

賴鴻政

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Pap smear has been used for more than half a century. The morphology-based cytology examination makes the screening of cervical cancer possible and improves mortality rate in developed countries where the infrastructure was deployed. As the new molecular concept and technology evolve, the information obtained from cervical scrapings is not only cervical epithelium, but may unveil the secrets of the whole Müllarian system, including endometrium, ovary and even the breast. These advances may shed a new light on new gynecology including cancer detection and reproduction.

Endometrial cancer detection is an example. After decades of efforts in cancer research, the improvements in the incidence and survival of most cancers are encouraging. However, one of the exceptions is endometrial cancer (EC), the most common gynecologic cancer, for which both the incidence and mortality rates are increasing. Abnormal uterine bleeding is the most frequent symptom of endometrial cancer, but many other disorders give rise to the same symptom. Transvaginal ultrasound and invasive procedures such as suction curettage, dilatation and curettage under anesthesia and hysteroscopy have been used to exclude endometrial cancer. There is a need for a better method for endometrial cancer screening.

The application of DNA methylation as a biomarker for cancer detection or patient stratification has been increasing. Our previous comprehensive methylomics study illustrated a methylation panel of genes for predicting EC risk using cervical scrapings. The PCR-based detection of methylated BHLHE22/CDO1 genes has been further prototyped in a retrospective cohort with a sensitivity of 84.8% and a specificity of 88.0%. In Taiwan, a multicenter, two-stage confirmatory study was conducted to validate the performance of MPap, including BHLHE22/CDO1/age/BMI. In stage 1, the sensitivity, specificity, and PPV and NPV of MPap were 92.9%, 71.5%, 39.8%, and 98.0%, respectively, for 249 patients. These values were validated in stage 2, where they were 92.5%, 73.8%, 40.2%, and 98.1%, respectively, for 245 patients. MPap outperformed transvaginal ultrasound in all these aspects. MPap uses the infrastructure for cervical cancer screening and provides a feasible alternative for endometrial cancer detection, which may broaden the use of convention Pap for endometrial cancer screening in the future.

Establishment of an instant and rapid whole-genome sequencing analysis system for clinicians

建立即時快速全基因定序臨床分析系統

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Next generation sequencing (NGS) is one of the most important tools for the development of precision medicine. It has greatly improved the ability of sequencing and has become an important tool in disease diagnosis and medication. Through the popularization and maturity of this technology, the cost of sequencing has been greatly reduced and the output of information has become faster and faster. Meanwhile, the efficiency of analyzing huge genome sequence data in the back-end had become more and more important. Our center cooperates with a current bioinformatics service company to jointly develop a rapid diagnosis platform for whole-exon sequencing and whole-genome sequencing. For whole-exon sequencing, the analysis results can be obtained for less than 5 minutes. The platform has a concise, user friendly and easily understand interface. This allows us to quickly upload the whole gene sequencing data and analyze according to the doctor's needs in real time. The platform provides accurate analysis results in a short time and assists clinicians in the diagnosis of diseases. Through the development of the real-time analysis system, patients with rare genetic diseases will be able to obtain rapid diagnosis and early treatment. Moreover, if other disease-causing gene mutations were found during the analysis process, personal prevention/medical plans can be formulated for each individual's situation. Furthermore, through pharmacogenomics analysis, a more accurate and safe medication guide is tailored for each person. We hope this system can make the analysis of WES/WGS more accessible and useable for general physician and then it could promote the development of precision medicine in Taiwan.

Using big genomic data to improve complex: Trait prediction and more with AI

AI 基因體大數據分析改善複雜疾病預測與其他應用

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Biomarkers are an emerging field that can potentially guide the diagnosis, prognosis, and treatment course in disease. To identify such biomarkers many artificial intelligence (AI) systems are developed to help finding genetic variations that contribute to common, complex diseases, such as diabetes, cancer, heart disease, asthma, autoimmune disorders, and mental illnesses. However, the immense amount of available data on SNP phenotype associations merely explains a small portion of heritability.

In this work, we use our recently developed AI-based system, Strata Finder, designed to handle whole genome sequencing (WGS) data so that a vast amount of potentially available information is kept for complex disease analysis. To validate Strata Finder, severe asthma is chosen as our target disease because asthma is a heterogeneous complex disease characterized by reversible airway obstruction, airway hyperresponsiveness, and variable inflammation. Though GWAS have successfully uncovered numerous asthma loci, gaps remain in our understanding of the genetics underlying asthma risk.

Severe asthma patients represent a significant portion of healthcare usage (by asthma patients). Here, we present a whole-genome sequencing analysis comparing severe asthma patients to healthy elderly controls. Our results show the world's best prediction accuracy and several previously reported common asthma related genes are also identified genome-wide. In addition to excellent complex disease risk prediction, our new system has potential to further support medical scientists for exploring patient cohort data to test hypotheses, developing patient stratification schemes, and finding alternative treatment options.

Rapid trio exome sequencing: Where are we now and where should we go?

兒童急重症高速次世代基因診斷的現在與未來

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Genetic diseases have become one of the major causes affecting the health of infants and children. Around 10-30% NICU admission children may have an underlying genetic disease. In addition, rare genetic disease is also the leading reason for hospitalization and mortality in infants. Around 30% of children born with a rare disease may not live over five years of age. Although some patients have diagnosis shortly after birth, still several patients are in a critical condition in 1st stack. However, the diagnosis of genetic diseases is often not fast enough in patients in critical status. We performed rapid trio whole exome sequencing and developed an artificial intelligence-assisted variant interpretation tool for patients in pediatric intensive care units and neonates or with emergent newborn screening results over one year period. Genetics diseases were diagnosed in 50.4% patients with a turnaround time of 5.7 ± 1.2 days (median 5.3, range 3.0-9.9). Sixty-night percent of the positive cases received specific treatment while 74.1% of positive cases had redirection of treatment. More than half of the diagnosis were first reported in Taiwan. The turnaround time of exome sequencing can be shortened by improvements in workflow and variant interpretation tool. Our results revealed an efficiently diagnosis of genetic diseases in infants and children with critical illness.

Molecular diagnostics for severe community: Acquired pneumonia in children

分子診斷於兒童嚴重社區型肺炎的應用

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Background: Community-acquired pneumonia (CAP) is a serious concern for children. The lack of accurate diagnosis may hinder well-established pathogen-directed treatment plans. To solve the diagnostic problem, we evaluated the clinical application of multiplex PCR panels and respiratory metagenomics in children with CAP admitted to the intensive care unit.

Methods: We conducted a prospective observational cohort study at a tertiary medical center. Children aged 0-18 with severe CAP requiring ICU admission were enrolled. Critical cases were defined as CAP patients with septic shock or respiratory failure requiring endotracheal ventilator support; severe cases were others without complications. Multiplex PCR panels on upper and lower respiratory tract specimens and respiratory metagenomics were used to test clinical performance. Bacterial composition was determined by metagenomic sequencing. We integrated standard-of-care (SOC) diagnostic tests and quantitative PCR for orthogonal validation. Diagnostic performance was assessed by detection rates, percent positive agreement (PPA), and percent negative agreement (NPA). Pathogens in the upper and lower respiratory tracts were compared.

Results: Between December 2019 and November 2021, a total of 60 children were enrolled during the study period, including 30 critical cases and 30 severe cases. The combination of multiplex PCR panels and SOC tests could detect at least one pathogen in 98% of all 60 CAP cases. The PPA and NPA of all analytes for multiplex PCR panels were 89% and 98%, respectively. The distribution of pathogens was similar in the upper and lower respiratory tracts, and the titers of pathogens in the lower respiratory tract were equal to or higher than those in the upper respiratory tract. Critical cases had significantly lower diversity of respiratory microbiota, revealing the possibility that respiratory dysbiosis may be involved in these critical situations.

Conclusion: The combination of multiplex PCR panels and respiratory metagenomics had powerful diagnostic performance that could help pediatricians make pathogenic diagnoses and establish management practices. The pathogens in the upper respiratory tract had predictive diagnostic values for lower respiratory tract infections. Respiratory dysbiosis were more profound in children with more severe community-acquired pneumonia.

Very early parameters in childhood predict the late complications of chronic HBV infection in adulthood

兒童期的早期臨床指標預測成人期慢性 B 型肝炎晚期併發症的意義

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Chronic hepatitis B virus (HBV) infection remains a global public health threat, which results in an estimation of 240-250 million persons with chronic HBV infection and more than one million deaths per year due to the complications of chronic HBV infection. Chronic HBV-infected patients are noted to have an increased risk of hepatitis flare, liver fibrosis, cirrhosis, chronic liver insufficiency, esophageal varices, portal hypertension, ascites, hepatopulmonary syndrome, portopulmonary hypertension, hepatic encephalopathy, spontaneous bacterial peritonitis, portal hypertension, and even the occurrence of hepatocellular carcinoma (HCC).

Based on our very long-term chronic HBV cohort conducted since more than 35 years ago, our study group reported many precious data about the natural course, antiviral effect, and host-viral interaction of chronic HBV infection from children to adults. Hepatitis B e antigen (HBeAg)-negative hepatitis is a clinical indicator of poor outcome for chronic HBV infection, and is noted to increase the risk of liver fibrosis and cirrhosis. Male gender, HBV genotype C infection, HBeAg-seroconversion after 18 years of age, and lamivudine therapy prior to HBeAg seroconversion were predictors of HBeAg-negative hepatitis in HBeAg seroconverters. HBeAg-negative hepatitis subjects carried more A1762T/G1764A, C2063A, and A2131C HBV gene mutations than those without HBeAg-negative hepatitis. Male sex, age ≥18 years, elevated α-fetoprotein level, and HBeAg-negative hepatitis are risk factors for liver fibrosis. IL-1β is involved in the progression of liver fibrosis in subjects with HBeAg-negative hepatitis.

We further investigated the role of the percentages of basal core promotor (A1762T/G1764A) mutation on the natural course of HBV infection, and demonstrated the percentage of BCP mutation is positively correlated with the HBeAg-seroconversion age. The percentage of BCP mutation ≥20% after HBeAg-seroconversion was predictive of liver fibrosis in adulthood. HBsAg and HBcrAg are serum markers of both HBV covalently closed circular DNA and integrated HBV genome. We demonstrated HBsAg >4.23 log10 IU/mL at 10 years of age, and genotype C HBV infection are predictors of advanced liver fibrosis in adulthood.

These precious data may assist clinicians to detect high-risk, chronically infected children early, and manage them aggressively using appropriate therapeutics.

Precision medicine of developmental origin of health and diseases in the first 1000 days of life

胎幼兒關鍵一千天之精準醫療

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Background: As increases in senile parturient and artificial reproduction, the maternal death rate remains high, and the infant mortality in Taiwan even ranks the second highest in the OECD countries. It is known that prenatal environment influences developmental origin of health and disease (DOHaD) which has been linked to development of health or diseases in children, and even diabetes, hypertension, and heart disease in adults. World Health Organization has alerted that the first 1000 days of life determines 80% of health or disease.

Study hypothesis: Switching from a questionnaire to an App design on algorithm of health big data about personal biomarkers and environmental factors: nutrition balance, vitamin intake, air pollution, passive smoking, fried food, and microbiota, we could alarm, predict, and prevent diseases from maternal, infant diseases and beyond.

Objectives include 1) inputs of decoded data from 10000 retrospective participants'cohort information and 1600 prospective participants data on environmental exposures, sonograms, noninvasive prenatal diagnosis (NIPD), placental doppler vascularity, and biophysiological parameters, followed by tracing of high risk pregnancy or premature delivery; 2) studies of risk factors, blood vitamin D levels and urine immune mediators by chips and gut/vaginal microbiota for the correlation to health or disease of fetal, infant, and childhood; 3) Algorithm of the big data from perinatal environmental exposures and biomarkers for prediction and prevention of diseases from premature lung and brain health and diseases.

Progress reports: We have 1) identified several perinatal risk factors to allergic diseases; 2) found low vitamin D3 levels were prevalent in pregnant women and supplementation of vitamin D3 decreased pre-eclampsia; 3) filed one patent in regard to predict and prevent premature birth by urine exosomes; 4) will further translate the leaky gut syndrome of children in regard to perinatal imprints among microbiota, vitamin D3 and zonulin; and 5) identify the potential link between perinatal vaginal and fecal microbiota and the development of autism and attention-deficit/hyperactivity disorder (ADHD).

Correlation of microbiome with allergies

微菌叢與過敏的關係

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A human being consists of ~40 trillion cells and ~22,000 human genes, but as many as 100 trillion microbial cells (the microbiota) and ~2 million microbial genes (the metagenome) have been found indwelling in the external and internal parts of human body. Recent studies of human microbiome have shown its strong association with immune system development, susceptibility to infectious and chronic diseases, drug response, and even behavior. Understanding the microbial side of commensal function and its interaction with host mucosal immunity become critically important to learn the panorama view for keeping health as well as in the preventive and treatment for human inflammatory diseases. Allergic diseases, such as atopic dermatitis (AD), allergic rhinitis (AR) and asthma (AS), food allergy (FA) and anaphylaxis, are increasing in prevalence in developed countries. In Taipei, one in every five primary school children have AS symptom, and more than half of them have AR symptom. In fact, more than one million Taiwanese suffered from asthma attack in a year. Allergic diseases have the same underlying etiological (e.g., Th2 deviated immune responses against environmental allergens) and pathological mechanism behind mucosal inflammation. Human mucosal membranes that form the first-line defense in our body immune systems not just only in contact with allergens, but also inhabited by niche-specific communities of microbes including bacteria, fungi, and viruses. Many studies have shown that early life environmental microbial exposure contributes to protection against asthma and allergy and is linked with an early activation of the innate immune system and the development of regulatory immune responses. In fact, dysregulation of immunity at mucosal surfaces due to the disruption of homeostasis between mucosal immunity and nosocomial microbiota is thought to be responsible for the alarming global increase in mucosal inflammatory diseases, such as those affecting the gastrointestinal (Crohn's disease, ulcerative colitis and irritable bowel syndrome) and respiratory (asthma, allergy and chronic obstructive pulmonary disorder) systems. However, the detailed mechanism of reciprocal interaction between human microbiome and the development of allergic diseases is still unclear. In this talk, I will present our study on the beneficial of probiotics on the gut microbiota in AD and asthma patients as well as the microbiome change during and after asthma exacerbation. We hope these results can have a new preventive and therapeutic modality in using live bacterial therapy for allergic disorders.

A precision medicine approach to kidney health promotion for mother and child

運用精準醫療促進母親和兒童腎臟健康

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The global burden of chronic kidney disease is increasing. The best strategy to promote global kidney health requires early prevention and treatment. During the first 1,000 days, our bodies can adapt to environmental insults by altering morphology or function (i.e., developmental plasticity). During this special period, adverse environmental conditions can cause developmental programming resulting many chronic diseases in later life. Kidney development can be affected by a variety of environmental factors, including malnutrition, maternal disease, chemical exposure, drug use, infection, and exogenous stress. Today we will address environmental risk factors related to developmental programming of kidney disease, and will describe common mechanisms involved in renal programming. These mechanisms include oxidative stress, dysregulated nitric oxide signaling, abnormal activation of the renin-angiotensin system, and gut microbiota dysbiosis, etc.

The use of precision medicine can accurately classify diseases during treatment, give effective treatment, and accurately stage diseases during prevention. Therefore, we should take different preventive measures in different periods of disease. With precision medicine approach, implementing effective preventive measures to promote kidney health from pregnancy to 2 years of age will be an important key to avoid kidney disease in the future. Primary prevention aims to prevent kidney disease before it occurs. The modifiable risk factors should be avoided. Secondary prevention is the early detection of disease through screening and prompt treatment of kidney disease at the earliest stage. Precision medicine provides different preventive and therapeutic measures based on differences in biomarkers to achieve the best results. We will also report our recent work regarding discovering biomarkers associated with cardiovascular disease risk in early childhood chronic kidney disease.

Kidney health should be a policy that needs to be successfully achieved through the collaboration of physicians, medical practitioners, researchers, policy makers, etc. We believe that through these efforts, through advances in precision medicine and developmental programming, together we can improve the future of global kidney health.

Late onset sepsis in premature infants and gut microbiome: Expanding new horizons in prevention and treatment

早產兒晚發性敗血症與腸道微菌叢：預防與治療的新視野

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Neonatal sepsis is an important cause of morbidity and mortality in neonates and infants. There is still no effective strategy to prevent neonatal sepsis. Early-onset sepsis (EOS) is defined as symptoms appearing within the first 72 hours of life, while group B *streptococcus* (GBS) infections is defined as occurring within 7 days of birth; late-onset sepsis (LOS) is defined as symptoms appearing at more than 72 hours of life, while GBS infection defined as occurring beyond 7 days of age. The pathogens of neonatal sepsis can be acquired through vertical or horizontal transmission, in which the gut may plays a key role in spreading pathogenic bacteria to cause sepsis. We carried out a prospective study in preterm infants. We longitudinally surveyed the gut microbiota of the preterm infants and recorded if they developed sepsis or not after birth. The causative isolates were genome sequenced and specific primers were designed accordingly to genome sequences, to check if gut is the source of the infection. The study proved that gut was a reservoir for bacterial colonization and transmission. Additionally, we found that preterm infants with gut dysbiosis had a higher risk of neonatal sepsis. Preterm infants with sepsis had lower microbial diversity in gut at birth, compared with preterm and term infants without sepsis. We also noted that the composition of gut microbiome in preterm infants was similar to healthy terms at birth but evolved towards dysbiosis with increasing *Proteobacteria* and decreasing *Firmicutes* weeks later. Prolonged antibiotic exposure significantly reduced beneficial *Bifidobacterium* and *Lactobacillus* in gut. Pathogenic bacteria can colonize the gut before neonatal sepsis and persist after the infection. Gut dysbiosis plays an important role in causing sepsis. The association of increased *Proteobacteria* abundance and decrease in microbiome diversity suggests the need for interventions targeting the gut microbiome to prevent dysbiosis and sepsis in preterm infants.

Novel regulatory mechanisms of ductus arteriosus: Looking beyond prostaglandin

動脈導管存開放之調控：前列腺素以外的新機轉

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DA closure is a complex process including two mechanisms: functional and anatomical closures. Functional closure is a transient response mediated mainly by vasoconstriction caused by abrupt increase of oxygen tension and postnatal withdrawal of vasodilatory PGE2. Anatomical closure is a constitutive process of luminal obliteration characterized by intimal thickening, resulting in progressive DA vascular remodeling and permanent DA closure. Current clinical approach for management of DA patency is mainly targeted on the PGE/cAMP pathway. However, recent studies have shown that PGE can promote DA remodeling through EP4 receptor while maintaining DA vasodilation. Therefore, novel pharmacologic strategy regulating vaso-reactivity and remodeling would be helpful for manipulation of DA patency.

The purposes of this talk are to review the complex mechanisms regulating DA patency, and share our studies in novel pharmacologic targets, including B-type natriuretic peptide, sGC/cGMP pathway and Notch signaling. An improved understanding of the mechanistic pathways regulating DA patency may yield novel or additional therapeutic strategies for patients with PDA and DA-dependent CHDs.

Current studies of gene therapy for spinal muscular atrophy in Taiwan

台灣脊髓性肌肉萎縮症基因治療研究之新進展

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Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease, the leading genetic cause of infant mortality in the world, caused by deletion or mutation of the SMN1 gene. The spectrum of severity at diagnosis ranges from presymptomatic newborns to symptomatic patients which is divided into four subtypes based on age at onset and best achieved motor function. SMA type 1 (SMA1) is the most common and severe form, which presents within the first 6 months of life, unable to sit independently lifelong. The onset of SMA type 2 (SMA2) is between 6 and 18 months of age and the highest motor milestone achieved is sitting independently. Patients with SMA type 3 and type 4 typically show onset from 18 months of age and adulthood, respectively, have the ability of walk alone initially.

FDA approval of three disease-modifying therapy (DMT) for SMA including RNA drug-Spinraza, Gene therapy- Onasemnogene abeparvovec, and oral drug- Evrysdi since 2016, has dramatically changed the disease natural course and improved the prognosis. Study of the Taiwanese natural history of 111 SMA1 patients, who have not received DMT interventions, revealed the median age at death was 8.8 months (Brain & Dev 2021).

In patients with SMA1, a single intravenous infusion of adeno-associated viral vector containing DNA coding for SMN resulted in longer survival, superior achievement of motor milestones, and better motor function than in historical cohorts (NEJM 2017). US FDA approved onasemnogene abeparvovec for SMA children less than 2 years old in 2019 and EU EMA approved for SMA children with 1-3 SMN2 copies and less than 21 kg in 2020 (Lancet Child Adolesc Health 2021). Onasemnogene abeparvovec administered during the first 6 weeks post-partum to presymptomatic infants with 2 or 3 SMN2 copies at risk for SMA1 or SMA in phase III SPR1NT trial alters the natural course of disease and results in better motor outcomes, ventilator-free survival, and nutritional and respiratory independence as compared with untreated patients with SMA1 or SMA who those treated after symptom onset (Nature Med 2022).

This presentation will report the current presymptomatic infants and symptomatic SMA patients received onasemnogene abeparvovec treatment via managed access program, and the status of ongoing SMART and STEER trials in Taiwan.

Current studies of gene therapy for Fabry disease in Taiwan

台灣法布瑞氏症基因治療研究之新進展

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Fabry disease (FD) is an X-linked lysosomal storage disease, caused by genetic mutations on *GLA* gene encoding alpha-galactosidase A enzyme (α-GLA). The incidence of FD was around 1/50,000 worldwide, but relatively higher at approximately 1/1,600 in Taiwan. The biological function of GLA is involved in the breakdown of globotriaosylceramide (Gb3) in lysosome. Lack of GLA enzyme activity resulted in accumulation of Gb3 and caused life-threatening diseases such as stroke, cardiac, and renal failure. The enzyme replacement therapy (ERT) is the most common therapy for FD. However, ERT has several disadvantages, such as short half-life of protein drug and extremely expensive. Therefore, development of a new therapeutic strategy for FD is highly demanded.

Recently, gene therapy has become a promising therapeutic approach for genetic diseases. We have developed AAV viral vectors encoding *GLA* and applied to *Gla* knockout ($Gla^{-/y}$) mice, a model of FD. Our results showed that the GLA enzyme activity was significantly higher in plasma, liver, heart and kidney of FD mice after treated with AAV9-GLA while the enzyme activity can sustain for at least 3 months. Moreover, AAV9 group ameliorated proteinuria when compared to untreated groups.

We had also developed gene editing strategies for the specific mutation IVS4+919 G>A via the CRISPR/Cas9 system *in vitro*. The first strategy was to use the CRISPR/Cas9 system to excise the sequence that cause aberrant mRNA splicing through non-homologous end joining (NHEJ) pathway. The second one was to use the adenine base editor (ABE) for a direct correction of the aberrant splicing donor sites. Both strategies demonstrated the *GLA* mRNA splicing manner was improved so that the gene function could be restored.

Our data demonstrated the therapeutic potential of AAV9 vector–mediated GLA gene therapy for FD and the efficacy of gene editing strategies in cardiac type Fabry disease cells. By using single administration of the gene therapy product, we can resolve the inconvenience and of repeated injection of ERT and improve patient's life quality. The use of gene therapy may become a new strategy for treating FD in the coming future.

2

人工智慧與精準醫療在心血管疾病的最新進展

State of the Art: Artificial Intelligence and Precision Medicine in Cardiovascular Medicine

時 間：111年7月16日 08:20~12:20

Time: July 16, 2022 08:20~12:20

地 點：臺北榮民總醫院 致德樓第二會議室

Place：The Second Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

人工智慧與精準醫療在心血管疾病的最新進展

State of the Art: Artificial Intelligence and Precision Medicine in Cardiovascular Medicine

Artificial intelligence in the detection of cardiovascular calcification and associated cardiovascular prognosis

人工智慧於心血管鈣化的檢測與預後

Tzung-Dau Wang

王宗道

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Cardiovascular imaging parameters, including cardiac/thoracic aorta calcifications and epicardial adipose tissue amount, are associated with increased cardiovascular events. Their clinical value is currently limited since clinicians are short of rapid quantification tools for these image parameters. We, the TW-CVAI (TaiWan CardioVascular Artificial Intelligence) team, established the big (3,500 cases), coronary centerline-annotated, cross-modality cardiovascular imagebank under the sponsorship from MOST from 2017 to 2020. All these data were uploaded and stored in LIONS cloud as well, which are open to all researchers. We recently developed an artificial intelligence-based segmentation and quantification model (**HeaortaNet**), which can reliably (accuracy >95%) calculate the amount of epicardial adipose tissue and calcifications of heart or segments of thoracic aorta in non-contrast chest computed tomography (CT) in 0.4 second. The **HeaortaNet** was developed by using 70,000 well-annotated non-contrast chest CT axial images with specially designed neural network based on SegResNet and Attention Gate. By applying this model to the imagebank of National Health Insurance (NHI) database (>5,000 cases), we established the first imaging-based cardiovascular risk-prediction model for Taiwanese people who underwent chest CT examination. The collaboration with NHI has been ongoing and encompassing non-contrast Chest CT from >300,000 cases.

Artificial intelligence electrocardiogram detects pulmonary hypertension

人工智慧心電圖檢測肺動脈高壓

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Background: Pulmonary hypertension is a disabling and life-threatening cardiovascular disease. Early detection of elevated pulmonary artery pressure (ePAP) is needed for prompt diagnosis and treatment to avoid detrimental consequences of pulmonary hypertension. We aim to develop an artificial intelligence (AI)-enabled electrocardiogram (ECG) model to identify patients with ePAP and related prognostic implications.

Methods: From a hospital-based ECG database, we extracted the first pairs of ECG and transthoracic echocardiography (TTE) taken within 2 weeks of each other from 41,097 patients to develop an AI model for detecting ePAP (PAP > 50 mmHg by TTE). The model was evaluated on independent datasets, including an external cohort of patients from Japan.

Results: Tests of 10-fold cross-validation neural-network deep learning showed that the area under the receiver operating characteristic curve (AUC) of the AI model was 0.88 (sensitivity: 81.0%; specificity: 79.6%) for detecting ePAP. The diagnostic performance was consistent across age, sex, and various comorbidities (diagnostic odds ratio > 8 for most factors examined). At their 6-year follow-ups, the patients predicted by the AI model to have ePAP were independently associated with higher cardiovascular mortality (hazard ratio [HR]: 3.69). Similar diagnostic performance and prediction for cardiovascular mortality could be replicated in the external cohort.

Conclusion: The ECG-based AI model identified patients with ePAP and predicted their future risk for cardiovascular mortality. This model could serve as a useful clinical test to identify patients with pulmonary hypertension so that treatment can be initiated early to improve their survival prognosis.

Application of artificial intelligence and precision medicine in hypertension

人工智慧與精準醫學在高血壓的應用

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Hypertension is a major global health risk, affecting 1.13 billion people worldwide. However, almost half of people are unaware that they have hypertension. It is therefore important to improve the diagnosis and monitoring of hypertension for better management of blood pressure (BP) and to reduce the risk of developing future cardiovascular diseases (CVD).

Masked hypertension (MH) or masked uncontrolled hypertension (MUCH) is defined as normotensive office BP and hypertensive out-of-office BP. MH refers to treatment-naïve patients and MUCH to patients with prior hypertension treatments. International registries show that MH/MUCH is a highly prevalent condition, present in up to one in three office-controlled patients. Patients with MH/MUCH have an increased risk of mortality and cardiovascular events. Currently, the diagnosis of MH/MUCH depends on out-of-office BP measurement, including ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM), which take at least 24 hours or 7 days, respectively.

Artificial intelligence (AI) approaches have revolutionized the way data can be processed and analyzed. Several studies have shown the potential benefits of AI in the prediction of cardiac arrhythmias, coronary artery disease, heart failure, and stroke. However, the application of AI in hypertension diagnosis or classification is still limited. We developed four models for MH/MUCH prediction using patient features obtained in a single outpatient visit and tested them. Our machine learning-based prediction models could assist physicians with their ability to detect MH/MUCH patients using clinical data obtained in a single outpatient visit. Through timely and proper handling of these models, patients with MH/MUCH could be able to receive early diagnosis and appropriate treatment to prevent cardiovascular events in the future.

Build up next-generation of innovative smart patient room (hospital)

建構下一代創新的智慧病房 (醫院)

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After COVID-19, we've seen tremendous requirements for Digital Healthcare Transformation in the world, and it is happening now. A lot of IT companies and hospitals are trying to use IoT-based wearable devices, cognitive situation awareness, digital twins, mixed reality, 5G Network, cloud platform, and AI related technologies to improve health team productivity, patient experience, end-to-end operation efficiency and so on. Although these technologies each offer highly potential for value creation within healthcare system, when these capabilities come together to enable vertical or horizontal integration, that the ultimate collaboration across different departments and people will achieve true value co-creation in the extended healthcare ecosystem.

Therefore, we realize that hospitals need trusted and integrated capabilities or platforms that makes it easier for hospitals to create personalized patient services, gives health team connected and collaboration tools, and adopts data global standards that are important to healthcare ecosystem. Hospitals can use almost no-code and low-code AI that combines multiples sources to gain full visibility on data insight, relieve administrative burden, and improve daily process and workflow automation to create actionable insight that delivers better care service in faster way and at a lower cost.

To summarize the challenges that most hospitals have and to build up next-gen of innovative hospitals, we come out four main pillars below that support hospitals to move forward:

- Enhancing Patient Experience: by enabling patient data to flow securely across the care continuum, creating individualized patient experiences, and delivering virtual health tools to facilitate communication between clinicians and their patients.
- Empowering Health Team Collaboration: by making it faster and easier to coordinate care, collaborate on shared and unified view of patient, and continually monitor patient across remote locations.
- Improving Clinical and Operational Insight: by uniting data silos and applying advanced analytics and AI to reveal actionable insights to make better, smarter, clinical and operational decisions. You can even trigger automated workflows based on patient or staff actions and predictive analysis.
- Protecting Health Information: by adopting global hybrid cloud platform to lower down the barrier for data compliance, security and privacy, to accelerate holistic smart healthcare transformation.

Comprehensive AI-integrated ECG system: The experience from Tri-Service General Hospital

全方位心電圖人工智能整合平台：三軍總醫院經驗

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The application of artificial intelligence (AI) to the electrocardiogram (ECG) has seen significant advances recently. Tools to automate ECG interpretation, extending human capabilities via massive scalability permit signal acquisition. Moreover, algorithms to identify conditions not visible to human readers by training networks to identify multiple, complex, non-linear patterns in the ECG signal to find occult disease, or impending disease had been established extensively.

Since the year of 2016, we have collected the ECG signals and proxy labels from the data of EMR (Electronic medical record) or gold standard labels to train our AI deep learning models. Several models had been developed well and been published, such as dyskalemia models, ST-segment elevation myocardial infarction models, aortic dissection models, low left ventricular (LV) ejection fraction (EF) models, and cardiac age models. There are a total of 13 papers published currently and these models exbibits a strong clinical performance with the area under curve (AUC)>0.90.

Such models had been applied in remote areas, ambulance systems, and emergency department (ED). Of note, the application of our AI-ECG system significantly facilitates the management of acute ST-elevation myocardial infarction, in both ambulance system and remote areas. In our ED, the AI-ECG system significantly shortened the door-to-balloon time. Additionally, our system helps to screen patients with asymptomatic atrial fibrillation and reduced LVEF in remote areas, which provides opportunities to early intervention for these potential lethal diseases.

The ECG is an ever-present diagnostic tool that has served medical practitioners for more than a century. With the support of deep learning AI techniques, it is clearly entering a new era, in which it may prove to be a powerful detector of subclinical and clinical cardiac diseases, going beyond the boundaries of human observation. In this talk, I will introduce the currently developed AI-enabled ECG system in our hospital, focusing on its integration and real-world practice.

A transferable in-silico augmented ischemic model for virtual myocardial perfusion imaging and myocardial infarction detection

智慧手錶於心血管疾病的應用

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This study proposed an innovative approach to generate a generalized myocardial ischemia database by modeling the virtual electrophysiology of the heart in silicon. We developed a strategy based on the clinical pathophysiology of MI to generate a heterogeneous database with clinical relevance and reduced computational complexity. Firstly, the virtual heart is simplified into adequate amount of regions that match the types and locations of MI diagnosed by 12-lead ECG, and the major arteries were divided into 3-5 segments from upstream to downstream according to the general anatomy. Secondly, the stenosis or infarction of the major or smaller branches of the coronary arteries can cause different perfusion drops and infarct sizes. To elaborate on possible ECG representations, we simulated the ischemic sites in different branches of the arteries by meandering the infarction location, altering the infraction's size, and changing the transmembrane potential (TMP) of the myocytes associated with different levels of perfusion drop. A total of 8190 different case combinations of cardiac potentials with ischemia and MI were simulated, and the corresponding ECGs were generated by forward calculation. Finally, we trained and validated our in-silico database with sparse representation classification (SRC) and tested the transferability to real-world scenario by PTB database. The overall accuracies for localizing MI region on the PTB data achieved 0.86, which is only 2% drop as compared to that derived from the simulated database (0.88). In summary, we have shown that the virtual ECG generated based on cell model, functional physiology, and anatomy is possible to transfer in-silico data to in-vivo target by a proper machine learning technique. This can also provide a promising alternative for machine learning even with insufficient real-world data.

Machine learning of treadmill exercise test to improve selection for testing for coronary artery disease

使用機器學習改善冠狀動脈疾病接受心導管病患的選擇

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Background: The high false-positive rate of the treadmill exercise test (TET) may lead to unnecessary invasive coronary angiography. We aimed to develop a machine learning-based algorithm to improve the diagnostic performance of TET.

Methods: Study included 2325 patients who underwent TET and subsequent coronary angiography within one-year interval. The mean age was 58.7 (48.1-69.3) years, 1731 (74.5%) were male, 1858 (79.9%) had positive TET result, and 812 (34.9%) had obstructive coronary artery disease (≥ 70% stenosis in at least one vessel). The study population were randomly divided into training (70%) and testing (30%) groups for algorithm development. A total of 93 features, including exercise performance, hemodynamics and ST-segment changes were extracted from the TET results. Clinical features included comorbidity, smoking, height, weight, and Framingham risk score. Support vector machine, logistic regression, random forest, k-nearest neighbor and extreme gradient boosting machine learning algorithms were used to build the predictive models. The performance of each model was compared with that of conventional TET.

Results: Four of the five models exhibited comparable diagnostic performance and were better than conventional TET. The random forest algorithm had an area under the curve (AUC) of 0.73. When used with clinical features, the AUC improved to 0.74. The major advantage of the algorithm is the reduction of the false-positive rate compared with conventional TET (55% vs. 76.3%, respectively), while maintaining comparable sensitivity (85%).

Conclusion: Using the information obtained from conventional TET, a more accurate diagnosis can be made by incorporating an artificial intelligence-based model.

Application of artificial intelligence in the diagnosis and treatment of atrial fibrillation

人工智慧在心房顫動診斷與治療的應用

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Artificial intelligence (AI) based precision cardiovascular medicine is on the rise. AI techniques have been applied in cardiovascular medicine to explore novel genotypes and phenotypes in existing diseases, improve the quality of patient care, enable cost-effectiveness, and reduce readmission and mortality rates. There are several AI algorithms have already been approved for cardiovascular medical usage by the American Food and Drug Administration (FDA). AI has given rise to a paradigm shift toward personalized precision cardiovascular medicine. The increasing use of AI tools in cardiologists' daily practice is continuing.

Catheter ablation is considered the first-line therapy for patients with symptomatic and drug-refractory atrial fibrillation (AF), for which circumferential pulmonary vein isolation (PVI) is the cornerstone treatment. Before ablation, the anatomic information of the left atrium (LA) is pivotal for the operator. However, the anatomic structure of LA and that of pulmonary veins are complex, which makes manual measurement and contouring time-consuming and challenging. In addition, the non-pulmonary vein (NPV) trigger has been reported as an important predictor of recurrence post-AF ablation. Elimination of NPV triggers can reduce the recurrence rate. We will apply the deep learning model as a primary analytic platform to overcome these problems. The convolutional neural network was utilized for pre-ablation pulmonary vein computed tomography geometric slices to create an automatic construction of geometry from LA and prediction for NPV triggers in patients with paroxysmal AF. As well, the possible AF drivers can be located by AI. We will discuss several cases for the demonstration of AI in catheter ablation.

Applying medical platform in clinical practice

如何建立醫療資訊網站並運用於臨床照護

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In the realm of medical oncology, there are often two colors: black and white; clinical analyses and basic cell studies despite world is colorful.

I am a medical oncologist and my expertise is in treating colorectal and skin cancer. Beyond the basic and clinical studies. I enjoy the world of program for years and I design many different systems for assisting in the field of medicine and studies by myself. In the brief talk, I will show you the possibilities of web-based application in clinical medicine. Also, I will show which language used in developing these systems, such as JAVA, Javascript, HTML, CSS, R python.

First of all, web site (domain name) could be a good business card. For example, “crc.uptocare.com” is my business card. It discloses many important focuses from patients’ viewpoints. Also, it could be the ROOT of many web-based clinical application. Secondary, Database is the core of web-application and I will share the idea of how to select a fitted database system. Third, the data collect is the entry of application, I will show how do I do in the field of medicine. Finally, I will show you the application of web-based system, such as dynamic nomogram, shiny-dynamic nomogram, image-process by canvas, Robot/.bat and python a little.

From the viewpoints of clinical physicians, the Code/Program is the myth of Pandora’s box. While we would like to open Pandora’s box, we should not only see the Evils escaping from jar but also see the Hope in the bottom of Pandora’s box.

Due to the time limitation, data analysis and papers is not shown here.

Application of the Metaverse in cardiovascular diseases

元宇宙於心血管疾病之應用

Ted Chang
張嘉淵
Quanta Computer Inc.
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The recent rapid rise of Metaverse creates new possibilities of future smart medicine in the virtual space. Most of the interest now focus on visualization and related applications of Extended Reality (XR) including AR, VR and MR for immersive social experience. In the talk, we shall focus more on the core operation of Metaverse, including digitalization, simulation and virtualization, together with its linkage to real world medical applications through Digital Twins with focus on the heart and related potential precision medicine.

To support the smart medicine in the new Metaverse, we shall also share our perspectives on the integration of Medical IoT(MIoT), Cloud Computing, Medical Big Data, Machine Learning and AI to build the Digital Twins of various medical and healthcare activities for different users and use cases involved.

3

核醫的精準治療：治療診斷學

Precision Medicine in Nuclear Medicine: Theranostics

協辦單位：中華民國核醫學學會放射碘及同位素治療委員會
財團法人中華民國輻射防護協會

時　間：111年7月16日　08:00~12:00
Time：July 16, 2022　08:00~12:00

地　點：臺北榮民總醫院 致德樓第三會議室
Place：The Third Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

核醫的精準治療：治療診斷學
Precision Medicine in Nuclear Medicine: Theranostics

Peptide receptor radionuclide therapy for neuroendocrine tumor

神經內分泌腫瘤執行肽受體放射性核種治療

Tse-Hao Lee

李哲皓

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臺北榮民總醫院 核醫部

Background: Peptide Receptor Radionuclide Therapy (PRRT) with Lu-177 DOTATATE has been approved for therapy of inoperable gastrointestinal and pancreatic neuroendocrine tumor, pheochromocytoma and paraganglioma. It targets somatostatin receptors expressed on the surface of tumor cells followed by internalizing into these cells. The tumor cells would be destroyed by beta particle emission from Lu-177. By standard now, Lu-177 DOTATATE PRRT is a four course therapy with eight weeks between each course. For each course, the treatment dosage is 7.4GBq. In this case series, we will report two patients who received PRRT in our hospital in terms of underlying tumor status, therapy course, adverse event and treatment outcome.

Methods: During September 2021 and March 2022, we included two patients, who are our total patients receiving PRRT during this period. For each therapy course, patient had pre-medication including anti-emetics followed by intravenous infusion of amino acid fluid (@LysaKare) for four hours. At least 30 minutes after amino acid infusion, 7.4 GBq Lu-177 DOTATATE was intravenously administrated to the patient by gravity method. For each patient, laboratory data (including complete blood count, liver function, renal function and electrolytes level) and radiological images (including CT or MRI) in pre-therapy and post- therapy phases were collected. Adverse event was also documented according to Common Terminology Criteria for Adverse Events (CTCAE). We also performed post-therapy scan in the day after Lu-177 DOTATATE infusion.

Results: All patients completed four course of PRRT. Post therapy scans were evaluated for radiotracer distribution and also compared to radiological images (CT or MRI) for evaluation of therapy outcome.

Conclusion: PRRT for inoperative neuroendocrine tumor is feasible practically and our patients could tolerate it.

Current status of Ra-223 therapy

鐳 -223 治療現狀

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高雄榮民總醫院 核子醫學科

Radium-223 dichloride (Ra-223) is the first alpha-particle emitting radiopharmaceutical to be approved for the treatment of the patients with castration-resistant prostate cancer and associated bone metastases. Based on the phase 3 ALSYMPCA trial (NCT00699751), Ra-223 significantly improved overall survival (median, 14.0 months vs. 11.2 months; hazard ratio, 0.70; 95% confidence interval [CI], 0.55 to 0.88; two-sided P=0.002) and confirmed survival benefit (median, 14.9 months vs. 11.3 months; hazard ratio, 0.70; 95% CI, 0.58 to 0.83; P<0.001). The following phase 3b trial of Ra-223 and concomitant therapies (NCT01618370 and EudraCT number 2012-000075-16) showed that median overall survival was also longer in patients who received Ra-223 plus abiraterone, enzalutamide, or both (median NA, 95% CI 16 months-NA) than in those who did not receive these agents (median 13 months, 12-16), and in patients who received Ra-223 plus denosumab (median NA, 15 months-NA) than in patients who received Ra-223 without denosumab (median 13 months, 12-NA). The subsequent phase 3 ERA 223 trial (NCT02043678) showed that the addition of Ra-223 to abiraterone acetate plus prednisone or prednisolone did not prolong overall survival (30.7 months vs. 33.3 months; hazard ratio, 1.195; 95% CI, 0.950-1.505) and improve symptomatic skeletal event-free survival (SSE-FS) (median, 22.3 months vs. 26.0 months; hazard ratio, 1.122; 95% CI, 0.917-1.374; P=0.2636), and was associated with an increased frequency of bone fractures compared with placebo (29% vs. 11%). However, in the real-world setting, incidence rates of SSE-FS were reduced when bone health agents were used. Additional trials are planned to explore concomitant therapies using Ra-223 plus enzalutamide (PEACE III trial, NCT02194842) or docetaxel (DORA trial, NCT03574571).

Development experience of F-18 PSMA in Taipei Veterans General Hospital

F-18 PSMA 的北榮發展經驗

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Prostate cancer is one of the most common malignancies in men, which means that prostate cancer has a very significant impact on men's health. Because most patients are asymptomatic during the early stage, illness is easily overlooked. As the result, they are usually diagnosed in the advanced stage of disease and are commonly associated with bone metastasis once symptoms have appeared. Given early diagnosis and proper therapy, patients' 5-year survival rate is nearly 100%. However, if the cancer cells metastasize beyond the prostate and nearby lymph nodes, the survival rate will drop sharply to be less than 30%.

The department of nuclear medicine at Taipei Veterans General Hospital (TVGH) had developed the PET tracer of PSMA (prostate-specific membrane antigen; F-18 PSMA-1007) last year, and had served more than 100 patients. PSMA is less expressed in normal prostate tissues. Nevertheless, PSMA is over-expressed on the cellular membrane of malignant prostate cells, either primary tumor or metastatic sites. Therefore, with radio-labeled (i.e., F-18, Ga-68, or Lu-177), PSMA is an ideal tracer for the diagnosis or treatment of prostate cancer. Ga-68 PSMA was applied clinically, however, the production of Ga-68 PSMA is processed via the Ge-68/Ga-68 Generator, while the Ge-68/Ga-68 Generator needs to be imported from overseas. In addition, the expiration date of this Generator is only about 9 months to 1 year, so it is relatively expensive in cost. TVGH has developed F-18 labeled PSMA to F-18 PSMA-1007. The half-life ($t_{1/2}$) of F-18 PSMA-1007 is around 110 minutes. Practically, because there is an on-site cyclotron in TVGH, it is no longer limited to the validity period of foreign breeders. A study of F-18 PSMA-1007 has currently passed the IRB of TVGH. Two major groups of prostate cancer patients are included in this study: (1) treatment course had been completed for years, but their PSA level was upraised again. No definite recurrence or metastases was found via other assessment methods. (2) After initial diagnosis, patients need a whole-body survey to exclude occult metastasis before receiving surgery or radiotherapy.

Radiolabeling of the F-18 PSMA-1007 is complicated and challenging. The multidisciplinary team contained diverse professionals (i.e., radiochemists, pharmacists, radiologists, physicians) who work together to achieve today's preliminary accomplishments. Nuclear Medicine at TVGH will continue to improve in order to provide the best care for patients in the future.

Current status of F-18-BPA PET in boron neutron capture therapy (BNCT)

FBPA 正子攝影應用於硼中子捕獲治療之現況

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Boron neutron capture therapy (BNCT) serves as a cellular-level radiation therapy which is based on the nuclear reaction of the ^{10}B nucleus in tumor cells, followed by thermal neutron radiation to induce ^{10}B nucleus fission reaction, which absorbs low-energy neutrons to produce two high-linear-energy transfer particles (^{4}He and ^{7}Li). These two particles have great biological effects on tumor cells, and the most advantage is that their cellular destruction of target lesions reaches only reach 4–9 μm, which confines just within a single tumor cell, causing little damage to the surrounding normal tissues.

The key elements of the success of BNCT lie in a high quality thermal neutron beam which could induce the reaction and a tumor-specific boron-containing carrier. Meanwhile, to illuminate the concentration of the boron-containing carrier with a non-invasive imaging method also becomes a critical issue to predict the efficacy of BNCT

Currently, most medical and research institutes use BPA as a ^{10}B carrier. BPA is an analogue of the essential amino acid phenylalaine. Meanwhile, the concentration of BPA in tumor cells and normal tissues could be monitored with ^{18}F- boronophenylalanine (^{18}FBPA), an ^{18}F-labeled radiopharmaceutical analogue of BPA which can be detected by PET imaging. The ^{18}FBPA-BPA theranostic combination gives us a crucial picture to calculate the estimated tumor dose to assure safety and efficacy of BNCT. Based on the information by ^{18}FBPA-PET, especially the tumors and normal tissues (T/N ratio), physicians can draw up treatment plans and confirm the irradiation dose from boron neutron capture reaction.

The role of ^{18}FBPA in BNCT is crucial, but some issues need to overcome during clinical use. In this section, the pros and cons of ^{18}FBPA will be discussed.

Radiation safety of radionuclide therapy

核種治療之輻射安全衛教

Chien-Hsin Ting

丁建鑫

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Medical radiation accidents and unintended events may lead to accidental or unintended medical exposure of patients and exposure of staff or the public. Most unintended exposures in nuclear medicine will lead to a small increase in risk; nevertheless, these require investigation and a clinical and dosimetric assessment. Nuclear medicine staff are exposed to radiation emitted directly by radiopharmaceuticals and by patients after administration of radiopharmaceuticals. Dose constraints should be set for planning the exposure of individuals. The preparation and administration of radiopharmaceuticals can lead to high doses to the hands, challenging dose limits for radionuclides such as ^{90}Y and even ^{18}F. The risks of contamination can be minimized by basic precautions, such as carrying out manipulations in purpose-built facilities, wearing protective clothing, especially gloves, and removing contaminated gloves or any skin contamination as quickly as possible. Airborne contamination is a potential problem when handling radioisotopes of iodine or administering radioaerosols. Manipulating radiopharmaceuticals in laminar air flow cabinets, and appropriate premises ventilation are necessary to improve safety levels.

Ensuring patient safety and minimizing the risk of incidents require efficient overall quality management. Critical aspects include: the booking process, particularly if qualified medical supervision is not present; administration of radiopharmaceuticals to patients, with the risk of misadministration or extravasation; management of patients' data and images by information technology systems, considering the possibility of misalignment between patient personal data and clinical information. Prevention of possible mistakes in patient identification or in the management of patients with similar names requires particular attention. Appropriate management of pregnant or breast-feeding patients is another important aspect of radiation safety. In radiopharmacy activities, strict quality assurance should be implemented at all operational levels, in addition to adherence to national and international regulations and guidelines. This includes not only administrative aspects, like checking the request/prescription, patient's data and the details of the requested procedure, but also quantitative tests according to national/international pharmacopoeias, and measuring the dispensed activity with a calibrated activity meter prior to administration. In therapy with radionuclides, skin tissue reactions can occur following extravasation, which can result in localized doses of tens of Grays. According to literature, proper instructions are fundamental to keep effective dose to caregivers and family members after patient discharge below the Dose constraints. The IAEA Basic Safety Standards require measures to minimize the likelihood of any unintended or accidental medical exposures and reporting any radiation incident. The relative complexity of nuclear medicine practice presents many possibilities for errors. It is therefore important that all activities are performed according to well established procedures, and that all actions are supported by regular quality assurance/QC procedures.

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2022年榮總台灣聯合大學系統
第18期合作研究成果發表會
2022 University System of Taiwan Research Presentation

時　間：111年7月16日　08:30~12:30

Time：July 16, 2022　08:30~12:30

地　點：臺北榮民總醫院 致德樓第四會議室

Place：The Fourth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

2022年榮總台灣聯合大學系統
第18期合作研究成果發表會
2022 University System of Taiwan Research Presentation

SEEG for MR negative and drug-resistant epilepsy

立體定位深部腦電波與大腦網路於於 MR 上無病灶、難治型癲癇之用：病灶定位、訊號分析及癲癇網絡之研究

Cheng-Chia Lee[a], Chien-Chen Chou[b], Chun-Fu Lin[a], Cheng-Ren Duann[d], Hsiang-Yu Yu[b], Yue-Ru Li[d], Syu-Jyun Peng[c], Chin-Po Lin[d], Sheng-Che Hung[e], Kun-Hsieh Chou[d]

李政家[a] 周建成[b] 林俊甫[a] 段正仁[d] 尤香玉[b] 李岳儒[d] 彭徐鈞[c] 林慶波[d] 洪聖哲[e] 周坤賢[d]

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[c] 臺北醫學大學 [d] 國立陽明交通大學 [e] 北卡羅來納大學 放射學系

Background: Stereo-electroencephalography (SEEG) is an invasive method to study electroencephalography for the presurgical evaluation of epilepsy. The main purpose is to reveal the epileptogenic zone. It provides an opportunity to resect the lesion for curing DRE patient. For the patients with lesion in the deep brain structures or focal cortical dysplasia (FCD) in MR negative, SEEG is an outstanding tool to define the regions which generate epileptic discharges directly. Nowadays, the application of SEEG is an indispensable technique for evaluating epileptogenic zone and the whole epileptic network. Good quality of SEEG is going to support the more precise clinical treatment for insidious FCD and other malformations without clear lesions, such as heterotopia, polymicrogyria (PMG). We aimed to precisely localize epileptogenic zones (EZ) and functional zones and refine surgical strategies.

Methods: We recruited 60 drug-resistant epilepsy patients during 2019-2022. All patients need to undergo presurgical evaluation including phase I scalp and video electroencephalography (EEG), neuroimaging studies including a brain magnetic resonance imaging (MRI) and a brain positron emission tomography study (PET), neuropsychological test and phase II stereo-electroencephalography (SEEG) and intracranial stimulation for mapping. The SEEG implantation scheme is based on the anatomo-electro-clinical hypothesis, sampling suspected lesions and any associated malformations.

Results: SEEG can demonstrate epileptogenic zone, seizure onset zone, and irritative zone clearly without minimal artificial signals. Intracranial stimulation study also shows the functional regions including motor, sensory, visual, auditory, even language areas within several malformation of cortical development. While phase I evaluations outlined potential epileptic regions, SEEG and stimulation study precisely delineated EZ and intralesional functional zones, respectively, allowing subsequent epilepsy surgery to resect or disconnect EZ without compromising functional cortex. Epileptic surgeries were carried out in all patients. Most of the patients had apparent reduction on seizure frequency. And 11 of them were seizure-free at follow-up (mean: 17 months) and had no post-operative neurological deficits.

Conclusion: SEEG study may provide the precise information about the FCD-DRE. In the near future, it will be part of planning for the epilepsy surgery, especially for MR-invisible epileptogenic foci.

Development of cylindrical zinc ion sensor for surgical applications

可應用於外科手術之圓柱狀鋅離子感測探頭開發

Li-Yin Chen

陳俐吟

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國立陽明交通大學 光電工程學系

Zinc ions are a rapidly changing and very important transition metal ion in the human body. Many acute brain injuries, whether from trauma, epilepsy, or after cerebral ischemia, are associated with zinc-induced neurotoxicity. Studies have shown that after brain trauma or stroke, zinc ions are released into the synaptic compartment along with excess glutamate, a neurotransmitter that is toxic to cells, and is involved in the death of neuroglia and neurons. Therefore, the sensing of zinc ions can be of great benefit in the monitoring of brain diseases. This research aims to develop a low-cost, highly reliable, and medically usable zinc ion sensor, and to develop a real-time sensor system for the medical treatment and monitoring of brain trauma-related diseases. This project is conducted by professionals in the medical and optoelectronic fields in Taipei Veterans General Hospital and National Yang Ming Chiao Tung University. The technology uses a hydrogel coated cylindrical symmetrical optical fiber structure to miniaturize the sensor and use the optical fiber system to detect zinc ions. The miniaturized cylindrical solid-state probe will be more suitable for brain injury diagnosis in the future and can be used with existing invasive brain detectors to detect injuries in the future with only minimally invasive surgery. The results of this project demonstrate that this cylindrical symmetric zinc ion hydrogel sensor can detect zinc ions in the range of 10-3M to 10-6M, meeting the demand for clinical sensors in the range of 10-5M to 10-6M for medical applications, and that this material system is non-cytotoxic and has the potential to provide further precision for clinical validation in the future.

Developing a novel bioreactor for the culture of tissue repairing precursor cells

研發並利用新穎生物反應器培養組織修復之前趨細胞

Shen-Liang Chen[a], Chung-Yuh Tzeng[b], Wei-Wen Hu[c], Chun-Jung Chen[b]

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Background: Bone is among the most frequently transplanted tissues with about 2.2 million procedures annually worldwide, so a musculoskeletal (MuSK) tissue generated *in vitro* is highly demanded for clinical transplantation. The precursor cells of muscle, tendon, and bone share their common origin from the embryonic tissue called somites in trunk. Currently, the culture systems of precursor cells for muscle and bone have been established but their integration into a functional musculoskeletal tissue remains to be established.

Methods: Primary stem cells and cell lines of bone and muscle were cultured on petri dishes to formulate/optimize the culture conditions for increasing their proliferation and differentiation, then the same conditions will be applied to cells cultured in a bioreactor, which can provided electric and contractile stimuli. Improving of the bioreactor culture system through modular design aiming at providing MuSK tissues was employed. Successfully amplified bone and muscle precursor cells or differentiated osteocytes and myotubes will be harvested for injection into damaged musculoskeletal tissue.

Results: A multifunctional bioreactor has been constructed using a highly stretchable conductive membrane that is prepared by depositing conductive and thermos-sensitive *N*-isopropylacrylamide (NIPAAm)/polypyrrole (PPy) onto elastic polydimethylsiloxane (PDMS) substrate. Therefore, muscle precursor cells after electric and stretching stimulations can be completely harvested as cell sheets through reducing temperature. This novel bioreactor provide prototype musculoskeletal tissue conserving more extracellular matrix (ECM) for transplantation. A myogenic kit consists of insulin, LiCl, T_3, and retinoic acid (RA) has been formulated, and its effect on C2C12 and primary satellite cells (muscle stem cells, MuSC) differentiation has been further demonstrated. This myogenic kit significantly increased the fusion index and MHC expression level of both C2C12 and satellite cell myotubes. The optimal osteogenic condition for MC3T3-E1 cells has also been established. Currently, we are combining the myogenic kit and the bioreactor to generate more MuSC and mature myotubes derived from primary satellite cells.

Conclusion: The combination of myogenic kit and novel bioreactor should provide environment for efficient proliferation and differentiation of myogenic and osteogenic precursor cells. These precursor cells and mature myotubes and osteocytes will be useful materials for clinical grafting into damaged musculoskeletal tissue.

Cardiac dysfunction in Fontan patients: A multimodal diagnostic study for optimal treatment

多向評估 Fontan 術後病人之心功能失調：對病人處置指標之建議

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Background: Patients with Fontan circulation nowadays have a well long-term survival with the improvement of post-surgery care and follow-up examination techniques. However, ventricular dysfunction and heart failure may occur in a decade after surgery. How to evaluate the risk of cardiac events in an early disease stage is an important issue for the patient management. The aim of this study was to investigate the systolic energy transferring in patients with Fontan circulation.

Methods: We recruited 32 Fontan patients (17.8 ± 4.3 y/o, M/F 20/12) and 37 age- and sex-appropriate normal volunteers (21.7 ± 1.1 y/o, M/F 22/15). The intraventricular and aortic kinetic energy (KE) was assessed by 4D Flow magnetic resonance. The time between peak intraventricular KE and aortic KE was defined as KE delay. The ratio of mean intraventricular KE and aortic KE was defined as KE efficiency.

Results: Compared to normal control, Fontan patients presented significantly decreased and prolonged peak intraventricular (1.58 ± 0.93 mJ vs. 2.07 ± 0.88 mJ, $p < 0.05$) and aortic KE (12.6 ± 6.7 mJ vs. 23.6 ± 6.6 mJ, $p < 0.05$). The KE delay increased (52.8 ± 17.8 ms vs. 21.7 ± 19.50 ms, $p < 0.001$) and KE efficiency decreased (7.2 ± 4.3 vs. 11.9 ± 3.9, $p = 0.01$) in Fontan patients. Significant correlations were found between intraventricular KE index to stroke volume, KE delay, KE efficiency, and ejection fraction (all $p < 0.05$) which may reveal the remodeling of energy transferring in Fontan patients.

Conclusion: In Fontan patients, the remodeling of intraventricular and aortic flow was correlated in the view of energetic transferring during systole. Further study is required to provide information about the impairment, compensation, interaction mechanism, and management in Fontan patients.

5

腎臟病的轉譯醫學研究：從基礎到臨床

Translational Research in Kidney Disease: From Bench to Bedside

時 間：111年7月16日 08:30~12:00

Time: July 16, 2022 08:30~12:00

地 點：臺北榮民總醫院 致德樓第五會議室

Place: The Fifth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

腎臟病的轉譯醫學研究：從基礎到臨床

Translational Research in Kidney Disease: From Bench to Bedside

Translational research in chronic kidney disease (CKD): From bench to bedside

慢性腎臟病的轉譯研究：從基礎到臨床

Yasuhiko Tomino

Juntendo University, Tokyo Japan

Outlines:

1) Chronic kidney Disease (CKD): Characteristics, Definition, Classification and Major causal diseases (IgA nephropathy is major cause of CKD)
2) IgA nephropathy: Definition, Clinical features, Hypothesis of Pathogenesis (Short Summary) and Specific Therapy (Tonsillectomy + Steroid Pulse Therapy. Short Summary)
3) Progression of CKD: Correlation between Intestine and Kidney
4) Common Therapy for CKD patients (AST-120 is one of the major treatments)
5) AST-120 (Kremezin®) treatment:
   ① Pharmacological action of AST-120 (Kremezin®): results of animal models
   ② Clinical effects of AST-120 (Kremezin®) for CKD patients
   ③ Clinical merit of newly developed AST-120 Rapid Disintegrating Tablet (KREMEZIN Tablets ®)
   ④ Effects of low dose Kremezin® treatment in aged patients with progressive CKD G3b
   ⑤ Conclusion: It is necessary to use specific and common therapies, i.e. Tonsillectomy + Steroid Pulse Therapy (TSP) therapy and Kremezin® treatment, respectively, for CKD patients such as IgA nephropathy.

Current and novel therapeutic strategies for IgA nephropathy

IgA 腎病變的當前和新的治療策略

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IgA nephropathy is the most common primary glomerulonephritis worldwide that can cause progressive renal deterioration and eventually end-stage kidney disease. Recent studies have provided new insights into the immunopathogenesis of this disorder. Moreover, through multicenter collaboration, there are several ongoing clinical trials for determining the exact role and the efficacy of immunotherapy in the treatment of IgA nephropathy. In this seminar, we will discuss about the current management strategies used to treat IgA nephropathy and also pay attention to the emerging therapeutic approaches that may improve the prognosis of these patients.

Update of diabetic kidney disease: From best clinical practice to latest bench research

糖尿病腎臟病的新進展：從最佳臨床照護到最新基礎研究

Szu-Yuan Li

黎思源

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臺北榮民總醫院 內科部 腎臟科

Diabetic kidney disease (DKD) develops in approximately 40% of patients who are diabetic and is the leading cause of CKD worldwide. Although ESRD may be the most recognizable consequence of DKD, The natural history of DKD includes glomerular hyper-filtration, progressive albuminuria, declining GFR, and ultimately ESRD, but DKD patients have a variety of clinical presentations and progression rates. In addition, although only a small portion of DKD patients eventually progress to end-stage renal failure, the majority of patients actually die from cardiovascular diseases and infections before needing kidney replacement therapy. In the present, we do not have sensitive and specific biomarkers to identify the high-risk DKD patients, nor specific therapies to reduce risk of DKD onset and progression. Widespread innovation is urgently needed to improve clinical outcomes for patients with DKD. Achieving this goal will require characterization of new biomarkers, designing clinical trials that evaluate clinically pertinent end points, and development of therapeutic agents targeting kidney-specific disease mechanisms. Additionally, we also need greater attention to dissemination and implementation of best practices in DKD patients.

6

心口醫學的交會：顳顎關節障礙論壇

The Interplay between Brain and Mouth: Temporomandibular Disorder Forum

共同主辦單位：臺灣顳顎障礙症學會

時　間：111年7月16日　08:30~12:00
Time：July 16, 2022　08:30~12:00

地　點：臺北榮民總醫院 致德樓第八、九會議室
Place：The Conference Room 8&9, Chih-Teh Building
Taipei Veterans General Hospital

心口醫學的交會：顳顎關節障礙論壇

The Interplay between Brain and Mouth: Temporomandibular Disorder Forum

Transitioning to chronic temporomandibular disorder pain

慢性顳顎關節症疼痛

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臺北榮民總醫院 口腔醫學部 口腔顎面外科

Based on a variety of studies conducted in recent years, some of the factors that might contribute to the negative treatment responses of some temporomandibular disorders (TMDs) patients have been elucidated. This speech describes known vulnerability factors that make individuals susceptible to developing TMDs, as well as those that contribute to the perpetuation of such problems. In addition, the topic of iatrogenesis is discussed as a major contributor to the negative outcomes that can be seen in this field. At the patient level, anatomical, psychosocial and genetic factors may contribute to individual vulnerability. The anatomy and pathophysiology of muscles, joints, disc and nerves may all be involved in predisposing to TMD symptoms, especially when the patients have pain elsewhere in the body. Among the psychosocial factors, some features may be elucidated by the DC/TMD axis II, while others (e.g. illness behavior, Munchausen syndrome, lack of acceptance of non-mechanical approaches) require careful evaluation by trained clinicians. Genetic predisposition to first onset TMDs and to chronification of symptoms has been identified for individuals with certain psychological traits, presence of comorbid conditions and certain abnormal clinical manifestations. Regarding iatrogenesis, sins of omission may influence the clinical picture, with the main ones being misdiagnosis and under-treatment. Joint repositioning strategies, occlusal modifications, abuse of oral appliances, use of diagnostic technologies, nocebo effect and complications with intracapsular treatments are the most frequent sins of commission that may contribute to chronification of TMDs. The patients who present with massive occlusal and jaw repositioning changes combined with persistent severe orofacial pain are not a rarity within TMD and orofacial pain canters; these patients are the most difficult ones to manage because of this horrific combination of negative factors.

The comorbidity of psychiatric and temporomandibular disorders in Taiwan

台灣顳顎關節障礙與精神疾病的共病現況

Ying-Jay Liou[a], Mu-Hong Chen[b], Chen-Jee Hong[a], Wen-Liang Lo[c]

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Despite affecting different systems, temporomandibular disorders (TMD), major depressive disorder (MDD), and anxiety disorders are all recurrent, chronic, and debilitating diseases. There has been mounting evidence suggesting the existence of associations between TMD, depression and anxiety. However, most of these results are based on symptom levels of depression and anxiety, which might not cause clinically significant functional impairments, rather than on psychiatric disease levels. Meanwhile, although there have been several reports showing an increased risk of TMD in patients with dysthymia or MDD, few studies investigate the effect of TMD on the incidence of MDD. Furthermore, to the best of our acknowledge, there is no study exploring the influence of anxiety disorders on the risk of TMD and vice versa. The presentation will show our findings of the bidirectional association of TMD with MDD and anxiety disorders based on the approach in a longitudinal retrospective cohort in Taiwan.

Can neuroimaging research help clinicians to treat temporomandibular disorders?

人腦神經造影研究能幫助臨床醫師診治顳顎障礙疾病？

Chia-Shu Lin

林嘉澍

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國立陽明交通大學 牙醫學系

Pain is the subjective experience associated with sensory and cognitive-affective processing of the information regarding injury/diseases. Psychosocial factors play a crucial role in individual differences in pain. Neuroimaging research has gradually elucidated the brain mechanisms of sensory/cognitive-affective processing of pain. However, the mechanisms why people respond differently to treatment, in the case of orofacial, have remained unclear. In this talk, I will summarize recent neuroimaging findings of chronic orofacial pain, focusing on temporomandibular disorders (TMD). First, I will introduce the neuroimaging methods and research design to study orofacial pain. Second, I will discuss recent evidence about the brain mechanisms of psychosocial factors of TMD pain. Third, I will discuss the limitation of neuroimaging, focusing on the argument about diagnosing pain by neuroimaging markers, and I will debunk the 'brain myth' in clinical dental care.

Non-invasive brain stimulation and treatment of chronic pain

非侵入性腦神經刺激對於慢性疼痛的治療效應

Cheng-Ta Li

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Chronic pain is estimated to affect more than 30% of people worldwide, and it exerts an enormous personal and economic burden. Patients with chronic pain have high comorbidities of depression, opioid use, and even suicide. Effective analgesic interventions are an urgent but unsettled issue for chronic pain. In today's talk, I would introduce different forms of non-invasive brain stimulation (NIBS), including repetitive transcranial magnetic stimulation (rTMS), theta burst stimulation (TBS), transcranial electrical stimulation (tES), and transcranial direct/alternative current stimulation (tDCS/tACS), as well as transcutaneous electrical nerve stimulation (TENS). These NIBS and nerve stimulation have been widely studied for treating several different forms of chronic pain. In today's talk, I will update recent research results of using NIBS for treating migraine, fibromyalgia, and orofacial pain which includes pain in temporomandibular joint disorders (TMD). You would be able to understand evidence-based parameters of NIBS for treating chronic pain in such examples after the presentation. Finally, I would also talk about potential analgesic mechanisms by using such supraspinal neuromodulation.

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臺灣智慧醫療應用在中醫藥之新發展

Intelligent Healthcare of Chinese Herbal Medicine in Taiwan

時 間：111年7月16日 08:00~12:00

Time：July 16, 2022 08:00~12:00

地 點：臺北榮民總醫院 致德樓第十會議室

Place：The Tenth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

臺灣智慧醫療應用在中醫藥之新發展

Intelligent Healthcare of Chinese Herbal Medicine in Taiwan

Wearable traditional Chinese medicine (TCM) SOC design

中醫穿戴式系統晶片設計

Sheng-Chieh Huang

黃聖傑

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國立陽明交通大學 電機工程系

This presentation will show the products of the tcm soc lab from 2011 to 2022.

Based on the research results of the circulation system, we proposed the image/video pulse blood pressure measurement app on Android, cosmetic chip and the w/me ring on kickstarter in 2011.

In 2012, the melanin chip was developed for the cosmetic product and the cuffless blood pressure measurement was built in the new company (maisense).

From 2013 to 2022, the image/video pulse measurement was been applied to the glucose measurement (2019), remote diagnosis for the leaders in company and the presidents (2020~2022).

Besides, it was also applied to the deepfake video detection (2021~2022).

A preliminary study on artificial intelligence in the diagnosis and treatment system of traditional Chinese medicine

人工智慧在中醫診療系統之研究初探

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Exploring the diagnosis and treatment mode of TCM is the goal of every physician's unremitting efforts. There are two ways to approach this goal. The first method is to directly understand the model of human disease development and its treatment methods revealed by the Yellow Emperor's Inner Canon. The second method is to study various clinical empirical experiences and understand the corresponding relationship between syndromes and treatment. We can now apply AI technologies to learn from these valuable clinical experiences and provide clinical guidance to physicians. In this speech, I will introduce three my preliminary studies in learning TCM diagnosis and treatment mode by using artificial intelligence technology in the past.

1. Based on neural network technology, a diagnosis and treatment system was established to learn the corresponding experience of TCM prescriptions and syndromes. The system can read into the TCM case experiences and Shanghan Lun, and after training to obtain the weight parameters of the whole system, then predict the prescription for the patient.
2. Using the data mining to explore the medical cases related to apoplexy in ancient Chinese medicine books, and find out the hidden messages behind the ancient books, so as to analyze the special data rules and laws of the treatment of apoplexy. The results proved the feasibility of this model through the verification of apoplexy.
3. Establish a set of AIOT system for traditional Chinese medicine of diagnoses. In the front-end of collection data part, a variety of Internet of Things technologies are used, including: combining D1 mini single chip and thermistor to measure temperature, and then learn the relationship between resistance and temperature through a neural network, then use it to measure human body temperature. In addition, the AD8232 biomedical sensor and single-chip module are used to measure the ECG and convert the heart rate. These Internet of Things data, patient's tongue diagnosis photos, five-layer pulse diagnosis data, and various consultation data, etc., can all be read through the self-written Chinese medicine APP and transmitted to the cloud platform.

The use of AI to learn the corresponding experience of various clinical syndromes and treatments is not effective in practical applications. Various possible reasons will be discussed.

Let artificial intelligence become a good tool for traditional Chinese medicine (TCM) accurate diagnosis and efficacy verification

讓人工智慧 (AI) 成為中醫精確診斷及療效驗證的好工具

Ming-Hsien Yeh

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大林慈濟醫院 中醫部 針傷科

Big data statistics and evidence-based results have verified the efficacy of traditional Chinese medicine (TCM) on a considerable number of diseases, and the results have been remarkable. The application of TCM AI to assist symptom collection and diagnosis will better verify the causes of TCM curative effects. TCM AI can identify the symptoms obtained from four diagnosis methods, using machine learning to learn and analyze a large amount of data and then feed it to TCM doctors.

So far, most TCM AI diagnostic systems are still not trusted by the medical community due to their black-box model. However, the "TCM Diagnosis System" research co-operated by Chung Cheng University and Dalin Tzu Chi Hospital was conducted to "know why." We have carried out the following essential works: standardized TCM symptoms, then developed a symptom recording system using the concept of LQQOPERA, and let ancient books synptoms can correctly record. Then, use the ICD-11 version as the basis for the standardization of TCM syndromes and design an algorithm to carry out accurate TCM syndrome differentiation, with a 0.864 differentiation rate. Based on TCM case report papers, the identification difference between the system and clinical TCM physicians has an approximation of 0.619, which is highly similar; In TCM AI prescription and acupoint selection system suggestions to achieve precise treatment drugs and acupoint suggestions in a multi-objective optimization way; Finally, mathematical and scientific analysis of the efficacy of TCM is used to verify the efficacy of patients according to the approach or distance of attribution.

TCM AI will produce the following changes in the future: First, the establishment of TCM symptom quantification tools, which will faithfully record quantifiable symptom information and transformable category information. Secondly, TCM syndrome differentiation will re-exhibit its advantages for systemic diseases, which can be used to conduct systematic correlation analysis between diseases and syndrome types. Finally, it is the recommendation of medical decision-making and the provision of public health statistics of TCM epidemiology, resulting in the most appropriate treatment method and result certification. Of course, telemedicine and the model of long-term health examinations will also be carried out in the future. We hope it can reestablish the ability to deconstruct traditional Chinese medicine and medical knowledge and re-construct the ability of traditional Chinese medicine to lead the times.

Traditional Chinese medicine (TCM) on a smartphone?

手機裏的中醫大夫

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Interest in complementary and alternative medicine (CAM) has increased substantially in western countries during the past decade. Patients and their families seem to have sought their health practitioners' opinions about various CAM modalities more frequently. Recent studies have demonstrated dramatic increases in the use of, and expenditure on, CAM in the United States, Canada, Australia and European countries. Traditional Chinese medicine (TCM) is an important category of CAM in Western opinion. Current TCM practices can be traced back more than 2000 years are commonly used by the Chinese . The increasing popularities of traditional Chinese medicine (TCM) and telehealth indicate a need for digitalizing major clinical assessment methods used during TCM practice. For example, the application of digital image processing techniques and machine learning methods to TCM has attracted strong interests in both academia and industry. On the other hand, Smartphones have become the major communication and portable computing devices. There are now more than 1.7 billion smartphones in the world, and the penetration rate is close to 25% (in Taiwan, it is more than 50%). In this talk, I will discuss the use of computer vision, IoT, and machine learning techniques for diagnosis and treatment of various TCM applications on top of the smartphone.

Intelligent operations, education and management of traditional Chinese medicine

智能中藥作業、教育與管理

Yung-Hung Hsieh

謝永宏

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光田綜合醫院 藥劑部

Intelligence replaces tradition, and technology creates value. Technology is a key factor driving the future of medical care. The medical team of Kuang Tien General Hospital combines information technology with medical procedures to create a new era of intelligence for traditional Chinese medicine management.

Intelligence is based on management thinking to integrate technology and practical operations, so that equipment and resources can be fully used, and various resources can be used in a reasonable, economical and effective manner to achieve the goal of convenience, information and intelligence. This article applies intelligence to five major projects: “Drug traceability “, “Dispensing operations”, “Inventory management”, “Quality and operation decision-making” and “Education and training”. There are 16 solutions in total, including: “Barcode management”, “Operation records”, “Light indicator system”, “Real-time inventory management system”, “Continuous replenishment program”, “Push notification system”, “Digital game-based learning” and “Digital learning process platform”, etc. We use advanced engineering technology such as software technology, network communication, and light indicator system to connect the information flow and operation chain from the manufacturers to the pharmacy, including the processes of drug acceptance, storage, dispensing, operating-system error prevention, inventory control, quality control and decision management. And we use new technology to assist education and training, so that personnel, equipment, materials, operations, and the environment can achieve the goals of technology, safety and high efficiency after the promotion of intelligence.

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AI創新賦能 共創精準醫療

Co-creating Empowering Innovations in Medicine - AI, Precision Medicine and More

時　間：111年7月16日　08:00~15:30

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Place：Medical Science and Technology Building
Taipei Veterans General Hospital

AI創新賦能 共創精準醫療

Co-creating Empowering Innovations in Medicine - AI, Precision Medicine and More

How to build up Data & AI-driven smart hosptial

如何打造以數據和人工智慧驅動的智慧醫院

Danny Chen
陳守正
Public Sector Lead, Microsoft Taiwan
台灣微軟 公共業務事業群

After COVID-19, we've seen tremendous requirements for Digital Healthcare Transformation in the world, and it is happening now. A lot of IT companies and hospitals are trying to use IoT-based wearable devices, cognitive situation awareness, digital twins, mixed reality, 5G Network, cloud platform, and AI related technologies to improve health team productivity, patient experience, end-to-end operation efficiency and so on. Although these technologies each offer highly potential for value creation within healthcare system, when these capabilities come together to enable vertical or horizontal integration, that the ultimate collaboration across different departments and people will achieve true value co-creation in the extended healthcare ecosystem.

Therefore, we realize that hospitals need trusted and integrated capabilities or platforms that makes it easier for hospitals to create personalized patient services, gives health team connected and collaboration tools, and adopts data global standards that are important to healthcare ecosystem. Hospitals can use almost no-code and low-code AI that combines multiples sources to gain full visibility on data insight, relieve administrative burden, and improve daily process and workflow automation to create actionable insight that delivers better care service in faster way and at a lower cost.

To summarize the challenges that most hospitals have and to build up next-gen of innovative hospitals, we come out four main pillars below that support hospitals to move forward:

- Enhancing Patient Experience: by enabling patient data to flow securely across the care continuum, creating individualized patient experiences, and delivering virtual health tools to facilitate communication between clinicians and their patients.
- Empowering Health Team Collaboration: by making it faster and easier to coordinate care, collaborate on shared and unified view of patient, and continually monitor patient across remote locations.
- Improving Clinical and Operational Insight: by uniting data silos and applying advanced analytics and AI to reveal actionable insights to make better, smarter, clinical and operational decisions. You can even trigger automated workflows based on patient or staff actions and predictive analysis.
- Protecting Health Information: by adopting global hybrid cloud platform to lower down the barrier for data compliance, security and privacy, to accelerate holistic smart healthcare transformation.

Precision medicine in diabetes

糖尿病精準醫學

Wayne Huey-Herng Sheu

許惠恒

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Recent advances in medical science, human biology, data science, and technology has imposed the emerging of new insights into the implementation of precision medicine. All these beauties had become realize only after collection of sufficient numbers of biospecimens with genotypes and sequencing information via biobank operations as well as international collaborations. It is particularly important as in how diabetes presents, its variable prevalence, and how best practice in treatment varies between populations. In past decade, various experts target areas of precision diagnostics and precision therapeutics (including prevention and treatment), and key barriers to and opportunities for implementation of precision diabetes medicine, with better care and outcomes. Cases where precision diagnosis is already feasible and effective (i.e., monogenic forms of diabetes) will be presented, while the major obstacles to the global implementation of precision diagnosis of complex forms of diabetes will be discussed. As a result, the appropriate therapy will change over time owing to the manner in which diabetes evolves within individual patients. It is hope that this speech will provide a roadmap for precision medicine in diabetes that helps improve the quality of life for all those with diabetes.

Issues on applying technology for privacy protection and fairness assurance

應用保護隱私與確保公平技術的議題

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How to harness the power of massive data and emerging technologies, such as machine learning, in an ethical and trustworthy is a very important question. The trade-off between data utility and privacy protection as well as between performance and fairness are two pressing issues when the harnessed power applied to real world practice.

For the data collection process in healthcare, I argue to gather individual informed consent is not only necessary to “respect for persons”, but can also be cost effective.

For detailed fine grain health dataset, to “de-identify” it to the degree that individual has no claim about the dataset, the utility of the dataset would be low.

A simple example will be presented to demonstrate the difficulty. With consents, we can explain our approach to privacy protection, so that a better trade-off can be achieved with individual’s blessing.

Model bias is a very important issue when applying the models to real world. Statisticians and computer scientists discover several measurements for fairness, and it is proved that we can not expect a model to satisfy all the measurements at once. Moreover, even if we do have one measurement, usually mathematics formulation will provide a fairness score and the acceptable threshold is up for the society to decide. The application of privacy protection technologies to practice has similar issue.

To find out the threshold that fits our context, we can do a survey to take a snapshot/sample of our society, or we can just copy what others have done.

As a concerned citizen, I worried that we can produce best hardware in the world but do we make enough effort to engage our citizen for the new wave of transformations?

VRx: How immersive therapeutics will revolutionize medicine

VRx：虛擬實境將如何徹底改變醫學

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Not so far in the future, instead of prescribing another pill, clinicians might prescribe a virtual beach vacation to ease aches and pains. Psychiatrists might treat social anxiety by inviting patients to a dinner party or reminisce with Alzheimer patients in a replica of their childhood home. Hospitals might immerse children in fantastical play lands while they receive chemotherapy or undergo frightening medical tests. It's all starting to happen now because of virtual reality (VR). For decades, scientists in elite universities have been quietly discovering the surprising health benefits of VR for ailments ranging from burn injuries, to stroke, to acute stress. Over 10,000 studies reveal that VR has an uncanny ability to lower pain, calm nerves and boost mental health without requiring pharmacotherapy. But the technology has historically been too expensive, unreliable and unwieldy for the research to translate beyond the pages of academic journals and doctoral dissertations. Explosive advances in delivering low-cost, portable and high-quality VR have now spawned a new field the FDA now calls *Medical Extended Reality*, or *MXR*. In this lecture, Dr. Brennan Spiegel will describe stories of using VR in over 3000 patients at Cedars-Sinai Medical Center and will review his lab's latest clinical research, including a trial testing VR in the hospital setting, a new virtual clinic for patients with irritable bowel syndrome, and NIH sponsored research testing VR for managing acute and chronic pain.

Learning objectives (general)

- Introduce the new field of Medical Extended Reality (MXR)
- Explore how VR is used to manage acute and chronic pain in the context of the opioid epidemic
- Evaluate clinical data using VR to support mental health
- Discuss implementation challenges to scaling MXR across healthcare

Digital health with MEMS IMU sensors

微機電重力感測器於智慧醫療之應用

Kuei Ann Wen

溫瓌岸

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國立陽明交通大學 電子研究所 及 國際半導體產業學院

Background: Most diseases present as initial signs of movement disorders and mass-market MEMS sensors will be well suitable for movement analysis. With either digital signal processing or AI modeling, MEMS sensors can provide either 6x or 9X signals of acceleration, gyro as well as magnetic for feature extraction in either time domain like walking speed or space domain like gait length or even frequency domain like termer which can provide doctors for disorder evaluation also for self-diagonals. NYCU team is working with tens of doctors and EE/CS engineers for Parkinson's disease, spinal disease, seizure, hunchback as well as dementia analyses.

Methods: To combine with semiconductor, EE, CS teams, we developed IMU platform for data collection and signal processing. Doctors advised the parameters to be extracted, also the medical evaluation of the patient's condition. EE/CS team figure out the correlation in between tons of parameters and disease condition. Accuracy of algorithm are verified by high-speed camera system. With doctors' help, correlation in between IMU signals and medical data, e.g. X-ray or EEG, is now trying to get surresponse. Since IMUs are friendly used wearable device, it might be used for self-diagonals for early finding and accessing medical treatment.

Results: Team had done primary analysis based on official evaluation standard like UPDRS, MMSE and also subject research of epilepsy and spinal disorder and got nice correlation in between IMU and disorder conditions. Team also developed IMU games for dementia analysis. One of the valuable part is , with IMU, precision and analyzable data can be generated real-time for AI judgement. With subject research experience, EE/CS team is moving forward to develop more user friendly devices and APPs for mobile healthcare.

Conclusion: We are glad to gather together AI/DSP/Semiconductor/Electronic/APP/Firmware/Wearable Device partners to work with doctors. We believe that with these twin strength, it's rather promising to provide digital health with IMU especially for the coming super-aging society.

How to use automated AI platform to accelerate smart medical

使用自動化 AI 平台加速智慧醫療的發展

Po-Ching Lee

李柏青

InventAI entrepreneurship team of ChungHwa Telecom Incubation Center

中華電信 InventAI 育成團隊

Background: AI Model is a small fraction of real world ML systems. About 65% of a data scientist's time is spent on non-data science tasks, for example: DevOps, hardware and software configuration across diverse compute architectures, versioning, data management, tracking experiments, visualization, deployments, monitoring performance and more. The ML code (also called ML Model) is at the heart of a real-world ML production system, but that box often represents only 5% or less of the overall code of that total ML production system. About 41% of companies took more than 1 month to deploy ML model into production. 18% of them need more than 3 months to deploy model. While building a good ML model is only the first step to developing an integrated ML system that continuously operates in production.

Methods: DeepFlow is an automated AI platform that has actually landed in different industries. Such as government agencies, medical centers and manufacturing. It has two important core technologies: AutoML and MLOps. AutoML enables developers or domain experts with limited machine learning expertise to train high accuracy models specific to their business needs. Building their own custom machine learning model within 3 steps. MLOps could help developers or domain expert easily manage, deploy and monitor their model.

Results: Dr. Albert C. Yang and his team member have completed a lot of machine learning tasks on the DeepFlow platform, including diagnosis and detection of atrial fibrillation. As well as the automatic model for sleep analysis, and the models for predicting dementia, using brain images. Or using brain EEG(Electroencephalogram), or brain waves data to predict the depression. According to Dr. Albert C. Yang's adoption of automation platform (DeepFlow), the time of developing 3D brain imaging AI was greatly reduced by 20%, and the accuracy was increased from 85% to 91% with optimization of hyperparameters in AI models.

Conclusion: DeepFlow is an One-stop AI platform, from Data Acquisition to Inferencing. DeepFlow covers the pipeline of developing AI/ML projects. In just three steps, domain experts can quickly complete machine learning modeling. No need for AI experts, Improve Efficiency and Models can be deployed quickly. DeepFlow has Resource Management, Collaborative Workspace and Model management etc., to help enterprises manage various AI projects and resources, and shorten the process of adoption AI.

Innovative application of AI and new exploration of medical personnel training and health promotion development

人工智慧創新應用與醫療人才培育暨健康促進發展之新探索

Ying-Ying Yang

楊盈盈

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The recent WHO analysis of the current situation of artificial intelligence and medical health care development in the global digital health strategy from 2020 to 2025 and the work plan for 2019 to 2023 clearly pointed out that the strategic and innovative use of information and communication technology will be beneficial to the promotion of national Health coverage can also reduce the risks associated with urgent medical needs, thereby achieving the United Nations' 2030 goal of promoting sustainable development of human health. The WHO uses people-oriented digital information technology in the world. Among the development of artificial intelligence applications, medical image recognition and diagnosis are the most common.

Recent reports have pointed out that although the coverage rate of vaccine administration has gradually increased, it still cannot prevent the spread of the virus, mainly because the implementation of personal protection needs to be further strengthened, and laboratory-related epidemic incidents also emphasize the operation of wearing and taking off protective clothing. Therefore, the training of all people in washing hands, wearing masks, and putting on and taking off protective clothing should be implemented.

A recent study published in The Lancet Public Health in France pointed out that the average daily walking pace of Taiwanese is 5,000 steps, ranking 26 out of 46 countries. Further research also pointed out that 47,471 subjects walked every day. The number of steps taken is divided into four equal parts, including 3553, the second is 5801, the third is 7842, and the other is 10901. The more you have, the lower the mortality rate, so you need to walk more. The speed of walking will also affect the health of the patient. Walking at least 20 minutes a day and at least 1 hour a week can reduce the risk of heart failure. In addition, JAMA pointed out that a survey conducted in the past on 34,481 elderly patients with an average age of 73.5 years, tracked for 15 years and found that people who walked faster lived longer.

We have established relevant google store online free downloadable teaching materials, through augmented reality and virtual teaching assistant/coach technology, to achieve national health promotion and paperless. The relevant teaching materials in this digital learning network have been provided in the hospital, surgery, thoracic, orthopedics, intensive respiratory, rehabilitation outpatient clinics or wards, branch hospitals, entrusted hospitals, primary medical clinics, etc. , patients, family members) generally like the related content of such virtual teaching assistant software, and are more interested in engaging in related training. To achieve the training of CPR for all people, we have developed and created the AI interactive Internet of Things for CPR, and the sensor is worn on the operator. To simplify the preparation of material resources, standardize teaching and feedback, etc., there are still many places for artificial intelligence to be developed in the future for talent cultivation and health promotion.

Migraine care: From clinical to data and back

偏頭痛照護：由臨床到訊息擷取，再用回臨床

Shuu-Jiun Wang
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Migraine is a quite prevalent disease, accounting for approximately 9.1% of general population in Taiwan. It has also long been ranked as the second most disabling disease worldwide, especially in the young productive group, causing tremendous socioeconomical burden. Although most of the patients suffered from episodic attacks (i.e. episodic migraine, EM), in a subgroup of patients the headache frequency may gradually increase to near daily occurrence (i.e. chronic migraine, CM). Despite medications are available for both acute and preventive treatment for patients with migraine, the respond rates are far from satisfactory, which may partly be related to the underlying clinical heterogeneity. A thorough clinical phenotyping is of crucial importance, and owns the potential for treatment prediction.

Thus, we developed a web-based inquiry system, not only to collect the headache profile, but also other comorbidities that may be associated with treatment response. Meanwhile, a full set of physiological signal was also collected, including sensitivity to thermal and mechanical pain (via quantitative sensory testing, QST), electroencephalograph (EEG), electrocardiography (ECG), as well as structural and functional neuroimaging by magnetic resonance image (MRI). The hidden information derived from these data were tested to see if they are associated with the clinical response to either acute or preventive treatment. Intriguingly, each physiological signal owns its potential for treatment prediction, and by fusion such information altogether, an excellent prediction rate up to near 85% is achievable. We are now conducting a follow-up study to evaluate the reproducibility of such model. Hopefully, we can lessen the pain that patients suffered from by selecting a more suitable acute or preventive medication in advance.

Applications of AI for sudden sensorineural hearing loss patients treatment

人工智能在突發性耳聾患者治療中的應用

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Sudden sensorineural hearing loss (SSNHL) is an emergency disease, and its pathogenesis is still largely unknown, making it difficult to diagnose and develop a therapeutic strategy. To predict the treatment outcomes and further customize the treatment strategy, we used a physician decision support system that incorporates complex information from electronic health records.

The Hearing Scale Test (HST) employs ten stratified hearing scales from S1 to S10 for children, (S1 to S15 for elderly) each hearing scale contains four test tones with adjacent scales differ from each other by 5 dB, ranging from 1dB (S1) to 71 dB (S15). The starting hearing scale of the HST is S5 (1000, 2000, and 4000 Hz at 20dB, and 500 Hz at 25 dB). The HST test reports: scales S1–S5 indicate normal hearing; scales S6 and S7 indicate possible hearing impairment, and scales S8–S15 indicate confirmed hearing impairment. The HST audiometer is designed for early detection of unidentified hearing impairment children, which can replace the routine hearing screening currently and tuning fork test.

We developed the IOS application- Ear Scale App and combined with cloud monitoring and hearing detection to verify patients with sudden deafness in the TVGH. This study confirmed that there is a strong correlation in hearing results between conventional pure-tone audiometry and the proposed smartphone-based Ear Scale app in a cohort of patients with possible SSNHL. The smartphone-based approach can assist in the evaluation of SSNHL, particularly in clinical settings where conventional pure-tone audiometry is not available. For new patients with sudden deafness, cloud-based hearing monitoring is performed using the hearing value APP to assist in the auditory rehabilitation process and improve the therapeutic prognosis of the patients.

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智慧明醫：創新、精準、高效、友善

Digital Health for Future Medicine: Innovation, Precision, Efficacy, Friendliness

主辦單位: 臺北榮民總醫院、中華醫學會
合辦單位: 國立陽明交通大學
協辦單位: 臺中榮民總醫院、高雄榮民總醫院
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地 點：臺北榮民總醫院 介壽堂
Place：Jie Shou Hemorial Hall
Taipei Veterans General Hospital

智慧明醫：創新、精準、高效、友善

Digital Health for Future Medicine: Innovation, Precision, Efficacy, Friendliness

Smart medicine in the Metaverse

元宇宙的智慧醫療

Ted Chang
張嘉淵
CTO, Quanta Computer Inc.
廣達電腦

The recent rapid rise of Metaverse creates new possibilities of future smart medicine in the virtual space. Most of the interest now focus on visualization and related applications of Extended Reality (XR) including AR, VR and MR for immersive social experience. In the talk, we shall focus more on the core operation of Metaverse, including digitalization, simulation and virtualization, together with its linkage to real world medical applications through Digital Twins. To support the smart medicine in the new Metaverse, we shall also share our perspectives on the integration of Medical IoT(MIoT), Cloud Computing, Medical Big Data, Machine Learning and AI to build the Digital Twins of various medical and healthcare activities for different users and use cases involved.

The current status of medical artificial intelligence development of Taipei Veterans General Hospital

臺北榮民總醫院醫療人工智慧發展現況

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高壽延

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This talk will share with you the current status of medical artificial intelligence development in Taipei-Veterans General Hospital(VGH). The development of medical AI in Taipei-VGH is based on the medical AI development center and AI committee in the hospital to promote all research projects and functional organization from the roots of basic infrastructure, multiple service platforms to various innovative applications which are supported by all specialty departments or centers in the hospital. In the beginning, the AI development was primarily sponsored by the funding of governmental projects, then extended to our own institute and industry cooperation year by year. Very good outward connection has been established with National Yang Ming Chiao Tung University (NYCU), the Academia Sinica and many other institutes. While AI is the tool of God and the precision medicine is the goal of development, lots of productions from projects has been successfully developed in many specialty departments on the roadmap of AI development in Taipei-VGH. I would illustrate some of them in this talk and optimistically look forward to seeing more in the future. On the other hand, we highlight the importance of establishing a nation-wide consortium to include hospitals, research institutes and industry to promote the medical AI development in Taiwan. It is very important to have wonderful industry cooperation to promote any novel idea to project, project to proto-type of product for verification and clinical use. Therefore, the concept of the software as medical device named “SaMD” is proposed to define the AI related medical tool or applications. The future development of medical AI in the hospital or even the whole health care system should account for huge investment on the talented AI manpower, cross-fields cooperation, and funding support from both government and industry.

Artificial intelligence for dementia screening: An innovative aproach with ScreenMat

應用人工智慧用於失智症之篩檢：使用 ScreenMat 之創新方法

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Drawing, such as a pair of interlocking pentagons, is a useful measurement to evaluate the visuospatial functions of people with dementia. With the advancement of technology, drawing behaviour can be real-time captured with digital platforms. We proposed digital analytics on a simple drawing platform and hypothesized that this platform can be used for preliminary screening for dementia. This digital screening platform was designed on a portal tablet and named "ScreenMat". Patients with Alzheimer's disease (AD) and Montreal Cognitive Assessment (MoCA) score below 22 were recruited from the Geriatric Research Clinic, and subjects without AD and with MoCA score of at least 22 were recruited from the Osteoporosis Research Centre. An automated scoring platform for interlocking pentagons was developed. All drawing behaviour was digitalized, such as the time of drawing for each line, and hesitation moments between the drawing lines. Some features of the drawing image were automatically identified, such as overlapped and closure pentagons. All time and image features between AD and control were compared by T-test or Chi-square test. A multivariate logistic regression model was fitted for the predictors of AD. Analytics of the digital behaviour of simple drawing is an effective method for dementia screening. Further investigation with machine learning techniques may increase data interpretability and potentially enhance the diagnostic accuracy for dementia screening.

Constructing a smart community hospital: A BioICT approach for better care

建構智慧社區醫院：生醫科技策略的優質照護

Liang-Kung Chen

陳亮恭

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臺北市立關渡醫院（北榮經營）及 國立陽明交通大學 健康長壽與老化科學研究中心

Utilization of smart technology in the health care services enables the new potentials to improve quality and efficiency of health care services. The smart technology in health care services not only reduces the workloads of healthcare professionals, but also creates new service model and quality assurance programs. Taipei Municipal Gan-Dau Hospital as a community hospital aims to provide comprehensive and community-based health services across primary, secondary and tertiary prevention, and to empower healthy longevity for community inhabitants.

To achieve the goals, we first clearly define goals for the hospital, which is “Promoting Next-Generation Livable Community with Healthy Longevity”. With this goal, we specified four dimensions for action plans, including “cloud-based smart hospital”, “healthy aging communities”, “virtual smrt hospital”, and “virtual healthy aging communities”. All dimensions are connected by person-centered data flows via the cloud-based SaaS platform.

In the hospital, integrated health services to promote healthy aging were developed and implemented, including integrated outpatient services, post-acute care services, person-centered functional re-ablement programs, and community-based health promotion intervention programs. Moreover, the hospital administration and management were shifted to web-based real-time monitoring, and all wards and nursing hommes were equipped with smart mattress to detect risk of accidental falls and patient positioning, as well as facial recognition system to identify early mood changes, cognitive declines and neuropsychiatric symptoms of dementia. Besides, all employees were included in a smart insurance poicy to encourage engagement in health promotion activities. In particular, the hospital is re-designing a cloud-based HIS and NIS system that connects all health data of individuals to improve their health services.

Overall, the BioICT approach aims to improve the quality and efficiency of care to promote healthy longevity for all community inhabitants, which requires much more than simply devices and algorithms. Like all previously developed biomedical innovations, the most impactful achievement is the quality of disease diagnosis, treatment and prognosis. Hence, the BioICT approach should also aims the same goals with novel data collection, modeling and interpretation to change the models of health care services.

Real-time artificial intelligence-based hemodialysis prediction system

即時血液透析人工智能預判系統平台 - 運籌毫秒，決勝千里

Der-Cherng Tarng

唐德成

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The prevalence of dialysis in Taiwan is the highest all over the world. There are more than 90,000 patients undergoing dialysis, and more than half of the dialysis patients died of cardiovascular disease and heart failure. In our institution, we initiated the first phase artificial intelligence (AI) project to instantly predict the risk of heart failure and pulmonary edema, as well as the adequate dry weight of our hemodialysis patients. We teamed up to develop AI risk prediction model for hemodialysis patients and cooperate with the worldwide top data analysis manufacturers. We used the research database from the big data center of Taipei Veterans General Hospital (TPE-VGH) and 200 parameters changed produced by the kidney dialysis machine every millisecond to train the AI system for predicting the risk of heart failure. The accuracy of risk prediction rate is 90% for heart failure. We further found out the most critical key factors for the risk of heart failure judged by hundreds of parameters, and the accuracy of risk prediction rate is 95% for heart failure. These data were presented on the dashboard as the reference to the medical staffs. In addition, our team also used the AI system to train the dry weight prediction, and we successfully reduced the error value of the dry weight from 400 grams to 40 grams, and the error value was reduced by 80%. In the future, we will expand the development system, including conducting the clinical trials in our hospital and applying for the Taiwan Food and Drug Administration (TFDA) Software as a Medical Device (SaMD). We will promote this SaMD to the dialysis centers or facilities to reduce the burden of medical staffs, and to improve the outcomes and increase the safety to the hemodialysis patients.

Double SMART homespital

健康零醫院 數位鄰醫院

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In the era of digital transformation, smart care should cover the whole patient journey between home and hospital. **Homespital** is a term to represent the scenario of "hospital without wall", including critical and concierge care.

As we know that if we just implement the smart devices without de-implementing the low-value patient care process, there will be another disaster to clinical staffs. There are **double SMART** core elements for clinical innovation, including both physical "**S**ervice, **M**anagement, **A**rchitecture, **R**esearch, **T**echnology" and digital "**S**ave, **M**obile, **AI**, **R**obotics, **T**elecare".

Medical directors are the key drivers of digital transformation in clinical care. They are in a prime position to facilitate change and improve physician alignment with systemwide goals. We are designing the paradigm shift models for the young digital generation to facilitate the transformation of clinical care by their own way.

Telecare is surely one of the solutions for the current pain points in medical ecosystem for the next decade. First example, in Mercy Virtue hospital, the world's first facility dedicated to telehealth, they propose the "**Hospital without beds**" project. Dr. can "see" patients where they are. They are the Virtue Intelligent Physicians(VIP) in the era of Digital Medicine(DM).

Another example is the "Journey with Guided Care" in Cleveland Clinic Medical Center showing their great core value, "Every patient deserves world-class care. "

In conclusion, we are facing the great challenges in our care of patient journey including overloading, shortage of workforce, burnout of professional providers and finally collapse of the entire medical care system. The new model of **double SMART homespital** will be the possible trend in the next decade.

AI+HI interactive critical care with machine-learning based clinical decision supportive system

AI+HI 互動智慧重症診療輔助決策系統

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Intensive Care units (ICUs) are equipped with many monitoring systems to provide comprehensive and continuous intensive care. Despite the increasing application of artificial intelligence (AI) technology in many fields, the practical application of AI in the medical field remains limited. To employ AI in critical care for improved quality and efficiency of critical care medicine, we have established a multidisciplinary team consisting of intensivist and information technology engineers at Taichung Veterans General Hospital (TCVGH), AI Center at Tunghai University, an information system engineer at ADVANTECH. Using the big data of ICUs, we create a machine-learning-based clinical decision system for respiratory, renal, bacteremia, and mortality risk. Those models are integrated into the AI+HI interactive critical care dashboard, which provides real-time inferences and guideline-based clinical recommendations. We wish the system would improve patient safety and quality and unload the burden on clinical staff.

Revolutionize patient care via next generation health information system

推動病患照護創新應用的次世代智慧醫療資訊服務平台

Tai-Yi Huang

黃泰一

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Along with medical regulation relaxation and technology breakthrough, most hospitals in Taiwan have been caught in a dilemma of renovating Health Information System (HIS), which in general is considered legacy because of the system complexity, data limitation, and information silo. Current HIS in use is usually composed of various subsystems of clinical, administrative, and financial managements. Since the subsystems are possibly developed in different programming languages, among which some are outdated and rarely used, the burden of integration and operations has been increased. Moreover, the data schema of HIS is originally designed for health insurance declaration. To retain more information on patient's care, data columns should be expanded, and systems require upgrades. This process can be done only if HIS is shut down temporarily. In addition to the potential cost, extra efforts are needed when integrating and utilizing data among subsystems because of the inconsistency of the data models, let along data integration among hospitals.

ASUS Next Generation Health Information System (xHIS) is a powerful AI-embedded platform that aims to give healthcare providers a modularized, hybrid cloud-based, and FHIR-enabled information service. Modularized architecture with microservices equips xHIS with smooth development and easy operation since each microservice is independently deployed and extended, causing rare influences to the others. Cloud-based platform enables compatibility, extensivity and portability. Existing HIS systems can be integrated less painfully to xHIS, which allows IT to develop patient-centric services effectively to enhance the healthcare quality. With web-based applications, each service is accessible any time, any where, and any device. Furthermore, FHIR-based data model accords with international standard, licensing interoperability among hospitals locally or internationally.

As a platform, xHIS favors internal groups to develop applications to given purposes, as well as third-party developers to launch new proprietary services. This breakthrough of medical technology will bring more momentum to this industry and complete the ecosystem.

Smart hospital management

智慧醫院管理

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The Taipei Veterans General Hospital (TVGH) serves around 10,000 outpatient and 3,000 inpatient patients by 8,000 employees every day. For providing high-quality, safe, effective, efficient, and patient-centered care, TVGH has continuously streamlined and digitalized its administrative processes over the past three decades.

Patients can find doctors for specific discomforts using keyword searches on the hospital website and make appointments using APPs on smartphones. Less than 10% of all outpatients need to queue for appointments. There are interactive kiosks providing tour guides for the outpatient environment in different languages. Patients can also pay the bills either using automatic transfer machines on every floor or APPs. Electronic medical records have covered nearly 98% of all previously paper-based records. The fully paperless goal is to be achieved before the end of 2022. Clinical doctors can access patients' laboratory, imaging, and pathology studies result over the past 10 years online at the point of care. AI-assisted outpatients have been established for several diseases since 2019. During the COVID-19 pandemic in 2021, telemedicine and remote consultation were provided for 8,000 patients with chronic illnesses and the quarantined at home. Patients or their families paid the bills through APPs.

All inpatient services are fully supported by advanced information and communication technologies. The brand-new operation system empowers medical staff to access patients' information stored at different locations timely. The widely deployed Wi-Fi system at every ward enables medical staff to explain clinical reports to patients at the bedside. To make the inpatient services efficiently utilized, the length of stay, occupancy rate, and many other parameters are automatically collected and analyzed as a reference for real-time patient flow management. Patients can make a discharge procedure and pay the bill at nursing stations. A smart hospital steering committee has been established in 2018 to organize administrative and clinical departments toward more advanced and patient-centered efforts in management, medical care, research, and clinical training.

On synthetic images for federated learning of medical images

研發以合成影像促進醫學影像之聯邦學習

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Federated Learning (FL) provides the feasible approach to jointly train the machine learning model without accessing private data in various medical institutions. However, the resulting FL model could be biased towards institutions with larger training datasets. Institutions with a relatively limited amount or heterogeneous types of data may have lower accuracy. In this study, we propose the framework of Synthetic Images for Federated Learning (SIFL) that integrates the information of local institutions with heterogeneous types of data. The main concept of the SIFL is to develop the resulting global model that can handle the diversity in heterogeneous types of data collected in local medical institutions by synthetic images similar to minor types in local collections. We use the chest X-ray images of COVID-19 and the color fundus images of glaucoma to compare the results from the centralized learning and several decentralized learning frameworks. The result demonstrates that SIFL-based models outperform the conventional FL models. For institutions with the relatively limited amount of heterogeneous types of data, the model performance of SIFL is improved in these empirical studies.

Innovation application of medical AIOT in clinical practice

醫療人工智慧物聯網創新應用

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The most important revolutionary breakthrough in modern industry is automation technology. The development of Internet of Things (IOT), cloud computing, 5G, artificial intelligence (AI), and blockchain has contributed to the development of industrial Implementation of automation. At present, one of the important areas in the development of the new industrial era is the research and development and implementation of smart healthcare. How to use information technology to provide affordable, efficient, safe and reliable health care services is an important challenge for the development of smart healthcare in the next decade.

Smart healthcare can use technologies in different fields. In addition to making the operation of the medical system more intelligent, it can also combine advanced networks to integrate patient data and promote the development of telemedicine. At the same time, combined with big data and AI and other information and communication technologies, we have developed technologies that use AI technology to medical wearable devices that can record personal health conditions at any time, helping doctors to quickly and accurately evaluate physiological conditions of patients. On the whole, it can not only reduce the burden of medical staff, but also improve the efficiency and quality of medical services.

These innovative applications are three-folds; each focuses on a specific area of medical care, including health monitoring, remote care, and acute care. For health monitoring, we have developed an AI-based home sleep monitoring platform that can differentiate patients from insomnia with obstructive sleep apnea (OSA), and used medical wearable device of saturation monitor to evaluate the severity of OSA, as well as heart rate monitor to evaluate sleep stages based on AI algorithms.

Next, for the remote care, we developed a remote solution for automatically monitoring patient's saturation and heart rate in the quarantine setting. With the aid of AI algorithm, the platform can notify the patient and nursing staff when the patient has deterioration in physiological conditions, such as silent hypoxia. We have implemented these services during the COVID-19 outbreak in Taiwan.

Finally, we developed a sepsis warning system for acute care. The system involved wearable devices that can measure blood pressure, heart rate, saturation, respiratory rate, and body temperature. Using this vital signs data, our AI algorithm can achieve high accuracy of prediction of onset of sepsis in the earlier time, allowing the management of those patients with risk of sepsis in the timely manner.

Taipei VGH cancer information system: Site-specific factors

臺北榮民總醫院癌症資訊系統：癌症部位特意因子

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The central hub of Taipei VGH Cancer Information System (**CIS**) is Cancer List module, which was created to meet the challenge of the very first accreditation of cancer care program in 2008. With the funding from "Establishment of a Cancer Research Excellence System Program" of MOHW, Taipei VGH started the lengthy 6-year software development process of CIS from April 2010.

Applying service-oriented architecture and parameterized program control, Taipei VGH has successfully implemented an expandable, comprehensive, research oriented and clinical workflow-compliant CIS, supporting both common requirements of all cancers and specific needs of individual cancers. CIS, centered on patient's cancer diagnosis, is seamlessly integrated into hospital information system with the following modules: cancer list/diagnosis, cancer stage and site-specific factors (**SSF**) database, pretreatment work-ups, comorbidity and history, cancer treatment plan (**CTP**), multi-disciplinary team (**MDT**) case conference, peer-auditing quality control, adverse event logging, patient follow-up status and failure pattern report, cancer registration, case management, cancer care consultation fee reimbursement claiming, and visualizing analysis.

One of the many good features of CIS that are not implemented in peer institutes is expandable SSF with strict data standards. The MDT could update and add new SSF without limitation. A new SSF data item could be used for a specific cancer in about 5 minutes of setting reference table without the need of changing the programming code.

For cancer research, the parameters/variables could be obtained from cancer list/diagnosis, cancer stage and SSF database, treatment/intervention in CTP, while the end points from patient follow-up status, failure pattern and adverse event.

This talk focuses on the SSF with the following topics: (1) The origin of the SSF. (2) SSF of Taiwan Cancer Database/Cancer Registry. (3) SSDI of National Cancer Database. (4) The implementation of SSF in Taipei VGH: Classification and Composite SSF. (5) Source data of SSF.

Application of information technology in surgical services: Patients' journey in Taipei Veterans General Hospital

資通訊科技於外科醫療的實務應用：以臺北榮總為例

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In the era of artificial intelligence, the tradition of surgical service is challenged, including the burden of data integration, patient care delivery and digitized operation system. These patient-centered topics on the surgical journey need to be redefined by remodeling the data infrastructure, experts in data processing as well as analyzing, deep inspection of user experiences. To achieve this goal, the surgeons, nurses, and information technicians in Taipei Veterans General Hospital has transformed the data flow of the surgical patients' journey via a series of IT system development and continuous formation of an eco-system of IT innovation for all the employees in our hospital to join the revolution.

At the very beginning in out-patient clinic, the IT system recognizes those of first visits and raise the awareness to clinicians by triaging the disease status within a page of questionnaire offered via App or webpage. The collected information is further integrated into the medical chart at clinics. A serial of exams is then arranged after coordinating the schedules of different departments to facilitate the process without prolonged waiting time. All the schedules are listed on the calendar provided in the App developed by department of Surgery with multi-factor authentication and entity verification to ensure the privacy of personal health data. At the meantime, all the information in relation to the choices of treatment including the advantages and risks of surgery as well as the resources of shared-decision-making (SDM) are pushed to the patients' mobile device according to the ICD-10 codes or operation schedules documented and retrieved from the backend of the electric medical records. At this point, couple of AI models has been developed to improve the process of decision making, including the Patients-similarity-based Colorectal Cancer Outcome Visualization Platform, and I-SWAT non-invasive skin wound diagnostic tool provide by Plastics. Hence the concept of digital twin in hospital is shaping.

When it comes to the surgery, pre-operative discussion with 3-dimensional reconstruction of CT images is applied in living donor liver transplantation to ensure the safety of the healthy donor without compromising the successful rate of the surgery. Besides, vital signs data, operative video and sounds as well as radiographic images are synchronized during surgery to provide full-dimensional information to the surgeons. For all the surgical patients, more than 15 real-time checkpoints are recorded to monitor the process for clinicians and console the families timely. The critical time points are also structurally documented for surgical notes and raising alarms after machine learning. After the surgery, the patient can be discharged earlier to comfortable environment with confidence since our App can help the patients to report their conditions, such as side effects, unexpected changes of wound and drains without delay. All of

these services are maintained by the surgical case management system. By close monitor and computerized analysis of electric health data retrieved from patients outside of hospital, we continuously proceed to the Utopia of Homespital.

The achievements can not be accomplished by the clinicians only. IT companies and scientists with domain know how of medical are the key factors. With standardized API and data format, there are endless chances of applying information technologies to the surgical field. We look forward to cooperate with all sort of resources to create a tempered, warmth environment on the surgical patients' journey.

Digital pathology with AI in the era of precision medicine

精準醫學世代之人工智慧數位病理

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Digital Pathology has revolutionized the practice of pathology and the efficiency and efficacy of clinical diagnostics. The current practice of pathology based on eyeball observation under the microscope has evolved into interpreting photogenic details on computer screens. In addition to the “subjective” morphologic data analyses facilitated by special stains and immunohistochemistry, currently, testing with genetic and cytogenetic methodologies have been vigorously used in this era of precision medicine. Along with the development of next generation sequencing for genomic studies, management of the “bid data” has become the seminal factors influencing the treatment and management of patients with all different diseases, either neoplastic or non-neoplastic. With the rapidly increased application of artificial intelligence (AI) to medical imaging, the essence of AI has become more and more seminal in the routine clinical practice, on top of the contribution by digital pathology. We have to face this trend and well prepare ourselves to battle with the digital images with the help from AI, the final common ways of scientific affairs in the very near future.

Development of a novel real-time analysis and disease diagnosis platform based next-generation gene sequencing

開發新穎次世代基因定序即時分析診斷平台

Dau-Ming Niu

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Next generation sequencing (NGS) is one of the most important tools for the development of precision medicine. It has greatly improved the ability of sequencing and has become an important tool in disease diagnosis and medication. Through the popularization and maturity of this technology, the cost of sequencing has been greatly reduced and the output of information has become faster and faster. Meanwhile, the efficiency of analyzing huge genome sequence data in the back-end had become more and more important. Our center cooperates with a current bioinformatics service company to jointly develop a rapid diagnosis platform for whole-exon sequencing and whole-genome sequencing. For whole-exon sequencing, the analysis results can be obtained for less than 5 minutes. The platform has a concise, user friendly and easily understand interface. This allows us to quickly upload the whole gene sequencing data and analyze according to the doctor's needs in real time. The platform provides accurate analysis results in a short time and assists clinicians in the diagnosis of diseases. Through the development of the real-time analysis system, patients with rare genetic diseases will be able to obtain rapid diagnosis and early treatment. Moreover, if other disease-causing gene mutations were found during the analysis process, personal prevention/medical plans can be formulated for each individual’s situation. Furthermore, through pharmacogenomics analysis, a more accurate and safe medication guide is tailored for each person. We hope this system can make the analysis of WES/WGS more accessible and useable for general physician and then it could promote the development of precision medicine in Taiwan.

Application of artificial intelligence and AIoT in acute myocardial infarction: From hospital to ambulance

人工智慧及智慧裝置在急性心肌梗塞的應用：由醫院到救護車

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It is widely known that rapid reperfusion is essential to successful ST-segment elevation myocardial infarction (STEMI) treatment. Door-to-balloon time (D2B) is a standard metric of the quality of STEMI treatment. To shorten the D2B time, we have developed AI algorithms, including an ASAP score and an automatic ECG classification system.

To identify the patients without typical chest pain symptoms, we designed an ASAP score using the most common symptoms in STEMI patients without chest pain. The ASAP score was used in the triage system in ER. To build an AI algorithm for automatic ECG classification, we used more than 3000 12-leads ECG signals with annotations obtained by consensus of 3 board-certified electrophysiologists as the criterion standard. The system could notify physicians automatically and has been used in the ER of CMUH, Taichung, since July 2020. The accuracy is more than 99%, and the D2B time is shortened significantly.

According to the development of telemedicine, we have collaborated with the AIoT company and developed a platform for ECG transmission. The platform has been used in the remote mountain region and on the ambulances of Taichung and Nantou since June 2021. Several STEMI patients were identified using this platform.

The combination of AI and AIoT can help patients in the hospital and also patients in the community. This system can shorten D2B time, as well as S2B (Symptoms-to-balloon) time. In addition, this algorithm was approved by TFDA Software as a Medical Device (SaMD) in December 2021. This algorithm can be used not only for research but also as a product in other hospitals.

Diagnosis of intracranial arterial stenosis by using automatic analysis of neck vascular ultrasonography based on machine learning approaches

使用機器學習方法分析頸部血管超音波來診斷腦動脈狹窄

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紀乃方

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Intracranial arterial stenosis (ICAS) is a unique and significant risk factor of ischemic stroke in East Asian people: ICAS exists in about 15 to 20% aging population. Unfortunately, ICAS is usually asymptomatic and most patients are aware of its existence after it causes stroke. In addition, patients with symptomatic ICAS have 10 to 15% annual stroke recurrence rate, which is much higher than stroke of other etiologies. ICAS can be treated by strictly controlling vascular risk factors. Therefore, it is essential to identify the existence of ICAS before stroke onset.

To identity the existence of ICAS, it is necessary to perform advance neuroimaging such as computed tomography angiography (CTA) or magnetic resonance angiography (MRA) of brain. However, these advanced neuroimaging techniques are not affordable for general population in health examination. Instead, ultrasonography is affordable and has been widely applied in health examination. However, although the ultrasonography is feasible for screening extracranial vascular disease, it has significant limitations in identifying ICAS, including low successful rate of transcranial ultrasonography, and suboptimal diagnostic accuracy of current methodology.

Currently, there are a lot of imaging techniques applying algorithms base on machine learning approaches to increase the diagnostic sensitivity and accuracy. One approach is to use support vector machine (SVM) to build a diagnostic model using the waveform features of extracranial cerebral arteries to classify the patients with and without ICAS. This method has many advantages: It uses extracranial vascular ultrasonography so it does not have the problem of low successful rate of transcranial ultrasonography, it does not need ultrasonography operators to modify their practice habits; and it can provide acceptable diagnostic sensitivity and accuracy of ICAS

The current speech is to share the experience of developing ICAS diagnostic techniques based on extracranial vascular ultrasonography and machine learning approach in the Taipei Veterans General Hospital and National Yang Ming Chiao Tung University.

Prediction of antidepressant responses to rTMS and treatment-resistant depression: Results from Precision Depression Intervention Center (PreDIC)

情緒精準醫療：預測腦神經刺激術抗鬱療效及頑固型憂鬱症

Cheng-Ta Li

李正達

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臺北榮民總醫院 精神部

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Treatment-resistant depression (TRD) is common in depressed patients and is associated with high disability, high healthcare costs, and high quality of life. Correctly predicting depressed patients with higher refractoriness could remind clinicians of more aggressive treatment and improve clinical outcomes of these patients. In addition, intermittent theta-burst stimulation (iTBS) and 10-Hz repetitive transcranial magnetic stimulation (rTMS) are effective antidepressant interventions for TRD but clinical responses across individuals vary. Therefore, reliable predictors for predicting TRD and for antidepressant response to iTBS or rTMS need further investigation. The advance of artificial intelligence, including different models of machine learning (ML) and deep learning (DL) highly enhances the possibility of reliable prediction in depressed patients with highly clinical heterogeneity. In this talk, I will introduce the AI results of using EEG, resting-state functional MRI and 18F-FDG PET to predict TRD and antidepressant responses to rTMS and iTBS. The selected features from the final model also provide hints about the underlying mechanisms of TRD and antidepressants of different forms of brain stimulation. In addition, I will introduce our recently-established specific treatment center for depression, “Precision Depression Intervention Center (PreDIC)”.

Implementation of P4 medicine models in the identification and management of high-risk features for subjects with cardiovascular aging

應用 P4 醫療模式進行心血管老化個案之高風險特徵的預測及處理

Hao-Min Cheng

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Heart disease is the second killer among the top ten causes of death in Taiwan. If combined with vascular diseases such as stroke, high blood pressure, diabetes and kidney disease, it has far exceeded the number of lives claimed by cancer. Preventive strategy can help reduce the development and progression of cardiovascular diseases. To effectively control the impact of cardiovascular diseases, medical institutions and many industry and research units are actively developing better prevention, diagnosis, treatment and monitoring strategies. With a deeper understanding of the underlying pathophysiological mechanisms and causes, as well as the advancement of medical and computer technology, medicine is gradually changing from a reactive type to a proactive and preventive type of science. P4 Medicine is a method to make medicine more predictive, preventive, personalized and participatory. Its two main goals are to quantify health and predict and prevent disease. P4 Medicine represents the transformation of medical treatment from a mode of responding to diseases to as much as possible to keep individuals healthy or maintain a stable disease state. In this talk, we will present our results in implementation of the P4 Medicine model. The integration of artificial intelligence modules and novel protein biomarkers will develop into a novel disease prediction model and be applied to the development of personal health and disease prevention, diagnosis, treatment and monitoring strategies.

Digital transformation in healthcare: iAMS

醫療數位轉型：智抗菌平台

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Digital transformation in healthcare is about embracing and employing advanced technologies and innovative approaches to maximize benefits. Antimicrobial resistance (AMR) has been identified as a major problem globally, and overuse and misuse of antibiotics have become the main driving forces increasing AMR threats. Current conventional approaches require 48 hours to detect AMR, there is a need to shorten the duration to reduce mortality rates and the spread of AMR. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) has been used commonly in the clinical microbiology laboratory to identify bacteria. As MALDI-TOF provides mass spectra with distinctive signatures, MS data can be used as input to train ML algorithms in predicting AMR. ML has been used to improve biomedical workflow recently. In this study, ML models were developed to predict AMR for 8 different bacterial species from MALDI-TOF raw data. With ML approaches, AMR detection can now be performed in seconds and the whole process is shortened by 24 hours. iAMS combines clinical MALDI-TOF signals and machine learning models to identify drug-resistance bacteria. By comparing the differences in MALDI-TOF MS signals and using the model trained with the clinical big data to classify peak patterns of drug-resistant phenotypes in an hour. iAMS integrates clinical laboratory practice and machine learning technology to accelerate the digital transformation of medicine.

Medical imaging AI: Mega data building up and beyond

巨量資料在醫學影像人工智慧的研發

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臺北榮民總醫院 放射線部

Medical application of artificial intelligence (AI) is one of the hottest topics in medical community, nowadays. The application from its initiative to the destination, namely data collection and clean up, algorithm and model development, publication, patent filing, regulatory approval of clinical use and landing, and going to market, is a long journey before it, finally, benefits patients. Along the journey multiple disciplinary and group collaboration are the essence of success. Dataset, from which AI algorithm and model are generated, form the basis for the essence. Dataset to the AI ecosystem is like that of raw petroleum to the industry.

In general, dataset (imaging or non-imaging) are the bigger the better and the more heterogeneous the more powerful. There are basically two major ways, centralized and non-centralized, to build up mega medical imaging dataset when AI modeling is concerned. In hospital dataset is a typical example of centralized one. It is usually homogeneous; however, it takes longer time to become big. On the contrary, non-centralized dataset have the potential to become big by applying federated learning (FL) on the dataset. In the FL setting, all dataset from edge institutes are kept at local (edge) and only the models (initial and intermediate) and their statistics parameters of inference are shared (centralized). Compared with the centralized method, FL keeps the data privacy and integrity. It is also found that the performance of AI model that stems from FL is not inferior to centralized one.

There are multiple pros and cons between the centralized and FL settings in the sense of data collection, model development, software, and hardware demanding (computing and storage capacity) administrative challenges, and real-world application. In the speech, typical examples of the application of centralized and non-centralized/FL in developing imaging AI models will be presented. It is concluded from the initial studies and experience that both methods have the role-playing in model development for assisting clinical diagnosis of brain tumors on MR images. To familiarize the methods and optimize their clinical use in various scenarios, e.g., collaboration among hospitals/hospital series, or international studies is the way of well-using datasets for facilitating AI application in real-world of medical ecosystem.

AI and interactive medical care in cardiovascular disease

智慧互動式醫療運用於心血管疾病之照護

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There are different artificial intelligence (AI) models which constructed by the technique of classical mechine learning or deep learning in prediction of atrial fibrillation (AF). Indeed, deep learning model has been applied in image recognition to facilitate the clinical practice. In particular, the deep learning algorithms can be applied to electrocardiograms, capable of identifying abnormal heart rhythms and mechanical dysfunction associated with AF. Deep learning can be used in analyzing the big data of clinical parameters which may provide the prediction of outcome in AF patients.

We collaborated with NCTU to establish the AI models which can predict the outcome in AF ablation. The first AI model address that automatized extraction of left atrium volume from 2-dimensional computed tomography (CT) images using deep learning technique. On the other hand, we know that non-pulmonary vein triggers have been reported as an important predictor of recurrence post AF ablation. The deep learning *approach* was also applied in pre-ablation pulmonary vein CT geometric slices to create prediction models for trigger origin and recurrence after catheter ablation in patients with paroxysmal AF. We also collaborated with Quanta company to develop the remote ECG monitoring using AI algorithm. 14-days ECG monitoring device was tested in our center with high detection rate of arrhythmia. There are some gaps in the public's awareness and understanding of AF. (1) AF comorbidities require integration of care and professional advice to prevent confusion in people. (2) The treatment decisions and orders requires complete comprehension by the nurses, pharmacists, and patients for accurate implementation. (3) AI monitoring for the smart care of AF patients is required. Our solution is to create an intelligent communication platform that can met the needs for the management of 3 domains: Anticoagulation, better symptom control, comorbidity control.

An ergonomic double espresso for dipping triple thinking into smart medicine design and development

A Double Espresso for 三大思維談智慧醫療的設計與實踐

Tsung-Lung Yang

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高雄榮民總醫院 品質管理中心 & 研創中心

This short talk aims to focus on the use of triple thinking, including design thinking, critical thinking and replay thinking to harness the triple power of innovation, quality assurance and information technology. The introduction of human factors engineering is essential to bring innovation to the forefront of the life sciences and medical industry with the hope to form the closed loop of effective real world data, real world evidence and real world value with failure mode and effect analysis (FMEA) in mind.

Application of artificial intelligence in spine fields

人工智慧在脊椎領域之運用

Po-Hsin Chou

周伯鑫

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Recent advances in artificial intelligence (AI) and deep learning (DL) have shown great performance in identifying non-medical images, and the technology is thought to be the next technological revolution in the clinical application. Based on the current published papers, three main categories of clinical application by AI and DL in the spine fields are (1) automatic measurement (2) diagnosis in medical images (3) prognosis outcome prediction. Some of these published papers also provide Uniform Resource Location (URL) for open access algorithm in clinical applications.

Regarding our current AI model for vertebral fracture detection in the plain lateral radiographs of spine, the framework of AI deep learning model included object detection, data pre-processing of PLRs, and classification to detect VFs. The accuracy, sensitivity and specificity for the performance of AI model were 91.88%, 90.94% and 92.83%, respectively.

However, false positive and false negative rates were inevitably occurred. The factors of lung markings at thoracolumbar junction, X-ray technique, bean-can effect, normal variance of bi-concave appearance in the osteoporotic vertebral body and osteoporosis plays important roles in bias the performance of AI model. We also investigated that our AI model had higher accurate rate if the vertebral fracture was located at lumbar spine and patient's DXA T score $\leqq$ -2.5. Fortunately, our novel innovation of the AI model with ensemble method got patent in Taiwan and get the 18th National Innovation Award in the Academic Research Category.

The evidence suggests that AI models can be successfully used for spinal disease to manage its diagnosis, prognosis and outcome prediction. Further AI or DL algorithm retraining, generalizability of models, data standardization in neural networks, and focus on the application of AI or DL models as a tool in clinical spine practice, will augment decision-making efficacy.

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微創消化系手術的新境界

New Frontiers in Minimally Invasive Digestive Surgery

時　間：111年7月16日　08:20~12:00

Time：July 16, 2022　08:20~12:00

地　點：臺北榮民總醫院三門診9樓CiC創新沙龍

Place：The Clinical Innovation Center,
Taipei Veterans General Hospital

微創消化系手術的新境界
New Frontiers in Minimally Invasive Digestive Surgery

Illuminating the path in laparoscopic liver surgery

螢光顯影在腹腔鏡肝臟手術的應用

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林忠葦
Show Chwan Memorial Hospital, Changhua, Taiwan, ROC
彰化秀傳紀念醫院

The fluorescence of indocyanine green (ICG) can be used for real-time visualization of biological structure and tumor stains in hepatobiliary surgeries. Recently, it has been used in laparoscopic/robotic surgery. Intraoperative fluorescence imaging can be used to identify subcapsular hepatic tumors. Primary and secondary hepatic malignancy can be identified by intraoperative fluorescence imaging using preoperative intravenous injection of ICG through biliary excretion disorders that exist in cancerous tissues of hepatocellular carcinoma (HCC) and in non-cancerous hepatic parenchyma around adenocarcinoma foci. Intraoperative fluorescence imaging may help detect tumors to be removed, especially during laparoscopic hepatectomy, in which visual inspection and palpation are limited, compared with open surgery. Fluorescence imaging can also be used to identify hepatic segments. Boundaries of hepatic segments can be visualized following injection of 0.25−2.5 mg/mL ICG into the portal veins or by intravenous injection of 2.5 mg ICG following closure of the proximal portal pedicle toward hepatic regions to be removed. These techniques enable identification of hepatic segments before hepatectomy and during parenchymal transection for anatomic resection. Advances in imaging systems will increase the use of fluorescence imaging as an intraoperative navigation tool that can enhance the safety and accuracy of open and laparoscopic/robotic hepatobiliary surgery.

Laparoscopic liver resection of unfavorable location of the liver

困難位置之腹腔鏡肝切除手術

Shu-Cheng Chou, Hao-Jan Lei, Yi-Chu Kao, Cheng-Yuan Hsia, Gar-Yang Chau
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Laparoscopic liver resection (LLR) has been widely applied due to its advantage of minimal invasiveness resulting in earlier recovery and shorter length of hospital stay than open liver resection. In the initial, LLR was recommended for liver lesions less than 5cm, solitary and located in anterolateral segments (Segment 2, 3, 4b, 5, 6). Meanwhile, due to the technical difficulty of approach and liver parenchymal transection, large tumors and lesions located in posterosuperior segments (segment 1, 7, 8, 4a) are favored for open liver resection.

Owing to advancement of laparoscopic operative techniques, instruments and accumulated experiences, these limitations have been overcome. In the Southampton consensus guidelines in 2017 acknowledge LLR for lesions in posterosuperior segments are feasible and safe and should be considered as a valid alterative approach in expert centers.

The surgical techniques use for LLR in our hospital will be described including patient position, trocar placements, usage of flexible intraoperative ultrasonography for lesion identification and structure delineation, liver parenchymal transection, and inflow control. We analyze the peri- and post-operative results for patient with hepatic tumor in posterosuperior segments and anterolateral segments.

LLR of unfavorable location of liver is feasible and with acceptable operative time, hospital stay, resection margins and complication rates. The adaption of improved techniques, instruments and cumulative experiences has reduced the complexity of LLR in unfavorable locations.

Anesthetic aspect of minimally invasive pancreatic surgery including robotic pancreatoduodenectomy

微創胰臟手術包括機器人手術進行胰十二指腸切除的麻醉策略

Chun-Sung Sung

宋俊松

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Introduction and adoption of the Enhanced Recovery After Surgery (ERAS) pathway and multimodal analgesia lead to significant improvements in patient satisfaction and faster recovery, outcomes, reduction in cost of care, shortened hospital stay and significantly fewer complications. Meanwhile, rapid implementation of robotic transabdominal surgery has also resulted in the need for re-evaluation of the most suitable form of anesthesia. The overall objective of anesthesia is to minimize perioperative risk and discomfort for patients both during and after surgery. Anesthesia for patients undergoing robotic assisted surgery is different from anesthesia for patients undergoing open or laparoscopic surgery; new anesthetic concerns accompany robotic assisted surgery.

The minimal invasive surgery of the pancreas: Taipei Veteran General Hospital experience

胰臟的微創手術：臺北榮總經驗

Shih-Chin Chen

陳世欽

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Pancreatic surgery is one of the most challenging task for both general surgeon and patient. Successful pancreas surgery must take into account its retroperitoneal location, proximity to major vascular structures and the unforgiving nature of the gland. In recent years, minimally invasive surgery is undoubtedly the focus of modern surgery and the focus of surgical development. By minimally invasive surgery, patients could get less pain, smaller wounds, less bleeding, and shorter recovery time. Compared with laparoscopic instruments, robotic surgery platforms could achieve more stereoscopic vision and precise dissection and suturing technique, and are increasingly being used in pancreatic surgery. In this presentation, we would introduce the evolution and preliminary experience of minimal invasive surgery of pancreas surgery in Taipei Veteran General Hospital pancreas team.

Trend of surgery for early gastric cancer

早期胃癌外科手術的新趨勢

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Gastric cancer is the third leading cause of cancer-related deaths in the world. Surgery remains the main treatment for operable gastric cancer. For early gastric cancer, multiple modalities are shown benefits in improving surgical outcome and life quality.

Endoscopic submucosal dissection (ESD)is proved equal long-term oncologic outcome comparing with gastrectomy. We will discuss the absolute indication and expanded criteria of ESD.

Indocyanine green (ICG) fluorescence guided surgery was applied in gastrectomy in recent years. We will discuss the impact of lymph node retrieval, stage migration, sensitivity and specificity of lymph node metastases in this study.

For early gastric cancer, regional treatment without lymph node dissection was accessible and feasible. ICG guided surgery can achieve more accurate diagnosis and hence deliver proper treatment for patients in early gastric cancer.

Reconstruction methods after laparoscopic gastrectomy for gastric cancer

腹腔鏡下胃癌切除手術後胃腸道重建方式

Wen-Liang Fang

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Laparoscopic gastrectomy becomes more and more popular in the surgical management of gastric cancer, especially in Asian countries. Reconstruction after gastrectomy and under laparoscopic view is challenging and play an important role in the operative outcome.

In this topic, we will introduce various reconstruction methods following subtotal gastrectomy, total gastrectomy, and proximal gastrectomy. We will also demonstrate operative videos and our experience of gastrointestinal reconstruction following gastrectomy for gastric cancer.

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性別重置手術論壇

New Advances in Sexual Reassignment Surgery

時　間：111年7月16日　08:20~12:00

Time：July 16, 2022　08:20~12:00

地　點：臺北榮民總醫院　三門診9樓CiC創意谷

Place：The Clinical Innovation Center,
Taipei Veterans General Hospital

性別重置手術論壇

New Advances in Sexual Reassignment Surgery

Gender affirming surgery in Taiwan

性別重置手術在臺灣

Keng Chen

陳耕

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Increasing societal acceptance of gender dysphoria has led to comprehensive and individualized care plans. Among the treatment options, gender affirming surgery brings irreplaceable happiness and well-being. In this talk, I will introduce historical perspectives of gender affirming surgery worldwide and in our country. Apart from evolution of diagnosis and development of surgery, social awareness of transgender and non-binary issue and current guidance will be discussed as well. Being physician, we care people. Learning from the past, the knowledge and perception of gender affirming surgery make transition-related treatment integrated and fulfilled.

Male-to-female gender affirming surgery: My personal experience

男變女性別認定手術之個人經驗

Bing-Hwei Shen

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Gender affirming surgery is often the last and the most considered step in the treatment process for transsexuals with gender dysphoria. In male-to-female GAS, to achieve both aesthetic and functional results is not so easy. In the past decades, I developed some unique skills such as W-clitoroplasty, tubing of tunica albuginea, fat transposition and V-Y flaps technique of labia minora reconstruction. Those procedures actually improve the cosmetic outcome of external genital area. I used penoscrotal flaps, so called two-flaps, to build up the new vaginal lining. In addition, the modified technique of skin graft affords adequate depth and width of new vagina. However, the perioperative complications of male-to-female GAS are not uncommon, which include vaginal stenosis, bleeding, partial preputial flap necrosis and other unusual problems.

I personally had completed the surgery on over a hundred individuals who were diagnosed as male-to-female transsexuals with gender dysphoria. Here, I am going to exhibit my techniques and share the personal experience about male-to-female GAS.

Free flap phalloplasty for female-to-male gender affirming surgery

顯微重建於女變男性別重置手術之應用

Tien-Shiang Wang

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It has been more than 30 years since the Taiwan's first gender affirming surgery performed in Taipei Veterans General Hospital. The application of free flap transfer in gender affirming surgery was mainly in the phalloplasty. Free radial forearm osteofasciocutaneous flaps were used at first and then gradually replaced by fibular osteofasciocutaneous flaps. The neourethra design evolved from roll-in-roll to prelaminated vaginal mucosal graft and significantly reduced urethral complications. Glans sculpturing improved the neophallus appearance. In the current report, we will introduce the stages of phalloplasty and surgical techniques for female-to-male gender affirming surgery. In addition, the management of complications will also be discussed.

Clinical practice and literature review of metoidioplasty

陰蒂延長術

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Metoidioplasty, one of the female-to-male sex reassignment surgeries, is technically simpler than phalloplasty, costs less, and has fewer potential complications. However, phalloplasty patients are far more likely to be capable of sexual penetration (mainly due to size constraints) after they recover from surgery. In a phalloplasty, the surgeon fabricates a neopenis by grafting tissue from a donor site and a phalloplasty takes about 8–10 hours to complete. Metoidioplasty typically requires only 3–4 hours to complete and presents a good option for creating a male genitalia by straightening and lengthening a hormonally enlarged clitoris.

Urethral reconstruction based on flap technique achieved good outcome with voiding while standing and with minimal complications. Results in clitoral lengthening confirm the importance of the technique based on postoperative reports describing excellent sensation, erection, and good psychosexual features.

The clinical results after metoidioplasty are discussed and the literatures were reviewed. According to literature data, urethral fistula and stricture are reported in 7–15% and 2–3% of cases, respectively. Revision surgery includes excision of fistula with appropriate covering or stricture repair either by direct anastomosis or urethral dilatation. The main disadvantage of metoidioplasty is that the length of the neophallus is usually inadequate for penetrative sexual intercourse.

Transsexual surgery

性轉換手術

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Sex reassignment surgery (SRS), also known as gender reassignment surgery, sex reassignment surgery, transsexual surgery, etc., is a surgical technique and also a castration surgery. Sexually explicit traits will be changed to conform to socially stereotyped biological sex and their gender identity, and the original fertility will be lost. It is part of the treatment of gender dysphoria in transgender people. Related sex-specific surgery may also be performed in intersex infancy.The American Society of Plastic Surgeons (ASPS) calls this procedure Gender Confirmation Surgery or GCS. The connotation of gender reassignment surgery differs between trans women (transwomen, M-F) and trans men (transmen, F-M). For transwomen, this procedure usually involves testicular removal, vaginoplasty. In the case of transmen, procedures include mastectomy, and phalloplasty, uterus Resection, bilateral salpingo-oophorectomy, or plus total vaginectomy. People who have undergone gender reassignment surgery are usually referred to as transsexuals. The prefix “trans-” in English means “crossing, crossing, changing”, and “sexual” refers to sexual characteristics, not sexual orientation. Recently, people seeking gender reassignment surgery are more commonly referred to as transgender to include some transgender people who have not undergone gender reassignment surgery but whose gender identity differs from their gender designation.The key principle of transgender androgen therapy is to achieve as much as possible with the individual’s identified gender environment in order to alleviate gender dysphoria, including some suppressed endogenous hormones or hormone replacement therapy. Hormone therapy can partially affect reproductive function, so it is necessary to complete psychological counseling before treatment. The choice of hormone should take into account cost, the comfort of the drug injection, and whether low-dose gels will not achieve the purpose of menopause. Androgens are affected by fat redistribution (more fat in the abdomen), facial hair growth, a dull voice, clitoral hypertrophy, oily skin, acne, vaginal dryness, muscle gain, increased libido, and menopause. Androgen therapy is initially started with half the dose, and the target concentration is expected to reach 300-1000 ng/dL.

Evaluation and assessment for sex reassignment surgery in population of gender dysphoria in Taipei Veterans General Hospital

臺北榮民總醫院針對性別不安之病患，評估是否合適接受性別置換手術之經驗

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Although gender identity issues have generally been discussed as a human rights issue in this generation, gender dysphoria is not as easy to demise as it was in 1973 when American psychiatry depathologized homosexuality. The most important reason is that gender dysphoric people, different from homosexual groups, require numerous medical and surgical interventions in many of their issues, such as completing the legal procedure for changing the gender field of an ID card.

According to Taiwan's current law on changing gender registration, applicants for female-to-male transgender change must hold a diagnosis certificate assessed by two qualified psychiatrists, and a certificate of completion of the surgery that has removed female sexual organs, including breasts, uterus, and ovaries, issued by a qualified medical institution. The process of applying for a male-to-female transgender is similar.

So far, such a procedure for correcting the gender field has been carried out in Taiwan for nearly 45 years. However such clinical diagnoses have also evolved with the times, from transsexualism, to gender identity disorder, and finally to the name of the diagnosis of gender dysphoria, which means that on this topic, there are numerous worthy surgical, medical, or even psychological treatments to use new thinking to provide this ethnic group more appropriate help they needed.

At present, most of the medical services provided by Taiwan for people with gender dysphoria are relatively fragmented and lack of unity and consensus. It is hoped that in such a meeting, the experience of all advanced and colleagues will be brought together to build a benign intervention system for the minority group of gender dysphoria.

Floating ribs resection to achieve better waist lines

以浮肋截除術改善腰部曲線

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The waist lines locate at the central of the body. There are several ways to improve body contouring, including weight control, exercise, or surgical procedure such liposuction or abdominoplasty. However, there are still some limitations in male-to-female gender reassignment patients, mostly due to the lateral projection of floating ribs.

A retrospective review was conducted of 5 cases of bilateral floating rib resections within one year period from September of 2021 to May of 2022. Three were female and two were male-to-female transgender patients. The medical review noted the body mass index, waist circumference, previous abdominal procedures and underlying comorbidities. Patient satisfaction survey was also done three months after operation.

The average of waist circumference decreased 6.3 centimeters (2.5 inches) after floating ribs resection surgery, which also improved the waist-buttock ratio. The mean length of the resect floating ribs were 9.28 centimeters for 11^{th} rib and 6.4 centimeters for 12 rib, which were performed within a 4 centimeters incision over each side. All patients were satisfied with the final outcome.

Minimal painful sensation was noted by all patients. No major complication of the five cases. For aesthetic purposes, the removal of floating ribs procedure is considered relative safe.

Facial aesthetic surgery in transgender patients

性別重置患者的顏面整形手術

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As Taiwan becomes one of the more LGBT-friendly countries in Asia, people are starting to discover their true inner self and dare to escape from their biological boundary. As a result, more and more gender dysphoria patients seek to have facial aesthetic surgery as the first leg of their long journey. While the female-to-male patients might have different opinions about their looks, most male-to-female patients would like to have a more feminine facial contour and a girly-looking nose. In our clinic, facial feminization surgery usually starts with malarplasty, mandibuloplasty, and forehead augmentation, combined with rhinoplasty or other soft tissue procedures. Those procedures are often performed in one day, by three different plastic surgeons. After achieving a more feminine face, they can have the confidence to proceed to next level of gender affirmation surgery: breast augmentation and genital surgery.

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肛門疾病治療進展與發展

The Update of the Treatment in Anal Disease

時　間：111年7月16日　　13:30~17:30

Time：July 16, 2022　　13:30~17:30

地　點：臺北榮民總醫院 致德樓第二會議室

Place：The Second Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

肛門疾病治療進展與發展

The Update of the Treatment in Anal Disease

Update of hemorrhoid treatment

痔瘡治療的進展

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Haemorrhoids are common, affecting up to one quarter of all adults according to some estimates. Numerous interventions exist for their management, ranging from topical and medical therapies to outpatient treatments and surgical interventions that aim to fix or excise. Given the polysymptomatic nature of the disease, it is difficult to effectively judge which treatment option is best. Recently introduced novel haemorrhoid management techniques, such as Ligasure™ excision, hemorrhoid laser procedure and haemorrhoidal energy therapy (HET), aim to reduce harm whilst maintaining or improving on outcome. Whatever the intervention selected for treatment, it is clear that this should be tailored to the individual based on patient choice, convenience and degree of hemorrhoids.

Current surgical management of large external haemorrhoids: Where are we now?

目前痔瘡治療的新趨勢

Lim Yon Kuei Bernard

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Symptomatic haemorrhoids is a benign but common problem that has afflicted patients for a long time. Low grade or internal haemorrhoids can often be treated with medications or office procedures (band ligation, injection etc). Large prolapsing and bleeding external haemorrhoids is especially bothersome to a patient's quality of life and should not be ignored, and treatment usually entails excisional surgery. There is wide range of surgical techniques to treat such haemorrhoids which cannot be treated with medication. These include: conventional haemorrhoidectomy with energy devices (harmonic, ligasure etc), stapled haemorrhoidectomy, laser ablation with haemorrhoidopexy, doppler guided stitching and even embolization of haemorrhoids etc. A lot of the newer techniques have been introduced with modifications to achieve optimal results whilst minimising the dreaded post-operative pain. Generally, the less painful the procedure, the more likely the recurrence. Most randomised trials do compare various techniques but our experience has been that one need to have individualised approach to technique modifications for ideal results, which is one with good results whilst minimising postoperative pain and complications.

Standard technique of hemorrhoidectomy with LigaSure technology for internal hemorrhoid in our institute

利用 LigaSure 進行痔瘡手術的日本經驗分享

Nobuyoshi Miyajima

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Surgery for hemorrhoid is a frequently performed surgical procedure. In our institute, over 3000 cases of hemorrhoidectomy have been experienced per year. Usually open conventional ligation and excision method (LE) is employed. Some cases of Ligasure hemorrhoidectomy were experienced. Surgery is indicated for high-graded internal hemorrhoids (over Goligher III). Our standard LE procedure is 1) skin incision, 2) dissection and removal of hemorrhoid tissue, 3) ligation of hemorrhoidal vessels, 4)excision of hemorrhoid with mucosa, and 5) suture of mucosa. In usual procedure, Metzenbaum scissors are used for dissection in order to avoid injury to internal anal sphincter including burn. When Ligasure is applied, great care not to injure internal anal sphincter. Before applying Ligasure, Internal anal sphincter must be mede sure and preserved. after that, direction and volume to be excised are minutely designed. It is often said that Ligasure is “vessel sealing” or “tissue fusion”. However, anal canal moves and spread in defecation. Moreover, maximum resting pressure is over 60mmHg and maximum squeezing pressure is over 250 to 300mmHg. For these reasons, we think that hemorrhoidal vessels should be ligated with absorbable suture. After hemorrhoidal tissue was excised, mucosa may be seemed attached because Ligasure has ability of “tissue fusion”. But suturing of mucosa is added in order not to evoke dissociation of mucosa. Although some cares are necessary, intraoperative bleeding is smaller, operation time is shorter and postoperative course is not worse compared with conventional LE method. I would like to demonstrate the standard LE method with conventional and Ligasure method in our institute using video.

Basics and clinical application of anorectal manometry

肛門直腸壓力檢查的基礎及臨床應用

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Anorectal manometry is a basic examination for various functional anorectal disorders such as dyssynergic defecation, fecal incontinence, rectal intussusception or prolapse and neurological disease. Currently, both water-perfusion system and solid-state system are available but the absolute reported values are different depending on which catheter you use. Before performing anorectal manometry, the operator should be familiar with the machine and system in use, setting of the catheter, patient preparation, study protocol (IAPWG protocol), data acquisition and interpretation.

The indication and whole procedure should be well explained to the patient and gain the permission before performing anorectal manometry. Although the London Classification provides the diagnosis of disorders of anorectal function based on objective, physiological measurements, patient factors such as gender, advanced age, and parity should be considered because the normal range on sphincter tone and rectal sensory function will be influenced.

It is important to keep in mind that anorectal manometry alone is generally inadequate to establish the true final pathophysiological cause of anorectal disorder for guiding best treatment. Other tests such as colonic transit, balloon expulsion test, defecography, and transrectal ultrasonography are sometimes necessary to provide a comprehensive interpretation of patient's clinical issue.

The application of laser in the ablation of fistula tract

雷射治療於肛門廔管消融手術之運用

Ersin Öztürk

Bursa Medicana Hastanesi, Turkey

Laser technology has been the point of interest in proctology so far. Conventional surgical techniques may result in some degree of incontinence in 78% of patients. Major incontinence risk is around 20%.

What laser does is actually to apply the heat energy in a controlled manner. The heat transfer to the tissues is within desired limits and range. This, in proctology, prevents the damage to the internal anal sphincters which eventually results in less pain and faster healing besides decrease in incontinence risk.

This therapeutic advantage peaks in fistula surgery. The mechanism of laser therapy is to ablate the granulation tissue and infected mucosa within the fistula tract and then shrinkage of the tract causing fibrosis. However, since the diameter of impact is limited to 2 mms from the tip of the laser probe, fistulas that have tracts wider than 4 mms or tracts that present with active pus coming out from the tract might be initially treated with a loose drainage seton. 4-6 weeks later laser might be applied to the fistula. Besides combining the laser with VAAFT might increase the success rate. Closure of the internal opening is also another contributing factor to the success. The overall success rate for LAFT (laser ablation of fistula tract) is around 51% in the literature. However, most of the unsuccessful cases consist of turning of the fistula into a shorter sinus with a closed internal opening.

Careful patient selection, deciding when to perform a seton and proper application of the laser energy are the crucial steps for a successful LAFT. Nevertheless, the most important factor is the experience in proctology.

Biosimilars in the management of neutropenia: Focus on Nivestim (filgrastim)

生物相似藥品用於治療白血球低下：以 Nivstim (filgrastim) 為例

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Background: Advances in chemotherapy and surgery allows the majority of patients to survive cancer diseases. Yet, the price may be a proportion of patients dying of complications due to treatment-induced infectious complications, such as neutropenia. With the aim of decreasing morbidity and mortality related to infectious complications, recombinant human granulocyte colony-stimulating factor (G-CSF), filgrastim, and pegylated filgrastim have been used to reduce time and degree of neutropenia. A biosimilar is a copy of an approved original biologic medicine whose data protection has expired. The patent for filgrastim expired in Europe in 2006 and in the US in 2013.

Methods: Many review analyses the available evidence to be considered in order to design a strategy of use of G-CSF and its biosimilars. The clinical and safety outcomes of biosimilars are well within the range of historically reported data for originator filgrastim. This underscores the clinical effectiveness and safety of biosimilar filgrastim in daily clinical practice. Biosimilars can play an important role by offering the opportunity to reduce costs, thus contributing to the financial sustainability of treatment programs.

Results: Biosimilars have to prove efficacy and safety comparable to the original product. Biosimilars can play an important role by offering the opportunity to reduce costs, thus contributing to the financial sustainability of treatment programs.

Conclusion: Biosimilars can play an important role by offering the opportunity to reduce costs, thus contributing to the financial sustainability of treatment programs.

Taiwan society of colon and rectum surgeons (TSCRS) consensus for anti-inflammatory nutritional intervention in colorectal cancer

大腸直腸癌之抗發炎營養介入共識

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Background: Malnutrition and systemic inflammatory response (SIR) frequently occur in patients with colorectal cancer (CRC) and are associated with poor prognosis. SIR affects the brain, muscle, liver, and fat function , leading to anorexia, muscle wasting, suppressed anticancer drug clearance, and depletion of fat .Anti-inflammatory nutritional intervention is not only a way to restore the malnourished status but also modulate SIR.

Methods: Nine experts, including colorectal surgeons, physicians and dieticians from 5 hospitals geographically distributed in Taiwan, attended the consensus meeting in Taiwan Society of Colon and Rectum Surgeons for a 3-round discussion and achieved the consensus based on a systematic literature review of clinical studies and published guidelines.

Results: Developed consensus recommends that assessment of nutritional risk and SIR should be performed before and after CRC treatment and appropriate nutritional and/or anti-inflammatory intervention should be adapted and provided accordingly.

Conclusion: NLR is an economic and easily applicable inflammatory marker that predicts outcomes of cancers. Assessments for SIR and nutritional risk should be carried out before and after treatment. Accordingly, anti-inflammatory nutritional intervention not only provides energy but also modulates inflammatory response for patients at risk of malnutrition and SIR to facilitate optimal outcomes.

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生物製劑在呼吸道疾病的應用

The Role of Biologic Agent in Respiratory Diseases

時　間：111年7月16日　13:30~17:30

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地　點：臺北榮民總醫院 致德樓第三會議室

Place：The Third Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

生物製劑在呼吸道疾病的應用
The Role of Biologic Agent in Respiratory Diseases

The critical role of IL-4 and IL-13 signaling pathway in CRSwNP

IL-4 及 IL-13 訊息路徑在慢性鼻竇炎合併鼻息肉的角色

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Chronic rhinosinusitis (CRS) is a common disease in most of the world, and it refers to chronic inflammation of the nose and the paranasal sinuses lasting for more than 12 weeks. CRS leads to major symptoms such as nasal obstruction, rhinorrhea, postnasal drip, headache, facial pain, and olfactory dysfunction. These symptoms affect the quality of life of the CRS patients significantly. The etiology of CRS include multiple host and environmental factors. According to the endoscopic findings, CRS can be divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP).

In the era of precision medicine, phenotype classification base on the existence of nasal polyp is not sufficient. In recent years, researches on endotype classification is in full swing. Type 2 inflammation, which is characterized by eosinophil infiltration, IL-4, IL-5, IL-13 and IgE production, is prominent in CRSwNP in Western countries. Besides, the degree of type 2 inflammation was also associated with disease recurrence.

IL-4 is highly associated type 2 inflammation status and eosinophil trafficking into tissue. IL-13 play a role in mucus production and tissue remodeling. In this review, we will introduce the basic role of IL-4 and IL-13 in type 2 inflammation and CRSwNP. Besides, we also introduce their signaling pathway.

Evolving treatment landscape in CRSwNP: The role of the biologics

慢性鼻竇炎合併鼻息肉的治療：生物製劑的角色

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Chronic rhinosinusitis (CRS) is an inflammatory disease of the paranasal sinuses which significantly decreased quality of life. According to phenotype classification, CRS was sub-grouped as chronic rhinosinusitis with nasal polyp (CRSwNP) and chronic rhinosinusitis without nasal polyp (CRSsNP). In CRSwNP group, surgery and appropriate medical treatment were main treatment policies. However, even after above treatments, nearly 20% patients with CRSwNP need revision surgery in 5 years. Therefore, except phenotype, new classification of CRS and new treatment methods based on this classification are necessary.

According to endotype classification, CRS was divided into type 2 inflammation and non-type 2 inflammation ones and CRSwNP has close relation with type 2 inflammation. Therefore, biologics focused on type 2 inflammation cytokine as IL-4, IL-13 could be the new hope for patients with recalcitrant CRSwNP.

Biologics as Dupilumab (anti-IL4, IL-13) was then applied in patients with CRSwNP. In the phase 3 trial, Dupilumab can effectively reduce polyp size, improve smelling, increase life quality and reduce the revision surgery rate. Biologics was also advised in EPOS 2020 guideline for patients with recalcitrant CRSwNP.

According to previous research and treatment guideline recommendation, biologics played the role in recalcitrant CRSwNP treatment, but more local evidence base study is still necessary in the future.

Clinical positioning and experience of biologics in the treatment of CRSwNP: Taiwan experience sharing

慢性鼻竇炎合併鼻息肉的治療：台灣經驗

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Patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) are at increased risk for a decreased quality of life, olfactory dysfunction and associated with more severe asthma. For a long time, although endoscopic sinus surgery (ESS) has been proved to be an effective treatment, the recurrence rates after ESS are still significantly high, especially in type II CRSwNP cases. In recent, biologics therapy is a new treatment option for patients with type II inflammatory diseases, such as atopic dermatitis, asthma and CRSwNP. The potent biologics used for type II inflammatory diseases target specific cytokines (such as IL-4, IL-5, IL-13 or Ig E) in inflammatory pathways within a disease process. The recent research about the efficacy of biologics in refractory CRSwNP has led to promising therapeutic results. Biologics were reported to alleviate the nasal symptoms and the polyp size, improve the olfactory function, reduce the asthma attack, and decrease the need of surgery and oral steroids in several large-scale studies. However, in Taiwan, the TFDA approved the biologics (Omalizumab, Dupilumab) to treat in CRSwNP in recent months. The experience of biologics in treatment of CRSwNP are still limited. In this section, we will share our experience and results of biologics therapy in CRSwNP patients.

The role of biologics in the management of chronic rhinosinusitis with nasal polyposis: USA perspective

慢性鼻竇炎合併鼻息肉的治療：美國經驗

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Over the last several years, there has been increasing research on the role of biologics in the long-term management of chronic rhinosinusitis with nasal polyposis (CRSwNP). Currently, there are three biologic agents (omalizumab, dupilumab, mepolizumab) approved by the US Food and Drug Administration for treatment of CRSwNP. Though multiple clinical trials have demonstrated safety and efficacy in select patients, the exact timing of introduction and treatment duration for the various biologics, and where they fit into the treatment algorithm, remains unclear. Furthermore, consideration must be given to efficacy and safety in relation to existing treatments, such as endoscopic sinus surgery, costs of long-term use, and the uncertainty of long-term side effects. All in all, biologics present a viable adjunctive therapy for patients with CRSwNP refractory to established treatments, though further investigations are needed.

Unique role of IL-4 and IL-13 in severe asthma and transform treatable traits into clinical management

IL-4 及 IL-13 訊息路徑在嚴重氣喘的角色

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Asthma is a heterogenous disease with different pathological mechanisms which result in chronic airway inflammation, remodeling, variable airflow limitation and respiratory symptoms. About 3-5% of patients have severe asthma, which is defined by uncontrolled disease despite adherence with maximal optimized high dose inhaled corticosteroid and long-acting beta 2 agonist (ICS/LABA) and treatment of contributory factors, or that worsens when high dose treatment is decreased. Type 2 (T2) inflammation is present in approximately 50% of severe asthmatics, and interleukins (IL)-4 and -13 play a key role in its pathobiology. IL-4 is crucially involved in T helper 2 (Th2) cell differentiation, immunoglobulin (Ig) E production by B cell class switching from IgM, and eosinophil trafficking. IL-13 cooperates with IL-4 in promoting IgE synthesis, inducing goblet cell metaplasia and fibroblast proliferation, as well as elicits contractile responses and hyperplasia of airway smooth muscle cells. IL-13 also upregulates the expression and activity of inducible nitric oxide (NO) synthase causing elevated fractional exhaled NO (FeNO) levels which is easily detected and guide clinical management. Dupilumab is a monoclonal antibody directed against the IL-4 receptor and IL-4/IL-13 receptor complex and has efficacy in decreasing exacerbation rates and symptoms and improving lung function and quality of life in severe asthma. In this presentation, we will have a comprehensive discussion of the unique role of IL-4 and IL-13 in severe asthma and transform treatable traits into clinical management.

One airway, one disease: Multidisciplinary clinical management for patients with severe or moderate CRSwNP and asthma comorbidity

多專科治療慢性鼻竇炎合併鼻息肉及氣喘

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In asthma, comorbid conditions are frequently present, and they add to the burden of respiratory symptoms associated with the primary condition. They often contribute to a severe and difficult-to-treat asthma phenotype. However, application in clinical practice can be problematic, and an iterative, algorithmic approach modelled on identification first of common comorbid conditions may help general practitioners to diagnose, refer appropriately and, where possible, manage comorbid conditions in severe asthma. In our department, multidisciplinary clinical management for patients with severe asthma provides an effective approach to identify the causes of difficult-to-treat asthma and to manage the comorbid conditions.

The prevalence of chronic rhinosinusitis (CRS) ranges from 45–50% in severe asthma. CRS is an independent predictor of asthma exacerbations in severe asthma. Nasal polyps are associated with a more severe asthma phenotype. The presence of CRS is associated with lower asthma-related quality of life. CRS is also associated with poorer control and more exacerbations of asthma. In this speech, I will introduce the clinical practice of multidisciplinary discussion for managing difficult-to-treatment asthma and identifying comorbidities. Meanwhile, the diagnostic process of asthma in patients with CRSwNP will be revealed in this speech.

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免疫治療於肺癌各期別的應用

Implementation of Immunotherapy in the Treatment of Lung Cancer

時　間：111年7月16日　13:30~17:00

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Place：The Fourth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

免疫治療於肺癌各期別的應用

Implementation of Immunotherapy in the Treatment of Lung Cancer

Updates of neo-adjuvant and adjuvant immunotherapy for NSCLC

非小細胞肺癌新輔助與輔助免疫治療的最新進展

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Lung cancer is leading cause of cancer death in the world. The standard of care for early-stage non-small-cell lung cancer (NSCLC) includes surgery and adjuvant chemotherapy. Adjuvant treatment with platinum-based chemotherapy after surgery has been shown to improve survival in this setting. Nonetheless, some of these patients still have poor prognosis due to systemic or local recurrence. Only a minority of patients with resected NSCLC remain recurrence-free at 5 years. Because immunotherapy with immune checkpoint inhibitors have demonstrated survival benefits in advanced or metastatic NSCLC, it has been intensively studied as a novel approach to improve survival in patients with early-stage NSCLC.

The role of immunotherapy in the neoadjuvant treatment of resectable NSCLC was shown in a randomized phase III trial of neoadjuvant nivolumab. Among over 350 patients with resectable NSCLC, the addition of nivolumab to neoadjuvant platinum-based doublet chemotherapy significantly improved pathologic complete response rates, without hindering the completeness of surgical resection or increasing treatment-related complications. The role of adjuvant atezolizumab in resectable NSCLC was demonstrated in a randomized trial which enrolled almost 900 patients with stage II to IIIA NSCLC who had received surgical resection and adjuvant chemotherapy. Adjuvant atezolizumab had improved disease-free survival compared to the best supportive care group, with greater benefits among those with PD-L1 ≥1 %.

In this review, the published and updated data regarding recent clinical studies of immunotherapy in both neoadjuvant and adjuvant managements for early-stage NSCLC were summarized. More clinical trials are warranted to optimize the therapeutic remedies of immunotherapy in patients with early-stage NSCLC.

Recent advances of immumotherapy in unresectable stage III NSCLC

無法切除之第三期非小細胞肺癌的免疫治療新進展

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Stage III NSCLC is a heterogeneous disease that is treated with a multimodality approach, incorporating chemotherapy, radiotherapy, and surgical resection in selected cases. In patients with unresectable locally advanced (stage III) NSCLC, the standard of care has been definitive chemoradiotherapy since the early 2000s, with a platinum-based chemotherapy regimen in combination with concurrent chemoradiotherapy (CCRT).

Recently, several studies have explored the use of immunotherapy after definitive chemoradiotherapy for stage III NSCLC. A landmark study, the PACIFIC trial, published in 2017, revealed that durvalumab significantly improved survival outcomes in patients with unresectable stage III NSCLC without disease progression following CCRT. A 4-year update on survival outcomes in the PACIFIC trial demonstrated that 49.6% of patients who received durvalumab remained alive at 4 years compared with 36.3% who received a placebo. Several real-world analyses further verified its efficacy. Durvalumab consolidation treatment after CCRT has become the standard-of-care in the management of unresectable stage III NSCLC.

The evolving role of immunotherapy in advanced NSCLC

免疫治療在晚期非小細胞肺癌中的重要進展

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Lung cancer is the leading cause of cancer death worldwide. Although the diagnosis and therapy of non-small cell lung cancer (NSCLC) advance constantly during the years, the late-stage NSCLC patients still have poor prognosis. The metastatic NSCLC are generally treated with systemic therapy or palliative care. In recent years, lung cancer immunotherapy, such as immune checkpoint inhibitors, has showed significant survival benefit in particular patient populations. Some PD-1, PD-L1, and CTLA-4 inhibitors have shown favorable efficacy, and have been included in the clinical treatment of advanced NSCLC.

Patients with ≥50 % PD-L1 expression are typically treated with pembrolizumab or atezolizumab in advanced NSCLC populations lacking oncogenic driver gene mutations. Patients with rapid disease progression or very extensive disease could be treated with platinum-based chemotherapy plus pembrolizumab. For patients with <50 % PD-L1 expression, platinum-based doublet chemotherapy with pembrolizumab is the standard of care. Bevacizumab and atezolizumab in combination with platinum-based doublet chemotherapy is an alternative option for patients with non-squamous NSCLC. Nivolumab plus ipilimumab is an acceptable alternative for the treatment of metastatic NSCLC with ≥1% PD-L1 expression. Nivolumab and ipilimumab in combination with two cycles of platinum-based doublet chemotherapy is a reasonable alternative for metastatic NSCLC.

There are still many novel immunotherapy combinations in clinical trials that are expected to further improve the survival outcome of lung cancer patients. Herein, the landmark evidence supporting the success of immunotherapy containing regimens for advanced NSCLC were reviewed, and the clinical implications for combination strategies of immunotherapy were discussed.

The emerging treatment landscape of immunotherapy in SCLC

小細胞肺癌免疫治療的新進展

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Small cell lung cancer (SCLC) remains an aggressive, deadly cancer with only modest effect on survival from standard chemotherapy. In contrast to lung adenocarcinoma, which includes several effective targeted therapies against different driver oncogenes, SCLC is still approached clinically as a single disease entity. With the advance of molecular biology, researchers recently developed a new model of SCLC subtypes defined by differential expression of transcription factors (TF). A recent consensus proposal suggested grouping SCLC into four subtypes defined by RNA expression of ASCL1, NEUROD1, POU2F3, and YAP1, referring to these as SCLC-A, SCLC-N, SCLC-P, and SCLC-Y, respectively. By defining the unique therapeutic vulnerabilities of these subtypes of SCLC may accelerate therapeutic researches.

The addition of the anti-PD-L1 antibody atezolizumab or durvalumab to chemotherapy provided a significant improvement in overall survival and progression free survival, compared with platinum and etoposide alone. These regimens became a new standard-of-care in first line ES-SCLC. However, the benefit is relatively small and only a subset of patients could benefit from this combination. Gay et al., using unbiased clustering of RNA-seq data from 81 SCLC resections, report the identification of four transcriptionally distinct subgroups. Three of the four subgroups confirm those defined above. The fourth, previously undescribed subgroup, with low or absent expression of any of these TFs, was named SCLC-inflamed or SCLC-I. By re-analyzing the survival data from IMpower133, the researchers found that there was a trend toward SCLC-I tumors preferentially responding to chemoimmunotherapy treatment.

On the basis of chemoimmunotherapy combination, researchers continue to find other treatments to prolong survival in patients with this lethal disease. Other advance about immunotherapy in SCLC will be reviewed in this presentation.

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肝硬化及門脈高壓的新視野

New Horizons in Liver Cirrhosis and Portal Hypertension

時　間：111年7月16日　13:30~17:30

Time：July 16, 2022　13:30~17:30

地　點：臺北榮民總醫院 致德樓第五會議室

Place：The Fifth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

肝硬化及門脈高壓的新視野

New Horizons in Liver Cirrhosis and Portal Hypertension

The influences on liver cirrhosis-related complications after anti-viral agent treatment

抗病毒藥物治療後對病毒性肝炎合併肝硬化及其併發症之影響

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Cirrhosis is a dismal outcome of chronic viral hepatitis, and severe complication may develop, including ascites, spontaneous bacterial peritonitis, esophageal and gastric varices with bleeding, hepatic encephalopathy, hepatocellular carcinoma (HCC), and liver decompensation. The high viral load and hepatic inflammation are key contributing factors for the progression of cirrhosis. Several lines of evidences showed that antiviral therapy against hepatitis B or C can reduce the development of cirrhosis, cirrhotic complications, HCC and liver related mortality.

According to the CTEAM study to include 1315 HBV-related cirrhotic patients, longterm anti-HBV therapy reduces 62% risk of variceal bleeding, 94% risk of spontaneous bacterial peritonitis, 60% risk of HCC, 86% risk of liver related mortality, and 85% risk of all-cause mortality compared with patients without antiviral therapy. After the introduction of direct antiviral therapy, chronic hepatitis C can be cured easily. Patients with compensated cirrhosis who were cured of their HCV infection have a lower rate of complications; however, the rate of complications persisted in those with decompensated cirrhosis, and the need for liver transplantation remains.

Several issues need to be noticed. The risk reduction of cirrhotic complications is limited in patients with established portal hypertension and decompensated cirrhosis, indicating there is a “point of no return” even under persistent viral suppression. The risk of HCC was not eliminated, but possibly be delayed; therefore, continuous HCC surveillance is still mandatory in patients with cirrhosis. Liver transplantation may be still needed in patients with decompensated cirrhosis. These points suggest the need to control the virus earlier to reduce the cirrhotic complications.

Does cirrhosis resolution ensure recovery of portal hypertension-related derangements?

肝硬化改善是否必定伴隨門脈高壓相關異常狀況的改善？

Shao-Jung Hsu

許劭榮

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Chronic liver inflammation leads to fibrogenesis and eventually liver cirrhosis and portal hypertension. Liver cirrhosis has long been considered an end stage, but emerging data show that it is reversible. The control of liver injury promotes cirrhosis resolution. In chronic viral hepatitis C and B patients with appropriate treatments, cirrhosis resolution was noted in a median of 64% and 70%, respectively.

However, cirrhosis resolution indicates fibrosis regression but does not guarantee the normalization of portal hypertension. The hepatic venous pressure gradient (HVPG) decreased from 14.4 mmHg to 12.4 mmHg after one year of chronic hepatitis B treatment. In cirrhotic patients receiving direct anti-viral agents for chronic hepatitis C, the HVPG decreased from 13.1 mmHg to 10.4 mmHg. However, after a median follow up of 7.6 years, the esophageal varices regressed only in 22% of patients with hepatitis C virus eradication. The data suggest that cirrhosis resolution does not resolve all derangements of portal hypertension, but the features and mechanism have not been clarified.

Portal hypertension is derived from the pathologic change of liver, splanchnic and collateral system. In liver cirrhosis, the increased hepatic resistance accompanied by an increased portal inflow maintains the portal hypertensive status, which accelerates the formation of portosystemic collaterals. The collaterals develop initially with an attempt to divert the stagnant portal blood. However, the collateral vessels itself brings lethal complication.

This review will give a deep insight into the change of portal hypertension related hemodynamic derangements during cirrhosis resolution.

Acute kidney injury in cirrhosis

肝硬化之急性腎傷害

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國立陽明交通大學 醫學系

Acute kidney injury (AKI) is common in patients with cirrhosis, occurring in 20% of hospitalizations and is associated with poor prognosis and a high mortality rate. The most common causes of AKI in cirrhotic patients are prerenal azotemia (PRA), acute tubular necrosis (ATN), and hepatorenal syndrome (HRS). Indeed, the distinction among these diagnoses is extremely pivotal in setting an appropriate treatment strategy.

Nevertheless, current diagnostic strategies are often unable to make a clear differentiation between structural and functional kidney diseases, although HRS is typically considered a functional kidney injury. HRS is diagnosed mainly by way of the International Ascites Club (IAC) criteria, now set within a more broad classification system of AKI in cirrhosis proposed jointly by the International Ascites Club (IAC) and the Acute Dialysis Quality Initiative (ADQI). However, these criteria are still, not sensitive and specific enough. The IAC criteria for HRS are widely recognized and applied for their simplicity in that they can be employed easily to pick up the etiology of AKI without acquisition of the patient's entire hospital course. However, the major drawback is that the clear distinction between structural and functional disease may not be achieved via IAC criteria alone. While recent studies indicate that biomarkers are promising in clarifying the etiologies of AKI in cirrhosis, it is up to now unlikely any will result in a clear "positive" or "negative" cutoff, and the results have to be interpreted taken the overall clinical picture into consideration. A combination of multiple biomarkers is actually more informative than any alone. Therefore, this talk will review the state-of-the-art concepts of acute kidney injury in cirrhosis from the nephrologist's point of view.

Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations

肝硬化急性腎傷害之診斷及處置：最新的共識建議

Paolo Angeli

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Acute kidney injury frequently occurs in patients with liver cirrhosis. Among the various types of acute kidney injury, hepatorenal syndrome is the most dreadful one. Despite great advances made in diagnosis and treatment, the mortality rate of patients with hepatorenal syndrome is still high that there is still an urgent need to clarify the nature of this severe complication. Hepatorenal syndrome (HRS) has been defined as a purely ‘‘functional” type of renal failure. Nevertheless, new concepts, definitions, and diagnostic criteria have been developed by nephrologists and the definitions and characterisation of acute kidney injury have been refined by the joint efforts contributed by both hepatologists and nephrologists. Herein the latest revision of the nomenclature and diagnostic criteria of acute kidney injury in liver cirrhosis will be introduced and discussed.

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男性健康論壇2022

Men's Health Symposium 2022

時　間：111年7月16日　　13:30 ~ 17:00

Time：July 16, 2022　　13:30 ~ 17:00

地　點：臺北榮民總醫院 致德樓第六、七會議室

Place：The Conference Room 6&7, Chih-Teh Building
Taipei Veterans General Hospital

男性健康論壇2022
Men's Health Symposium 2022

Will different modality of testosterone replacement make a difference on fertility?

不同男性睪固酮補充方式對生殖能力是否有不同之影響？

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Hypogonadism may adversely affect multiple organ functions and quality of life. Patients with symptomatic hypogonadism (total testosterone < 12 nmol/L) without specific contraindications are suitable candidates to receive testosterone therapy for the beneficial effect on the clinical symptoms. Exogenous long-acting or continuous testosterone preparations such as injections, topical gels, patches and pellets appear to inhibit the gonadotropin releasing hormone pulse generator, leading to suppression of the HPG axis, and resulting in impaired spermatogenesis, sperm cell maturation and intratesticular testosterone producing. Therefore, testosterone therapy is contraindicated in hypogonadal men seeking fertility treatment.

A new frequent dosing (2-3 times daily) and short acting property of trans-nasal testosterone gel mimics physiological testosterone release as compared with other long-acting testosterone therapies. A hypothesis is proposed that this short-acting testosterone preparation can preserve spermatogenesis by maintaining release of gonadotropins.

Clinical studies revealed follicle stimulating hormone and luteinizing hormone levels were maintained within the normal range in 81.8% and 72.7% of patients at 6 months, respectively. Total motile sperm count was maintained with total motile sperm count greater than 5 million over the treatment period in 88.4% of men at 3 months and 93.9% at 6 months. It maintained spermatogenesis in more than 95% of men, in contrast to injections or transdermal gels (Ranjith, 2020).

Compared with traditional continuous exogeneous testosterone preparations, the new trans-nasal testosterone gel has the potential to be a safe and effective treatment for men with functional hypogonadism who wish to preserve semen parameters. Long-term studies are needed before we can safely prescribe for men interested in fertility.

Medical treatment of premature ejaculation: Oral drugs vs. topical agents

早發性射精的藥物治療：口服藥物和局部製劑之比較

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Premature ejaculation (PE) is a common complaint of male sexual dysfunction affecting man and his sexual partner causing significant persoanl and interpersonal distress. Various treatment options are currently available for patients with PE, including psychological behavioraltherapies, on-demand oral medications, regular oral medications, on-demand topical anesthetic agents, and surgery.

Dapoxetine, a short-acting, on-demand selective serotonin reuptake inhibitor (SSRI), is the first and only drug licensed for the treatment of PE. Its mechanism of action may increase serotonin action at pre- and post-synaptic receptors by blocking serotonin reuptake. At 12 weeks of treatment, the average Intravaginal Ejaculatory Latency Time (IELT) increased from a baseline of 0.9 minutes to 3.1 minutes with dapoxetine 30 mg and to 3.6 minutes with dapoxetine 60 mg. In addition to the IELT, dapoxetine significantly improved control over ejaculation, satisfaction with sexual intercourse, and other patient-reported outcomes. The efficacy of dapoxetine was similar between patients with lifelong PE and those with acquired PE.

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE. Several trials support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis thereby delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation. Fortacin™ is a metered-dose aerosol spray and contains purely base (uncharged) forms of the local anesthetics lidocaine 150 mg/mL and prilocaine 50 mg/mL. The special galenic properties of this product offer advantage of easy dosing and absorption. In the phase III 3-month studies involving 539 subjects, the Fortacin™ spray was applied 5 minutes before sexual intercourse and resulted in an increase in the geometric mean IELT from a baseline of 0.6 minutes to 3.8 minutes corresponding to a 6.3-fold increase compared to 1.7-fold after placebo ($p < 0.001$). The efficacy and safety of Fortacin™ have been proved by means of increased ejaculatory latency, control, and sexual satisfaciton in large scale studies demonstraing the significant benefts for both patients and their partners. Fortacin™ may become a firstline treatment choice for PE.

Hormone manipulation for NOA patients before microdissection testicular sperm extraction

非阻塞性無精症接受顯微睪丸取精術前之荷爾蒙治療

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Background: Microdissection testicular sperm extraction (mTESE) is the treatment of choice for men with non-obstructive azoospermia (NOA). Not uncommonly, the azoospermic men may co-morbid with hypogonadism. Prior to the mTESE, whether to correct/ improve the hypogonadism with hormone manipulation is still controversial.

Methods: Fourteen clinical studies and trials published in English literature were reviewed. And the clinical data of men received mTESE in our institute for the past 5 years was also studied.

Results: The available data of sperm retrieval rate in men with hypogonadism or normogonadism were pooled. The patients with normal testosterone levels had a significantly greater chance of sperm yield as compared to those with hypogonadism. ($p < 0.05$). Based on our cohort, the most valuable indication for hormone manipulation are: 1. Hypogonadotropic hypogonadism; 2. Hypospermatogenesis; 3. Late maturation arrest.

Conclusion: Hormone manipulation for NOA men prior to mTESE may have benefits for those who have hypogonadism, especially for those with 1. Hypogonadotropic hypogonadism; 2. Hypospermatogenesis; 3. Late maturation arrest. No definite evidence can be provided for other types of NOA.

Optimal treatment and management for men presented with aspermia

無精液症的治療

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Aspermia, mainly involved ejaculatory failure, including anejaculation and aspermia, represents a complex pathological condition characterized by a complete lack of semen expelled forwardly through the urethra. This can be due to either a complete inability to ejaculate (anejaculation) or semen propelled in a retrograde fashion into the bladder result from closure failure of the bladder neck during ejaculation (retrograde ejaculation). It is commonly encountered in men with a wide spectrum of possible organic etiologies consulting for infertility, such as spinal cord injury (SCI) or neuropathy due to diabetes mellitus (DM) or multiple sclerosis, and can be a sequela caused by disruption of thoracolumbar sympathetic chain.

The annual global incidence of SCI, both traumatic and non-traumatic, is estimated between 20 and 60 new cases per million population. Although the epidemiology and demographics of SCI varies in different regions of the world, the incidence is reported greatest in the late teens and early 20s, but the average age at such injury has gradually increase from 29 years to 42 years over the past 5 decades. Similarly, in another population who are likely to have the associated clinical feature of anejaculation or retrograde ejaculation, Six to 30% of the DM patients in their reproductive age may present with ejaculatory failure that may ultimately lead to infertility. Given that there has been a significant rise in the number of adolescent males with DM, along with the new SCI cases each year, an increasing number of men of reproductive age will in due course confront with infertility related issues. While medical treatment used to increase sympathetic tone or decrease parasympathetic activity at the bladder neck may offer chance for restore antegrade ejaculation, still 40% to 80% of men with retrograde ejaculation and a majority of anejaculation patients fail to respond to such treatment.

For men with ejaculatory failure who wish to father a biological child after unsuccessful medically assisted reproduction treatment, assisted ejaculation can be achieved by employing other approaches such as penile vibratory stimulation (PVS) or electroejaculation (EEJ). Although the reproductive outcomes of intracytoplasmic sperm injection (ICSI) were comparable with the use of sperm obtained by PVS versus EEJ in men with SCI, the semen retrieval rate is, nonetheless, lower in men using PVS, especially those level of injury is caudal to T10. Surgical testicular sperm retrieval may be performed if the aforementioned failed. The reported successful sperm retrieval rate can be achieved in 80% of men with SCI and take home baby rate can reach 70%.

Updates on the diagnostic evaluation of chronic pelvic pain in male

男性慢性骨盆腔疼痛的診斷新知

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Chronic pelvic pain syndrome (CPPS) in male is a complex syndrome of varied clinical presentation. Proper definition of different subgroups facilitates more specific patients' approach and better management strategies. Novel research design of MAPP study (Multidisciplinary Approach to the Study of Chronic Pelvic Pain) involves investigators with diverse clinical and research expertise, including urologists, gynecologists, gastroenterologists, rheumatologists, epidemiologists, biostatisticians, molecular and cellular biologists, neurobiologists, psychologists and psychometricians, and microbiologists. New insights attained from MAPP study give us the new understanding of the underlying pathophysiology and diverse symptomatology of CPPS.

One should avoid the traditional thinking of bladder-focused or prostate-focused to approach the patients with CPPS, but in a rather holistic way to evaluate them. The relationships between CPPS and other nonurological chronic overlapping pain conditions (COPCs), including fibromyalgia, chronic fatigue syndrome and irritable bowel syndrome might influence the severity and the prognosis of CPPS. In addition, clinical and molecular biomarkers, investigation of bacterial, viral and other infectious causative agents, multimodal brain imaging study were all taken into consideration to better understand the pathophysiology and to differentiate clinical phenotypes.

Updates on non-surgical management of chronic pelvic pain in male

男性慢性骨盆疼痛之非手術治療

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In this talk, we will review updates on non-surgical managements of chronic pelvic pain (CPP) in male, which comprised of medical treatments and non-medical treatments. There are several types of medication that urologists frequently prescribed, including antibiotics, alpha-blockers, anti-inflammatory, neuromodulators, 5-Alpha-reductase inhibitors (5-ARIs) and phytotherapy. Non-medical treatments included intraprostatic botulinum neurotoxin type-A injection, trigger point injection, pelvic floor physiotherapy, acupuncture, and extracorporeal shock wave treatment (ESWT). In current update data, only antibiotics with doxycycline, alpha blocker treatment, anti-inflammatory drug with celecoxib, phytotherapy with cernilton and quercertin, intraprostatic botulinum neurotoxin type-A injection, trigger point injection, pelvic floor physiotherapy, acupuncture, and ESWT showed significant improvement symptoms after treatment.

We should utilize the mnemonic “UPOINTS” during our practice, which is the acronym of urinary, psychosocial, organ specific, infection, neurologic, and tenderness. We should also encourage patient’s partner or spouse participating in the treatment course, together with the patient to realize the goal of treatment, including easing the annoying symptoms, and also learning some coping strategies to confront with unexpected symptom flare-ups.

Does surgery play a role in the treatment of chronic pelvic pain in male

手術治療在男性慢性骨盆疼痛之角色

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Chronic prostatitis and chronic pelvic pain (CP/CPPS), also known as National Institutes of Health (NIH)) category III prostatitis is an ill-defined and heterogenous condition with significant impact on quality of life. CP/CPPS affecting around 10-16% of men and it is most prevalent in men between 30 and 50 years. CP/CPPS carried as mixture of different clinical phenotypes that may present with lower urinary symptoms, pain, sexual dysfunction and psychiatric complaints, and results in resistant to mono-therapy. Selectively medical combination is the current mainstream of CP/CPPS treatment.

The rationale of surgery in treating CP/CPPS is completely removal the inflamed or infected prostate tissue. Transurethral resection of prostate (TURP) had been reported as alternative treatment in patients with unsuccessful medical treatment in retrospective studies. 70% of patients were reported as cured and 15% as improved. Besides, significant IPPS improvement without increasing complication rare was also reported. TURP may be considered in patients with high degree urinary tract symptoms suffering despite of medical treatment.

95% (20/22) CP/CPPS patients reported as symptoms free after radical prostatectomy (RP) had been reported in 6 case series. Erectile dysfunction was noted in 4 patients and incontinence in one patient postoperatively in 4 case series. RP carries risk of impotence and urinary incontinence, should not be considered as a primary therapy for CP/CPPS.

Surgical therapy of CP/CPPS might be a viable therapy option especially in patients with marked lower urinary tract symptoms; however, very limited data were available currently. Further randomized controlled trials are necessary to elucidate the indication and efficacy of surgical interventions in CP/CPPS treatment.

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次世代定序於病理實務與研究應用：臺北榮總經驗分享

Application of Next Generation Sequencing on Pathology Practice and Research Taipei Veterans General Hospital Experience

時 間：111年7月16日 13:30~17:00

Time：July 16, 2022 13:30~17:00

地 點：臺北榮民總醫院 致德樓第八、九會議室

Place：The Conference Room 8&9, Chih-Teh Building
Taipei Veterans General Hospital

次世代定序於病理實務與研究應用：臺北榮總經驗分享
Application of Next Generation Sequencing on Pathology Practice and Research Taipei Veterans General Hospital Experience

Exploration of potential predictive biomarkers for immune checkpoint inhibitors with omics data analysis

利用體學資料分析探索具有潛力的免疫檢查點抑制劑預測生物標記

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Cancer is the leading cause of human deaths worldwide. Many studies are dedicated to investigating the therapeutics to the disease, and immunotherapy, especially immune checkpoint inhibitors (ICIs), have emerged as one of the promising therapeutic approaches in recent years. Although ICIs have achieved impressive success in cancer treatment, however, treatment response is only observed in a minority of patients. Since those non-responders need to endure high treatment cost and toxicities with little benefit from the treatment, identification of potential predictive biomarkers is critical to optimize the benefits of ICIs in patients. Among all the potential indicators of patients who might benefit from ICI, microsatellite instability (MSI) status and tumor mutational burden (TMB) are the ones US FDA approved. However, there are still patients who are TMB-high or MSI-high but have no response of ICI, indicating that these biomarkers are imperfect. Therefore, we would like to explore other potential predictive biomarkers for ICIs with comprehensive multi-omics analysis. In this talk, the following topics will be introduced: (1) Development of a computational framework to construct a TMB estimation model to precisely estimate TMB and to accurately predict the treatment response for patients; (2) Establishment of a novel DNA damage repair gene panel as a biomarker of ICI response; (3) Investigation of the roles of tumor infiltrating lymphocytes and tertiary lymphoid structures in ICI response; (4) Investigation of the association between aging and common predictive biomarkers of ICIs. Hopefully, the identified predictive biomarkers can be validated by real-world data. In this way, the predictive biomarkers are able to guide the appropriate administration of ICIs in clinical practice, achieving the goal of precision medicine.

NGS helps classification of genitourinary neoplasms

次世代定序有助於生殖泌尿腫瘤分類

Chin-Chen Pan

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Next generation sequencing technologies, such as whole exome sequencing and whole transcriptome sequencing, offer a high-throughput platform to investigate the genomics of diseases, including neoplasm. Herein we introduce practical pipelines for the analyses of genomic alterations from pathologist's perspective. General procedures, as well as tools and examples of detecting recurrent mutations, copy number variation, structural variations for DNA-seq, and detecting fusion, differential expression, gene set enrichment for RNA-seq, will be presented. We will share our experience of NGS platform in classification of genitourinary neoplasm, including prostate stromal tumor, renal cell carcinoma and metanephric tumors.

Quality management of next generation sequencing in clinical laboratories

次世代定序之臨床實驗室品質管理

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Precision Medicine is currently the innovative approach to tailor disease prevention and treatment by taking into account a person's genes, behaviors, lifestyles and environment. Next generation sequencing (NGS), allowing massively parallel sequencing in an efficient and cost-effective manner, is the critical technology that brings Precision Medicine into clinical reality, especially in cancer management. The NGS workflow includes a two-step process: the "wet-lab" process, which is composed of nucleic acid extraction, library preparation and sequencing, and the "dry-lab" process, which is a bioinformatics analysis pipeline starting from sequence alignment and mapping to variant calling and annotation. Most of the NGS-based assays are laboratory-developed tests (LDTs) requiring the validation processes to demonstrate the assay performance before implementing into clinical service. However, the standardization as well as quality management toward NGS-based assays still awaits to be illuminated in Taiwan. The College of American Pathologists (CAP) checklist has released specific quality management programs that specify assay validation, quality metrics as well as quality controls to ensure the accuracy and reliability of NGS assay results in a clinical laboratory. This presentation, from the view of clinical practice, will introduce you the general considerations regarding analytical and clinical validation as well as quality management systems in NGS-based assays, and the experiences of our laboratory in the Department of Pathology and Laboratory Medicine at Taipei Veterans General Hospital will also be discussed.

Identification of unique fusion transcripts on difficult (undifferentiated?) sarcoma using targeted enriched NGS

標靶強化次世代定序辨識特殊融合轉錄體診斷困難肉瘤

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Sarcoma is a rare but important neoplasm. In comparison to commonly known carcinoma, the incidence of all sarcoma together is still far less than almost any single carcinoma. The annual incidence of sarcoma (including connective tissue, soft tissue and subcutis tumors) is very low, only a few hundreds. It only accounts for 0.5 % in all malignant tumors in Taiwan (data published by Health Promotion Administration, MOHW, 2020). For the importance, all sarcomas belong to a clone of specific mesenchymal cells which can be originated from fat, nerve, muscle, vascular, fibroblastic or even undifferentiated, mesenchymal progenitor cells. And all these sarcoma can be anywhere in human body. Traditionally, pathological diagnosis of sarcoma is largely depended on its distinctive morphological differentiation, and confirmed by specific immunological markers. However, most of fibroblast-like (spindle cell) and undifferentiated mesenchymal (round cell) sarcomas have ambiguous, or none of the above mentioned features. Thus these tumors were frequently put together in a waste basket, as malignant fibrous histiocytoma (MFH), malignant spindle cell tumor, undifferentiated sarcoma, or round cell sarcoma. It is worrisome since tumor is a disease of genetic mutation. Unlike somatic point mutations which are commonly seen in carcinoma, two thirds of sarcoma harbor distinct genetic disorders, mainly chromosomal translocation. Current studies have shown different chromosomal translocations could result in different growth behaviors and disease prognosis. Here, I will present two cases of rare sarcomas which were very hard to be diagnosed accurately by conventional pathologists. Although the cases are low grade sarcoma, due to the size and location, they could have been treated aggressively if under the original impression of undifferentiated sarcoma. These two examples emphasize the critical application of transcriptome NGS on soft tissue sarcoma.

Multiple lung cancers: Application of next generation sequencing in the distinction between separate primary lung cancers and intrapulmonary metastases

應用次世代定序鑑別多發性原發肺癌與肺內轉移

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葉奕成

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臺北榮民總醫院 病理檢驗部

With the advances of computed tomography imaging, multiple pulmonary tumor nodules are diagnosed with increasing frequency in clinical practice. Determining the clonal relationship of multiple lung nodules is of significant clinical importance, as tumor staging and therapeutic management are different between separate primary lung cancers (SPLCs) and intrapulmonary metastases (IPMs). The former is potentially curative by surgical resection, whereas the latter usually requires systemic therapy. Histopathology-based classification is the current practice, but it is subjective and affected by inter-observer variability. Over the past decades, several studies used molecular analysis to distinguish SPLCs from IPMs, including DNA microsatellite analysis, array comparative genomic hybridization, TP53, and oncogenic driver mutation testing, as well as the most recent one of gene panels using next-generation sequencing (NGS). Studies using large-scale NGS panels were generally more capable of distinguishing separate primary lung cancers from intrapulmonary metastases, with fewer ambiguous cases. Notably, histologic interpretation was discordant with NGS in around 20% of cases. These results highlight the importance of incorporating molecular information into the clinical management of multiple lung cancers, although the optimal approach for molecular classification of separate primary lung cancers versus intrapulmonary metastases remain to be defined.

Detection of NTRK fusion in head and neck cancer

偵測頭頸癌之 NTRK 基因融合

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Tumor agnostic therapy is an emerging trend in precision oncology since the USFDA approval of two tropomyosin kinase inhibitor, Larotrectinib (2018) and Entrectinib (2019), to treat solid tumors with NTRK rearrangements regardless the histologic type. In a recent study of 295676 cases receiving comprehensive genomic profiling, NTRK rearrangements are found in only 889 (0.30%) cases, with 45 different histologic types and 88 different fusion partner genes. These highlight the difficulty in detecting NTRK rearrangements in routine practice. In this talk, we will demonstrate real-world cases of NTRK-rearranged head and neck cancers, including secretory carcinoma of salivary gland and papillary thyroid carcinoma, and discuss our experience of NTRK testing approach, combining pathologic examination, pan-TRK immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and next-generation sequencing (NGS).

The role of genetic testing for DNA damage repair pathways in prostate cancer

前列腺癌 DNA 損壞修復路徑之基因檢測

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Prostate cancer is the most common non-cutaneous malignancy diagnosed in men in the western countries. Although its incidence is relatively lower in Asia, it is rapidly increasing in the last few decades, including in Taiwan. Similar to other cancer types, epigenetic and somatic or germline genetic modifications lead to higher risk of prostate cancer and its progression. Among these, impaired DNA damage response (DDR) pathways play an important role in prostate carcinogenesis and germline or somatic mutations in DDR genes have been found in both primary and metastatic prostate cancer. Prostate cancer with DDR defects may be sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors in a process of synthetic lethality, highlighting the importance of genetic testing in the appropriate settings. Among DDR genes, BRCA mutations have been found to be especially clinically relevant with a role for germline or somatic testing. In this talk, I will review important findings from genomic studies such as The Cancer Genome Atlas (TCGA) with regards to DDR defects and discuss potential utilities of integrating genetic testing into daily practice.

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眼科智慧及精準醫療之新進展

Smart and Precision Medicine in Ophthalmology

時　間：111年7月16日　13:30~17:30

Time：July 16, 2022　13:30~17:30

地　點：臺北榮民總醫院 致德樓第十會議室

Place：The Tenth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

眼科智慧及精準醫療之新進展
Smart and Precision Medicine in Ophthalmology

Potential application of artificial intelligence in the management of glaucoma

人工智慧用於青光眼診療之價值

Yu-Chieh Ko

柯玉潔

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Glaucoma is one of the leading causes of irreversible blindness, but under-diagnosed worldwide. With the advancement of image capture technology for fundus photography and artificial intelligence- assisted image diagnosis, automated glaucoma detection using fundus photographs may be an effective approach to increase the diagnostic rate of glaucoma through clinic- or population-based glaucoma screening. However, a generalizable glaucoma-detection algorithm is currently unavailable because the diagnosis of glaucoma is complicated necessitating thorough structural and functional assessment and comprehensive datasets with a large number of images for supervised learning are not available.

Contrarily, artificial intelligence has great potential in forecasting glaucoma progression. Detecting disease progression is a key element in the management of glaucoma. Glaucoma treatment should be individualized to fit the needs and rate of progression of each patient, which differs very much between patients. However, detecting glaucoma progression is challenging in clinical practice because the tests used to assess changes over time such as optical coherence tomography imaging and visual field (VF) testing suffer from considerable test-retest variability, making it difficult to discriminate true change from variability. Despite these challenges, several groups have proposed the potential of using unsupervised techniques and deep learning to identify patterns of VF loss, detect VF progression, or even forecast VF changes. These predictive models, including the rate and pattern of VF progression, may help clinicians and patients to set better individualized treatment strategies. Furthermore, the archetypes of VF loss patterns identified by these algorithms are clinically relevant and interpretable, which makes the model explainable for clinicians. However, none of these techniques have been incorporated into clinical practice currently, further verification of the generalizability of these models is critical before implementing artificial intelligence in glaucoma care.

Recent application of artificial intelligence in retina

近年人工智慧於視網膜疾病之應用

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Digital images can rapidly and non-invasively be analyzed in a comprehensive manner using artificial intelligence (AI), which can mimic cognitive thinking process such as learning and problem solving system by processing and recognizing signals from large amounts of data. The most common application of AI methods in retina is the detection of disease-related features on color fundus photographs and fluorescence angiography. With the advent of OCT in the early 2000s, automated segmentation has been applied to delineate anatomic and pathologic features in retinal diseases.

Feature recognition in retinal imaging modalities is well-suited for the application of AI to image analysis. It has been implemented in the screening and diagnosis of retinal diseases such as Diabetic Retinopathy (DR), Retinopathy of Prematurity (ROP) and Age-related Macular Degeneration (ARMD). With the rapid development of computing power and variety of algorithms, hundreds of studies utilized AI to approach their applicability, explanability, and reliability in diverse datasets and diseases.

Since COVID-19 pandemic is an impact on the delivery of ophthalmic healthcare, the rapid adoption of telemedicine and point-of-care system has emerged. Such a system may ultimately have a role in currently established tele-ophthalmology programs and other virtual clinics that are cost-effective approach to maximizing outreach to distant communities. This review organizes a summary of the leading-edge AI system in feature detection, disease differentiation, referral screening, prognosis prediction, and some implemented large-scale programmes for different retinal diseases during 2016-2022.

Genome-wide polygenic risk score for predicting high-risk eye diseases in individuals of Han Chinese ancestry

以全基因組多基因風險評分預測漢族人群之眼疾高罹病風險病患

Chih-Chien Hsu

許志堅

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Glaucoma and cataract are two common progressive blinding diseases. However, the underlying genetic factors and molecular mechanisms of these two diseases remain poorly understood. Previous genome-wide association studies (GWAS) have led to tremendous progress in SNP-based disease association and characterization. However, most of them are done for Europeans or Japanese. As differential genetic profiles between races are evident in glaucoma and cataracts, it is worthwhile to complete their genetic profiles from larger Asian populations. Here, we separately introduce two glaucoma- and cataract-related GWAS based on Taiwan Biobank. After clustering of genetically related SNPs (LD clustering), many independent SNPs were recruited to construct a polygenic risk score (PRS), not only in glaucoma but also in cataract. These models had a large area under the receiver operating characteristic curve (AUC), and models in the highest quantile of PRS had a very high fold increased risk of glaucoma or cataract compared to models in the lowest quantile. These studies demonstrate the validity of our polygenic risk score in predicting high-risk glaucoma or cataract Han population.

Heavy ion therapy for ophthalmic tumors

碳粒子治療在眼部腫瘤之應用

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Surgery, chemotherapy and radiotherapy are the three major anticancer treatment modalities. Radiotherapy plays a pivotal role in cancer treatment as about half of cancer patients receive this therapy. Contributed by significant advances in the fields of physics, radiobiology, and information technology, unceasing progress has been made in the field of radiotherapy. Although both benign and malignant ophthalmic tumors are relatively rare, these lesions are quite different in terms of the incidences, types and treatment modalities. Radiotherapy has been increasingly adopted for these lesions, ranging from optic glioma, melanoma, retinoblastoma, rhabdomyosarcoma, lymphoma to lacrimal gland tumors etc. as either a definitive or post-operative treatment. In addition to linear accelerator based conventional photon beam radiotherapy, the first proton therapy facility was commenced for cancer patient treatment in the United States in 1990. Subsequently in 1994, National Institute for Quantum Science and Technology (QST) in Japan began treating cancer patients with carbon ion radiotherapy. Carbon ion weighs 12 times more than proton particle, and is therefore categorized as heavy particle. As of now, it is estimated around 50,000 cancer patients have been treated with carbon ion radiotherapy. Carbon ion therapy is characterized by its large relative biological effect (RBE) and low oxygen enhancement ratio (OER). Therefore, it is relative potent to treatment hypoxic tumors and those refractory to conventional chemotherapy and radiotherapy. Significant results of carbon ion radiotherapy had been demonstrated in the treatment for patients of various cancers, including lung, liver, head and neck, recurrent colorectal, and gynecological cancers etc. There are also increasing number of reports regarding this modality for ophthalmic tumors. In this presentation, the background information, treatment results in the literatures, and potential landscape of carbon ion therapy for ophthalmic tumors will be reviewed.

The application of navigational surgery on periorbital diseases.

導航手術於眼窩疾病之應用

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The periorbital region involves the cranio-orbito-zygomatic (COZ) delta which is a unique anatomic subsite that plays important role on supporting the orbit and sinonasal structures. Meanwhile, it is the essential part of the lateral projection of facial profile. Orbitozygomatic deformities are frequently a sequalae after traumatic injuries or oncological resection. How to restore the facial contour and function is the utmost treatment goal. However, the complex nature of the structures challenges the surgeon's knowledge to anatomy, experience, and the perception toward surgical outcome. Furthermore, the COZ delta situated in the region, which is often neglected, and those patients are prone to be rotated between different specialties. As maxillofacial surgeons, our training background provides better understanding on the craniomaxillofacial structures, which is a new avenue to deal with the COZ delta. With the rapid development of digital technologies and computational algorithm, modeling/navigation techniques profoundly change the surgical practice in craniomaxillofacial surgeries. Volume rendering from different image sources allows the surgeon to analyze the patient in three-dimensional format and to manipulate deformed or missing facial structures by computational algorism such as mirroring, segmentation, or insertion of unaltered or ideal skeletal constructs. The execution of the virtual planning is then accomplished by using stereolithographic models (SLMs), implants, cutting guides, or through image-guided surgery in the form of intraoperative navigation. Precision and reduced operation time are the main benefits from using computer assisted approaches. When combing endoscope and remote surgical approaches, tumor resection and customized reconstruction could be done with minimal visible scar. The treatment flow has become a daily routine and a gold standard to optimize functional and cosmetic outcomes. In this presentation, I will share the Taipei Veterans General Hospital experience of practicing computer-assisted approach on COZ diseases.

High fold correction in revisional double eyelid surgery

雙眼皮降窄重修手術

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大學眼科

Double eye lid surgery is one of the most common cosmetic operations. However, the complexity of the operation and the individual differences lead to the variability and uncertainty of the results. Ptosis, asymmetry, retraction of the eyelid, and high fold are the common reasons for revision surgery. Revising double eyelids from wide to narrow is complicated and is more difficult than making a higher crease. There are many details to pay attention to. The steps can mainly be divided into two parts. First, release the adhesion from original crease, basically among the plane between septum and orbicularis muscle, and the plane between orbital fat and levator muscle. Second, rearrange the combination of tissue layers to make a beautiful double eyelid. As to whether to trim skin, whether to have fat transplant, or whether to perform levator aponeurosis/muscle advancement, it depends on the individual's situation.

Novel medical treatment for Graves'ophthalmopathy

甲狀腺眼病變的最新藥物療法

Yi-Hsuan Wei

魏以宣

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台大醫院 眼科

Thyroid eye disease or Graves' ophthalmopathy (GO) is the most common extra-thyroid manifestation of Graves' disease. The ocular manifestations represent orbital inflammation, tissue expansion, and fibrosis that often lead to substantial morbidity. The clinical signs of GO may comprise any of the following: conjunctival chemosis, periorbital soft tissue swelling, proptosis, eyelid retraction, restriction of eye movement, and decrease of vision due to exposure keratopathy or compressive optic neuropathy. The exact pathogenesis of GO has yet to be understood, and the disease remains a therapeutic challenge. Treatment strategies vary depending on disease severity and activity.

In this talk, we will focus on the novel medical treatment for GO, including teprotumumab. tocilizumab, and rituximab. Recently, attention has been drawn to hypercholesterolemia as a risk factor for GO. Some studies revealed an association between high total and low-density lipoprotein cholesterol concentrations and the presence of GO. In addition, two large cohort studies showed that the use of statins was associated with a reduced chance of developing GO among patient with Graves' disease. In our basic research, we explored the anti-inflammatory and anti-fibrotic effects of statin in cultured orbital fibroblasts derived from GO patients. Our data may be helpful to explain the possible molecular mechanisms through which statins reduce/inhibit GO development.

Further studies are warranted to clarify the role of statin therapy in patients with GO. It seems reasonable to suggested that hypercholesterolemia should be controlled in patients with Graves' disease regardless of whether there is orbital involvement.

Update of lacrimal stents and plugs

淚管支架與淚管塞之最新發展

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Epiphora and dry eye are distinctly different symptoms which are frequently encountered in eye clinic. Normal tear drainage occurs within nasolacrimal drainage (NLD) system. Tears exit the ocular surface via the upper and lower puncta, through canaliculus then into lacrimal sac then becoming the nasolacrimal duct, which opens beneath the inferior turbinate and into the inferior meatus of the nose. The lacrimal devices were placed within the nasolacrimal drainage system either to facilitate tear drainage such as lacrimal stents, and to the opposite, to block tears from leaving the eyes such as lacrimal plugs.

Nasolacrimal stents are small diameter tubes placed within the nasolacrimal system to maintain patency, which are used primarily in cases of obstruction or laceration of one or more parts of the tear drainage system. The nasolacrimal tubes are typically composed of silicone, or another similar semi-rigid yet flexible material with an open central lumen. Intubation of the nasolacrimal system is generally done temporarily, with stents remaining in place for several months. CIS-tube is commonly used in dacryocystorhinostomy (DCR) surgery, Jones tube in conjunctivodacryocystorhinostomy (CDCR), and mini-Monoka Stent placing in canalicular laceration. Nunchaku is a pushed silicone self-retaining bicanalicular nasolacrimal intubation stent that acts like a conformer, allowing tears to drain by capillarity.

Lacimal plugs, also called punctal plugs, are tiny devices used to treat dry eye syndrome, which help keep eyes moist and soothe any discomfort. Lacrimal plugs can be inserted fairly quickly and easily through punctal occlusion. Different types of materials determine how long they will last in the eye. Semi-permanent plugs are made of acrylic or silicone, and most are placed in the tear duct. Dissolvable lacrimal plugs may last up to about couple of months, which are made of material like collagen that will eventually be absorbed by the body.

The material and devices are updating among lacrimal stents and plugs, which bring new aspects of treating nasolacrimal duct obstruction and dry eyes. Although there are side effects and potential complications, lacrimal stents and plugs are useful in daily practice of treating tearing problem.

The essential applications of endoscope in precision medicine for nasolacrimal duct obstruction

內視鏡在鼻淚管阻塞精準醫療中的重要應用

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The utilization of endoscope in dacryocystorhinostomy (DCR) are getting more popular in the past years. The most eye-catching feature of endoscopic DCR over external DCR is no visible cutaneous facial scar. With the advent of newer generation of telescopes and surgical techniques, recent studies showed that the success rates were not significantly different between endoscopic DCR versus external DCR. The endoscopic DCR now are well accepted as the treatment of choice for acquired lacrimal duct obstruction.

Nasal lacrimal duct (NLD) is tear drainage system bridging the tear flow from conjunctival mucosa to nasal mucosa. The NLD system is deep to the skin and relatively close to nasal cavity. With the help of endoscope, it provides not only a minimal invasive approach to access the NLD system from the nose, but also high-resolution images and better anatomic observations.

The utilization of endoscope in lacrimal duct system can largely help to achieve a personalized medical assessment and strategy making, including pre-operative evaluation, post-op wound management, revision of complicated DCR, sinonasal anomalies, and conjunctiva-dacryocystorhinostomy (CDCR).

Inevitability, the initial challenges for oculoplastic surgeons in handling endoscope do exist, such as unfamiliar nasal anatomy and difficulty in achieving dexterity and instrument maneuvering withing the confines of nasal cavity. I will share our experience and cases in managing NLD disorders with endoscope in this section. The practice and learning of endoscopic lacrimal surgeries are expected to improve further.

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人工智慧在麻醉的應用

AI in Anesthesia

協辦單位：臺北榮總麻醉部、
財團法人麻醉醫學研究發展基金會、
臺灣麻醉醫學會

時　間：111年7月16日　13:00~17:30
Time：July 16, 2022　13:00~17:30

地　點：臺北榮民總醫院三門診9樓CiC創新沙龍
Place：The Clinical Innovation Center,
Taipei Veterans General Hospital

人工智慧在麻醉的應用
AI in Anesthesia

AI anesthesia information system in Taipei Veterans General Hospital

臺北榮總麻醉智慧資訊系統

Chien-Kun Ting

丁乾坤

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The AI anesthesia information system of Taipei Veterans General Hospital includes several important sub-systems in each perioperative stage before, during and after operation. Since its establishment three years ago, the original hand-writing paper-based anesthesia management system has gradually phased out, and a brand new anesthesia electronic record ecosystem has been implanted. The ecosystem which is center with anesthesia recording system includes comprehensive branches such as preoperative and postoperative visits, anesthesia supplies, instruments, controlled drugs and other management systems, anesthesia electronic billing system, patient surgical anesthesia dynamic monitoring system and real-time information HQ center, and anesthesia patient's vital signs alarm messages. The system focuses on information security and patient safety, supplemented by user experience and convenient UI, forming a solid foundation for the further AI and automation of the operating room in the future.

Machine learning in patient monitoring

生理監視器的機器學習

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Cardiovascular waveforms contain information for clinical diagnosis. Despite modern monitoring technologies, the mechanisms to maintain cardiovascular homeostasis and to integrate multiple organ systems might be intangible sometimes. A potential solution may lie in its waveform morphology. In addition to the well-known clinical knowledge, we may harness the power of machine learning to explore beyond the limits of the naked eyes. Here, we demonstrate that unsupervised manifold learning could become a general-purpose approach for cardiovascular waveform data processing. The presence of diverse geometric shape from the manifold coincides with known signatures of its complex and everchanging nature. We also demonstrate several approaches to integrate anesthesiologists' clinical insights into the data analysis process.

Artificial intelligence respiratory monitor device and clinical practice

人工智慧聽診器呼吸監測儀與臨床應用

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A double-lumen tube (DLT) is an endotracheal tube designed to isolate the lungs anatomically and physiologically, which provides independent ventilation for each lung. One-lung ventilation (OLV) or lung isolation is the mechanical and functional separation of the 2 lungs to allow selective ventilation of only one lung. The other lung that is not being ventilated passively deflates or is displaced by the surgeon to facilitate surgical exposure for non-cardiac operations in the chest such as thoracic, esophageal, aortic and spine procedures.

Complications of DLT include hypoxemia due to tube malposition, displacement, tube occlusion from secretions or blood. Malposition of the DLT can lead to life-threatening consequences. Ventilation can be severely impaired, leading to hypoxia, gas trapping, tension pneumothorax, cross-contamination of lung contents, and interference with surgical procedures.

Fiberoptic bronchoscopy is the gold standard for confirmation of correct placement of a DLT. Checking DLT placement is suggested when changes to the patient's position have been made, or changes have been made between normal ventilation and isolated lung ventilation.

In order to monitor breathing sounds more immediately and directly than fiberoptic bronchoscopy, Airmod, “Artificial Intelligence Respiratory Monitor Device” was created, which has the following features:

1. Digitize auscultation information.
2. Respiratory sound playback and ambient noise cancelling.
3. Visualized spectrogram for an uninterrupted understanding of medical condition
4. An AI algorithm to detect apnea and upper airway obstruction.
5. Breath-to-breath respiratory rate estimation.
6. Abnormal event alarm.
7. Clinical drive application UI

In Taiwan, many hospitals and ORs have experienced the AI respiratory monitor. The AI was trained by the most extensive auscultation breathing sound. The Airmod provides us with a new landscape on respiratory monitoring. We are expecting more and more clinical collaboration and finding from the Airmod.

Application of artificial intelligent in PCA database

人工智慧在 PCA 資料庫

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Anesthesiologists have been paying attention to the care of acute pain after surgery for a long time. Safe and effective pain management can not only relieve pain, improve the overall quality of medical care, but also speed up the recovery process of surgical patients and increase their satisfaction. Among them, the Patient-Controlled Analgesia (PCA) has proven to be a safe and effective postoperative analgesia, and it has been widely used as a pain management for many years.

Although analysis of PCA has many difficulties, the reasons are mostly due to the multiple factors inducing pain perception and the individual's differences, which makes the great variation of the patient's analgesia dosage and the PCA initial settings are mostly derived from the West. How to use the big data database to derive our formula for PCA and for better analgesic dose fitting is very important.

This lecture used the long-term PCA collected database from Taipei Veterans General Hospital, applied statistical modelling and artificial intelligent technique to improve the pain management of PCA for our acute pain service in the future.

Implementation of machine learning-based applications in the preoperative risk assessment for hip repair and open laparotomy surgeries

由機器學習所建立之術前風險評估軟體：運用於髖關節修復和開腹手術之心得分享

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Due to the advancement of computer science, machine learning algorithms could be a helpful tool in the pre-operative risk assessment of patients for surgery. Using database of Chi Mei Medical Center, we developed 2 machine learning-based Applications for assisting anesthesiologists in assessing patients' preoperative risks for hip and open laparotomy surgeries, respectively. Data of adult patients who underwent hip or intraabdominal surgery at Chi-Mei Medical Center from January 1, 2013 to August 31, 2020 were analyzed. Patients' features, including age, gender, body mass index, comorbidities, and major preoperative laboratory data from the database were included in the algorithms. The primary outcome was a composite of adverse events (in-hospital mortality, acute myocardial infarction, stroke, respiratory, hepatic and renal failure, and sepsis). Secondary outcomes were intensive care unit (ICU) admission and prolonged length of stay (PLOS). The data obtained were imported into 7 machine learning algorithms to predict the risk of adverse outcomes. Seventy percent of the data were randomly selected for training, leaving 30% for testing. The performances of the models were evaluated by the area under the receiver operating characteristic curve (AUROC). The optimal algorithm with the highest AUROC was used to build a web-based application, then integrated into the hospital information system (HIS) for clinical use. Our results demonstrated that the artificial intelligence assist applications developed using a machine learning algorithm were helpful for anesthesiologists in evaluating the risks associated with hip or abdominal surgery more efficiently and accurately than the traditional ASA-PS stratification method. Moreover, this web-based application gained a high satisfaction score from anesthesiologists, which implies an urgent need for automated artificial intelligence assistance in preoperative risk assessment.

Data science in emergency and critical care

急重症醫學數據科學發展

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Smart medical treatment is the future trend to solve the increasingly complex critical and critical illnesses. As the elderly and multi-comorbid severe patients are prone to worsening factors such as sepsis, delirium, acute kidney injury and acute respiratory distress syndrome, it is urgent to establish artificial intelligence (AI) for decision-making system to assist the emergency and intensive medical team in timely diagnosis and treatment. The foundation for the development of smart medical care is to have complete and correct clinical data for statistical analysis or machine learning. Therefore, the Taiwan Society of Emergency and Critical Care Medicine, the Taiwan Society of Critical Care Medicine and, the Australian New Zealand Intensive Care Medicine Society (ANZICS) Adult Intensive Care Unit Database build communication and cooperation. The AZNICS database was founded in 1992, and more than 160 intensive care units in Australia and New Zealand have joined the database. At the same time, with rigorous data, many papers have been published in the New England Journal of Medicine (NEJM) and the Journal of the American Medical Association. (JAMA), and this database also provides medical information for the Australian and New Zealand governments to formulate critical care policies to improve and enhance the quality of critical care. In recent years, 13 countries including Japan, India and Taiwan have also joined this database alliance, and makes it a total of 15 countries.

Currently, more than 12 hospitals in Taiwan have joined the Taiwan Intensive Care Unit Database Alliance. In addition, the MIMIC database and data science development of the teaching hospitals of the Harvard University and Massachusetts Institute of Technology are also partner of Taiwan with further collaboration in data science. Looking forward to combining critical care teams, data experts and statistical experts to find out key information such as monitoring, diagnosis, treatment and prognosis prediction from the collaborative data of multinational databases, training AI models, and inferencing this AI model into the clinical electronic medical information system. Hope it can assist the diagnosis and treatment in emergency and critical case to improve the quality of medical care and the prognosis of patients.

Predict postoperative risk with deep learning and natural language processing

以深度學習合併自然語言處理進行術後風險預測

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The prevalence of postoperative mortality is 0.5% to 2.8 % in patients receiving elective surgery. The risks are attributable to the patient's condition and can be modulated with adequate evaluation and planning before surgery and anesthesia. Several tools were developed to predict postoperative mortality, including the American College of Surgeons NSQIP risk calculator, the ASA physical status, risk quantification index, risk stratification index, and preoperative score to predict postoperative mortality.

Machine learning achieves better predictions of postoperative mortality than previous prediction tools. To stratify surgery types, previous studies have used the Current Procedural Terminology (CPT) codes or International Classification of Diseases (ICD) codes for surgical information. These methods are not widely applicable because CPT is not implemented worldwide, and ICD codes are seldom recorded before surgery.

Free text descriptions of the preoperative diagnosis and the planned procedure are available preoperatively. Unlike structured data, unstructured clinical text requires meaningful concept embeddings to be extracted before model training. Although reading the text helps anesthesiologists evaluate the risk of the surgery, it is difficult to include it in a classification tool. These deficiencies make it challenging to identify the small groups of patients with higher risks. Better tools for predicting postoperative mortality remain under investigation.

Natural language processing (NLP) is a technology for a computer to understand free text content. New tools were introduced recently because deep learning progressed rapidly, such as Word2Vec, Global Vectors, Embeddings from Language Models, and Bidirectional Encoder Representations from Transformers (BERT). BERT is a contextualized embeddings method that preserves the distance of meanings with multi-head attention. After being pretrained on the relevant corpora and proper architecture modification, BERT extracted meaningful embeddings from clinical text.

We combined the deep neural network model with BERT to extract information from clinical texts. This fusion deep learning model contains structured and unstructured features to predict postoperative mortality. This model had better performance than previously proposed models using no text. The NLP technique helps identify patients with higher risk from the text of surgical descriptions in electronic medical records.

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乳癌腫瘤異質性的精準醫療：正確選擇治療

Right Choice of Therapeutics: Precision Medicine for Breast Cancer Heterogeneity

時　間：111年7月16日　13:30~17:30

Time：July 16, 2022　13:30~17:30

地　點：臺北榮民總醫院 三門診9樓CiC創意谷

Place：The Clinical Innovation Center,
Taipei Veterans General Hospital

乳癌腫瘤異質性的精準醫療：正確選擇治療

Right Choice of Therapeutics: Precision Medicine for Breast Cancer Heterogeneity

Balancing efficacy and toxicity of PI3K inhibitors for HR(+)/HER2(-) metastatic breast cancer

均衡 PI3K 抑制劑在 HR(+)/HER2(-) 轉移性乳癌的療效與副作用

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林口長庚醫院 乳房外科

In recent years, several clinical studies have aimed to identify novel molecular targets, therapeutic strategies, and predictive biomarkers to improve the outcome of women with HR+/HER2- mBC. Overall, ~40% of hormone receptor HR+/HER2- mBC cases harbor alterations affecting the pathway. This pathway is a major target in oncogenesis, as it regulates growth, proliferation, cell survival, and angiogenesis. Lately, the pharmacologic targeting of PIK3CA in HR+/HER2- mBC has shown significant benefits after the occurrence of endocrine therapy resistance.

Alpelisib plus endocrine therapy shows promising efficacy for treating postmenopausal women with HR+/HER2- metastatic breast cancer. Available evidence supporting using alpelisib after disease progression on first-line endocrine therapy with or without CDK4/6 inhibitors justifies *PIK3CA* mutation testing upon diagnosing HR+/HER2- advanced breast cancer, which can be done using either tumor tissue or circulating tumor DNA.

With appropriate toxicity management and patient selection using validated testing methods, all eligible patients can potentially benefit from this new treatment. Further clinical trials to assess combinations of hormone therapy with PI3K, AKT, mTOR, or CDK 4/6 inhibitors, or studies in men and women with other breast subtypes are ongoing.

Daily practice changing for HER2 positive breast cancer care in this rolling pandemic phase

疫情時代下 HER2 + 乳癌病患治療之演進

Ta-Chung Chao

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The COVID-19 pandemic has underlined the need to use novel approaches that help to minimise pressure on our healthcare system.

Dual blockade target therapy of trastuzumab and pertuzumab combined with chemotherapy, has become the standard treatment of metastatic HER2+ breast cancer and node-positive early stage HER2+ breast cancer. Subcutaneous administration of trastuzumab and pertuzumab offers patients a faster and more convenient treatment option. The five-minute jab significantly cuts the Covid-19 infection risk for cancer patients by reducing the amount of time spent in hospital and frees up time for clinicians in chemotherapy units.

PHESGO is the subcutaneous injection form of both fixed dose trastuzumab and pertuzumab combining with hyaluronidase, an enzyme facilitating optimal local absorption. Randomized studies have demonstrated that PHESGO is associated with similar efficacy and better tolerability. This new injection, which can substantially cut treatment time for people with breast cancer, is the latest in a series of changes which have meant the hospital has been able to deliver vital cancer treatment while keeping patients safe from Covid-19.

Tailored treatment for HER2 positive EBC from trial-based and real-world perspective

以實證醫學及臨床經驗觀點打造 HER2 陽性早期乳癌的個人化精準醫療

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Modern treatment for HER2 positive EBC towards tailored treatment with diversity of modalities. Neoadjuvant systemic therapy (NST) is conducted in arising populations with HER2-positive early breast cancer as a platform to allocate patients in different risks. Whether the heterogeneity of HER2 overexpression determines response to treatment is challenged. Previous studies had demonstrated that the HER2 immunohistochemical (IHC) scores and HER2 copy numbers can provide information for prognosis and tumor response for HER2 positive breast cancer. In the coming era, precision medicine for breast cancer may not be satisfied with only tumor burden or staging, instead, genomic profiling or bioinformatics may provide precise information to meet the need. It is also crucial to elucidate the potential biomarkers to define who can truly benefit from NST or developing payloads. We here construct a practical protocol based on previous evidence from clinical trials and retrospectively review the real-world experience to propose the personalized strategy for early HER2 positive breast cancers.

How to change HER2+MBC patient's destiny with novel treatment?

如何藉由新一代的治療方式幫助 HER2 受體陽型晚期乳癌病患改變命運？

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Approximately 15 to 20% of metastatic breast cancers are characterized by overexpression or amplification of human epidermal growth factor receptor 2 (HER2). HER2 positivity was historically associated with high rates of recurrence and poor survival, but the availability of trastuzumab and other HER2-targeted therapies has substantially improved outcomes. The development of anti-HER2 agents has been one of the most meaningful advancements in the management of metastatic breast cancer, significantly improving survival outcomes. The recommended first-line therapy for HER2-positive metastatic breast cancer consists of the anti-HER2 monoclonal antibodies trastuzumab and pertuzumab given with a taxane, followed by second-line trastuzumab emtansine for patients who have disease progression. After progression during treatment with trastuzumab emtansine, no single regimen is considered the standard of care.

The maximal antitumoral activity of anti-HER2 agents is achieved in combination with chemotherapy, and this effect may be related to the heterogeneity of HER2 expression among other mechanisms of primary resistance. Based on the synergistic effects of HER2-inhibition and chemotherapy, a new class of drug have been developed. Antibody-drug conjugates (ADCs) are a class of therapeutics that combines an antigen-specific antibody backbone with a potent cytotoxic payload, resulting in an improved therapeutic index. HER2-targeted ADCs bind to HER2 on the cancer cell surface and are internalized by the cell, after which the cytotoxic drug component is released intracellularly and exerts its antitumor effect. ADCs may also be designed to stimulate the release of drug from the target cell into the extracellular space, which kills surrounding and bystander cells that may or may not express the target antigen. Therefore, novel ADCs have created a new era of targeted therapy for HER2-positive metastatic breast cancer.

New horizon of BRCA-mutated breast cancer: How BRCA status impacts treatment journey?

BRCA 基因突變乳癌新疆界：BRCA 基因突變如何影響臨床治療？

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Breast cancer is the most common type of cancer in women worldwide. In Taiwan, it's also the most frequent cause of cancer in women. Approximately 10% of breast cancer occur in women who have a first-degree relative with a history of breast cancer. A substantial proportion of hereditary breast cancer can be attributed to mutations in DNA damage repaired (DDR) genes, such as *BRCA1, BRCA2, TP53, PTEN, ATM, CHEK2*. Mutations in *BRCA1/2* constitute the largest proportion of these.

Since the first cloning of *BRCA1/2* in 1990's, testing for germline *BRCA1/2* mutations nowadays has an established predictive role in breast cancer risk assessment. In *BRCA1/2* carriers, the life time risk of breast cancer is up to 70% compared to around 12% in non-carriers. Thus a tighter surveillance scheme and risk-reducing surgeries are counseled for *BRCA1/2* carriers. Recent studies have also identified *BRCA1/2* status as clinically relevant in the selection of therapy for patients diagnosed with breast cancer. Emerging evidence suggested that BRCA status predicts responsiveness to platinum-based chemotherapy, as well as to poly (ADP-ribose) polymerase (PARP) inhibitors, given its ability to interrupt DNA repair pathways. As for PARP inhibitors (PARPi), phase II/III studies of single-agent PARPi have demonstrated encouraging progression-free survival results in patients with *gBRCA1/2*-mutated breast cancer.

In the era of precision medicine, determining *BRCA1/2* mutation status in breast cancer could potentially expand treatment options beyond current standard of care. From recent evidence and ongoing clinical studies, the role of *gBRCA* and PARPi is highlighted in both advanced and early stage breast cancer. Furthermore, more potential biomarkers are explored for future clinical application, including DDR genes beyond *BRCA1/2* and the concept of BRCAness. More research is warranted to solve the puzzle of breast cancer with DNA repair deficiency.

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人工智慧在內視鏡影像診斷臨床應用之新進展

Artificial Intelligence in Clinical Application of Endoscopic Diagnosis-Novel Advances

時 間：111年7月17日 08:00~12:00

Time：July 17, 2022 08:00~12:00

地 點：臺北榮民總醫院 致德樓第一會議室

Place：The First Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

人工智慧在內視鏡影像診斷臨床應用之新進展

Artificial Intelligence in Clinical Application of Endoscopic Diagnosis-Novel Advances

Application of artificial intelligence to gastroesophageal reflux disease

人工智慧運用於胃食道逆流疾病

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In the last decade, substantial progress has been made in artificial intelligence (AI) and its application in medicine including gastroenterology. Currently, most AI-based studies in clinical gastroenterology focus on images, endoscopy and early neoplasms. Some investigators have applied AI in the recognition of physiological signals such as esophageal manometry in the diagnosis of esophageal motility disorder. Application of AI in the diagnosis of gastroesophageal reflux disease is a relatively new explorative field. Early studies found that the performance of AI on questionnaires-based diagnosis of gastroesophageal reflux disease is good.

Since 2018 in Lyon consensus, 24-hour ambulatory multichannel intraluminal impedance-pH technique has been considered as gold standard in detecting gastroesophageal reflux episodes. However, interpretation of the data is not only time-consuming but also susceptible to interobserver inconsistence despite the utility of automated software. In addition, interpretation of pharyngeal reflux episodes remains challenging largely due to insufficient interobserver reproducibility.

We recently proposed diagnostic criteria of pharyngeal acid reflux episodes using hypopharyngeal multichannel intra-luminal impedance-pH technique and found a good interobserver reproducibility. We further developed a supervised deep learning-based AI, cascade MLSTM-FCN model, to detect pharyngeal acid reflux episodes. Our preliminary data showed that cascade MLSTM-FCN model is sufficiently accurate to diagnose PAR episodes in hypopharyngeal multichannel intra-luminal impedance-pH signals.

Artificial intelligence in high resolution esophageal manometry

人工智慧運用於高解析度食道動力學檢查

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High-resolution Esophageal Manometry (HRM) is considered as the gold standard in the diagnosis of esophageal motility disorders. Its interpretation and classification is mainly developed based on expert-derived algorithms, such as the well-established Chicago Classification (CC). While the CC algorithm provides a framework for uniform esophageal motility interpretation, manual and subjective input are required for feature extraction and final diagnosis relies on a pre-defined decision tree. Hence, the interpretation of HRM is subject to inter-rater variability and, consequently, rater associated inaccuracy, which also poses a challenge in medical training. Reliance on a pre-defined decision tree also leads to model biases and mis-classification. With the advance of big data, sophisticated modeling techniques and modern computing power, artificial intelligence (AI) could potentially alleviate some of the issues associated with the clinical interpretation of HRM, evidenced by its success in other spheres of medicine. In this talk, we will briefly discuss our recent efforts on AI research on HRM, at Northwestern GI center, with focus on high-level illustrations of model development and potential applications. First, a simple background on AI or machine learning will be introduced, with the emphasis on how it relates to HRM interpretation. Then, regarding on the model building, we will illustrate how collaboration between clinical experts and data modeling experts was essential during the whole cycle: from curation of well-labeled dataset, model design that mimics the information flow of CC algorithm, to model evaluations. Finally, potential clinical applications will be discussed, including certain challenges as well as limitation of current AI models. If the time is allowed, we will also briefly discuss certain new research efforts beyond HRM, such as multi-modal AI models integrating multiple data source (e.g. HRM data and questionnaire data) and biomechanics-augmented AI models that aim to derive underlying mechano-physiology.

Artificial intelligence in inflammatory bowel disease

人工智慧運用於發炎性腸道疾病

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Following advances in artificial intelligence (AI), this novel technology is being applied for the diagnosis and evaluation of disease severity in patients with inflammatory bowel disease (IBD), particularly in those with ulcerative colitis (UC). The Mayo Endoscopic Subscore (MES) is commonly used to evaluate the disease severity of UC in clinical practice and in clinical trials. Mucosal healing is a therapeutic goal in patients with UC. Endoscopic remission is associated with lower rates of colectomy, relapse, hospitalization, and colorectal cancer. However, differentiation of UC-induced mucosal inflammation depends on the clinicians' experience and subjective judgment.

Recent studies show that AI, including machine and deep learning may be useful to automatically assess still colonoscopic images and full endoscopic videos and determine the severity of UC. The results of these studies prove that AI-guided MES estimation is an accurate and promising strategy. Maeda et al. developed a computer-aided diagnostic system using AI to predict histopathological inflammation on endocytoscopic evaluation. Reportedly, video capsule endoscopy using deep learning algorithms is useful for automated detection of ulcers in Crohn's disease. We designed a computer-aided diagnostic system based on deep and machine learning (DLML-CAD), which we use at our hospital to accurately diagnose mucosal healing in patients with UC. The diagnostic accuracy was 94.5% for endoscopic mucosal healing (MES 0–1 vs. MES 2–3) and 89.0% for complete mucosal healing (MES 0 vs. MES 1) based on our DLML-CAD model. Furthermore, this model was useful to assess the multiclass classification of the MES (0–3), and the diagnostic accuracy of the MES was 76.4%.

In my presentation, I will highlight the current advances and limitations of AI in cases of IBD and its possible applications in clinical practice, together with a discussion of our limited experience in this field.

Artificial intelligence in clinical application of colonoscopy: VGHTPE experience sharing

人工智慧運用於大腸鏡：臺北榮總經驗分享

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Computer aided diagnosis based artificial intelligence algorithm had been proved to accurately detect colon polyp and differentiate adenomatous polyps between hyperplastic polyp. With artificial intelligence assistance, the colon polyp detection rate during colonoscopy increase, and adenoma detection increase without increasing examination time. Computer assisted colonoscopy is expected to be standard clinical practice in near future. Artificial intelligence may be applied for other functions, including autodetection of different abnormalities and even combined with auto reporting. Also, artificial intelligence may be used to further help colon preparation evaluation to improve colon cleanliness in clinical practice. We used colonoscopy pictures obtained during colonoscopy in Taipei Veterans General Hospital to train a artificial intelligence algorithm in detecting multi-type of lesions during colonoscopy. Also a colon cleanliness evaluation algorithm was also developed to help evaluate the real colon cleanliness quality during colonoscopy. These models may help during endoscopy training and clinical practice in the future. Computer assisted colonoscopy is expected to be standard clinical practice in near future in helping improving colonsocopy quality and even patients long term outcome.

Artificial intelligence in clinical application of colonoscopy : Cathay General Hospital experience sharing

人工智慧運用於大腸鏡：國泰醫院經驗分享

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洪志聖

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Computer assisted artificial intelligence (AI) has been widely developed in medical image diagnosis in recent years. AI can help doctors to identify image abnormalities easily from deep neural network learning experiences. This new computed technology changes the traditional medical science and help physicians to early find abnormalities with the help of artificial intelligence.

Cathay General hospital and Aether Techology company set up a computer training model to use Deep Convolutional Neural Network learning to help gastroenterologist to mark and identify colon polyps and differentiate the mucosa pattern of polyps during colonoscopic examination.

We collected more than one hundred thousand colon polyp images in Cathay General Hospital-Taipei from January 1st -2016 to April 30th -2020. All these images were sent to AI training model (Yolov 4, CSPDarknet53, set up by Hong-Yuan Mark Liao and Chien-Yao Wang). Normal colonic mucosa、small fecal particles、air bubbles、colon cancer and colon polyps were marked by endoscopists previously and we trained computer how to differentiate polyps from other abnormalities (fecal materials, air bubbles, colon malignancy etc) and normal colonic mucosa. We also trained the computer (named as Aether AI Endo) how to identify adenomatous polyps and hyperplastic polyps after deep neurological learning.

The colon polyps detecting rate in real time colonoscopic examination and adenomatous polyp detection rate by Aether AI Endo will be presented in this forum.

Artificial intelligence in colonoscopy- Current status and future development

人工智慧運用於大腸鏡 - 現今狀況與未來發展

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Adoption of artificial intelligence (AI) in clinical medicine is revolutionizing daily practice. In the field of colonoscopy, major endoscopy manufacturers have already launched their own AI products on the market with regulatory approval in Europe, Asia and the US. This commercialization is strongly supported by positive evidence that has been recently established through rigorously designed prospective trials and randomized controlled trials. According to some of the trials, AI tools possibly increase the adenoma detection rate by roughly 50% with its polyp detection function (so-called CADe) and contribute to a 7%–20% reduction of colonoscopy-related costs with its polyp characterization function (so-called CADx). Given that reliable evidence is emerging, together with active commercialization, this seems to be a good time for us to review and discuss the current status of AI in colonoscopy from a clinical perspective. Today's presentation will focus on the advantages and possible drawbacks of AI tools and explore their future potential including the possibility of obtaining reimbursement and implementation of cancer screening programs. I hope we can share and discuss this interesting topic in an interactive way.

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病毒性肝炎根除新展望

Toward Elimination of Viral Hepatitis in Taiwan

時 間：111年7月17日 08:00~12:00

Time：July 17, 2022 08:00~12:00

地 點：臺北榮民總醫院 致德樓第二會議室

Place：The Second Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

病毒性肝炎根除新展望

Toward Elimination of Viral Hepatitis in Taiwan

Strategies to prevent HBV reactivation in special population

特殊族群之 B 型肝炎復發預防策略

I-Cheng Lee

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HBV reactivation with its potential consequences of significant morbidity and mortality is an important concern when patients are exposed to either chemotherapy, immunosuppressive or biologic therapies for the management of cancer, rheumatologic conditions, bone marrow or solid-organ transplantation. The population at risk for HBV reactivation includes those who either currently are HBsAg-positive or have had past exposure to HBV (HBsAg-negative, anti-HBc-positive). It is important to screen HBV status prior to the start of immunosuppressive therapy. The risk of HBV reactivation should be evaluated based on the HBV serological status of the patient and the potency of immunosuppression. Based on the type of immunosuppressive therapy stratified by the HBsAg-positive or HBsAg-negative but anti-HBc positive status, the risk of HBV reactivation can be classified as high (>10%), moderate (1–10%) or low (<1%). The risk of HBV reactivation after novel immunosuppressive agents still needs continuous evaluation. Recent studies showed that some novel biological agents, particularly abatacept, and combination immunosuppressive therapies with glucocorticoids may have high risk of HBV reactivation. HBV infected patients with hepatocellular carcinoma (HCC) are also at high or intermediate risk of HBV reactivation depending on the type of HCC therapy. Because HBV reactivation is largely preventable, several guidelines have been proposed for HBV screening at baseline and antiviral prophylaxis during immunosuppressive therapy. Antiviral prophylaxis with high potency nucleos(t)ide analogues to prevent reactivation of HBV infection should be considered based on the risk stratification.

Application of artificial intelligence to predict hepatocellular carcinoma in patients with chronic viral hepatitis

應用人工智慧預測病毒性肝炎之肝癌風險

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Hepatocellular carcinoma (HCC) is one of the most important causes of morbidity and mortality worldwide. While most clinical risk prediction methods were developed using traditional regression analysis techniques, deep learning models proposed in recent years outperform traditional methods in general. Deep learning and artificial intelligence (AI) models directly learn predicting parameters from all available parameters from data while minimise bias. We will first adopt explainable uncertainty-aware convolutional recurrent neural network for irregular medical time series to predict HCC in patients with chronic viral hepatitis. In view of different disease stages of patients, they receive monitoring at variable intervals so that large volume of irregular medical time-series data is produced in real-life settings. HCC prediction from such irregular medical time series is challenging because the intervals between consecutive records significantly vary along time. To address this issue, we have recently developed a novel Uncertainty-Aware Convolutional Recurrent Neural Network (UA-CRNN) by introducing the uncertainty information in the generated data, which is superior to the stage-of-the-art methods for HCC prediction. To deal with the complex medical data with sub-series of different frequencies, the uncertainty information is further incorporated into the sub-series level rather than the whole sequence to seamlessly adjust different time intervals. Specifically, a hierarchical uncertainty-aware decomposition layer is designed to adaptively decompose time series into different subseries and assign them proper weights according to their reliabilities. Meanwhile, frequency-aware filters are incorporated into different channels of the decomposition layer to ensure that each decomposed subseries contain similar frequencies and properties, while different subseries contain components of different frequencies. Furthermore, an adaptable attention module is introduced to identify key factors from different input variables by incorporating with the uncertainty information, which provides the explainable clinical risk prediction results and improves the prediction performance. We will further investigate how to design a novel structure and incorporate it into the UA-CRNN. In this way, we can directly model the irregular medical data and apply for AI HCC prediction.

Hepatitis B virus cure: Targets and future therapies

治癒 B 型肝炎之標的與未來治療策略

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Hepatitis B virus (HBV) infection is a leading cause of chronic liver disease worldwide. Nucleos(t)ide analogues (NAs) strongly suppresses HBV replication and slows the rate of progression to cirrhosis and hepatocellular carcinoma. However, HBV is often reactivated after stopping NAs because NAs alone do not directly target covalently closed circular DNA (cccDNA), which is the template for all viral RNAs. Therefore, although suppression of HBV replication is achieved in the majority of patients with currently NAs, hepatitis B surface antigen (HBsAg) loss is rarely achieved in Asians despite long-term antiviral therapy.

The treatment goal for HBV infection is functional cure, defined as sustained loss of HBsAg based on assays with a lower limit of detection of 0.05 IU/mL. Complete cure is defined as elimination of cccDNA with sustained HBsAg loss and undetectable serum HBV DNA. HBV treatments include agents that directly target the virus life cycle and others that indirectly modulate host factors and the host immune response.

Various clinical trials have been conducted on agents that terminate the HBV life cycle in hepatocytes, including inhibitors of HBV-DNA polymerase, virus entry, core assembly, and secretion of HBsAg. Especially, selected novel therapies are currently in clinical development, including HBV core inhibitors, siRNA/capsid assembly modulator, nucleic acid polymers, capsid assembly modulator, GalNAc-conjugated single-trigger RNA interference agent and vaccine. Potentially curative HBV treatment strategies and novel agents are emerging. Combinations of current and new anti-HBV agents will likely increase the rate of HBsAg seroclearance. The final effective regime may include an immunotherapeutic agent to eliminate the cccDNA.

How to predict the risk of hepatocellular carcinoma in patients with chronic hepatitis B: The role of novel biomarkers

慢性 B 型肝炎之肝癌風險預測：新穎生物標記之角色

Tung-Hung Su

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Chronic hepatitis B (CHB) is a global health problem, which is a major cause of hepatocellular carcinoma (HCC), and results in nearly 1 million deaths annually. The risk of HCC in patients of CHB has been reduced significantly after prolonged antiviral therapy; however, HCC still develops even in patients with persistent viral suppression. HCC surveillance had been recommended by major guidelines for patients with CHB, and risk stratification for HCC is important to determine the strategy of surveillance and timing of antiviral therapy.

CHB infection is orchestrated by virus and host immunity with resultant a spectrum of liver diseases ranging from hepatitis to cirrhosis. The measurement of viral replication, severity of liver fibrosis and novel tumor markers had been used as biomarkers for HCC prediction. Quantitative HBsAg or HBcrAg reflect the transcriptionally active cccDNA of HBV in hepatocytes. For patients with low or intermediate viral load, quantitative HBsAg and HBcrAg levels predicts the risk of HCC.

Liver cirrhosis is a major risk factor for development of HCC. Mac-2-binding protein glycosylation isomer (M2BPGi) is a novel biomarker to reflect the severity of liver fibrosis. Growing evidences demonstrate pre-treatment or on-treatment high M2BPGi levels predict the risk of HCC, even in cirrhotic patients with antiviral therapy induced viral suppression. Prothrombin Induced by Vitamin K Absence or Antagonist-II (PIVKA-II) had been used as a diagnostic marker for HCC. Recent studies showed PIVKA-II level alone or in combination of alpha fetoprotein may predict the development of HCC in patients with CHB.

These novel biomarkers enable the physicians to stratify the risk of HCC in patients with CHB, and help to optimize the surveillance of HCC.

Influence of nonalcoholic fatty liver disease on the risk of cirrhosis and hepatocellular carcinoma

脂肪肝與肝硬化、肝癌風險之影響

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With a global prevalence of 25% in the adult population and substantial associated health-care expenses, the public health burden of nonalcoholic fatty liver disease (NAFLD) is considerable. The spectrum of NAFLD ranges from steatosis to a more progressive nonalcoholic steatohepatitis (NASH) that can lead to fibrosis and cirrhosis. NAFLD has also become the second leading indicator of the need for liver transplantation and the third leading cause of hepatocellular carcinoma (HCC). Because liver conditions attributable to chronic hepatitis viral infection have been substantially reduced by hepatitis B vaccination programs and effective direct antiviral agents for hepatitis C, NAFLD is likely to become a key health concern in the future. Although the incidence of NAFLD-related HCC is considerably lower than that of other HCC-related etiologies, such as chronic hepatitis B and C virus infection, the prevalence of NAFLD is higher than that of chronic viral hepatitis. However, only approximately 4% of patients with NAFLD had advanced fibrosis, suggesting that the prevalence of severe liver disease was low despite the high NAFLD prevalence. Risk stratification for the targeting of patients with NAFLD for HCC surveillance would allow clinicians to more effectively plan secondary prevention strategies for advanced liver disease. Because of notable differences in lifestyles and body composition between Asian and non-Asian populations, the findings should be cautiously interpreted to apply on non-Asian populations. In the talk, we reviewed the risk of cirrhosis and HCC by comparing individuals with or without NAFLD to understand the impacts of NAFLD. The potential factors to stratify risks of advanced liver diseases among NAFLD will also be presented, providing insights to monitor individuals with NAFLD and to guide for behavior modifications.

Risk of hepatocellular carcinoma and extrahepatic malignancy after HCV cure

C 型肝炎治癒後之肝癌與肝外癌症風險

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Successful antiviral therapy greatly reduces 30-40 % risk of hepatocellular carcinoma (HCC) in chronic hepatitis C (CHC) patients with a sustained virological response (SVR). However, HCC remains to occurs in a subset of patients and the risk may persist for decades after viral eradication. The mechanisms include but are not limited to fibrogenesis, insulin signaling oncogenesis, genetic polymorphism and epigenetic modification. Plenty of risk factors and surrogate biomarkers have been identified for HCV related HCC after viral eradication. Briefly, the predictors could be categorized as fibrosis-based, model-based and machine-learning-based predators. Regional guidelines have different recommendations for HCC surveillance in the post-SVR era. AASLD adopts the loosest standard whereas APASL suggests the most stringent strategy. On the other hand, due to the immunological and lymphotropic nature of hepatitis C virus, CHC patients may present with many extrahepatic manifestations including noon-HCC malignancy. Direct insertion mutagenesis and chronic antigen stimulation of B cell closely link HCV infection to lymphomagenesis. HCV eradication not only decreases the risk of lymphoma but also improves the hematological outcomes in terms of cancer treatment response and progression-free survival. The benefits of anti-HCV therapy in reducing other cancer risks such as gastric cancer and oral cancer have been addressed in large cohort studies. Nevertheless, the pathophysiological mechanisms and potential confounders warrant to be clarified.

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影像導引腫瘤消融最新發展

The State of the Art in Imaging-Guided Tumor Ablation

時 間：111年7月17日 08:00~12:00

Time：July 17, 2022 08:00~12:00

地 點：臺北榮民總醫院 致德樓第三會議室

Place：The Third Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

影像導引腫瘤消融最新發展

The State of the Art in Imaging-Guided Tumor Ablation

Cryoablation for oligometastasis: Current evidence

個數有限之轉移性腫瘤的冷凍消融：目前的證據

Shu-Huei Shen

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臺北榮民總醫院 放射線部

Cryoablation is a minimal invasive surgical technique. The cryoprobe could cause a low temperature range surrounding its needle tip. There are several advantages of cryoablation, including 1. Less invasiveness: percutaneous cryoablation could be performed in out-patient base or only one night hospital stay, which is much shorter as compared to surgery. 2. Less pain, as compared to other heat thermal therapy (radiofrequency ablation, RFA and microwave). 3. Less damage to collagenous tissue and less damage to collecting system and vascular wall as compared to other thermal technique. 4. Under imaging guidance, especially MR and CT, the ablation zone could be monitored and controlled, and unnecessary injury to adjacent normal structure could be thus avoided.

Oligometastasis is a state of limited metastasis that is potentially amenable to ablative local therapy. Patients with limited number of detectable metastatic tumor was in a transitional state between localized and widespread systemic disease. Local control of oligometastasis may yield systemic control. Cryoablation has been proved to be an effective and safe treatment for many locations of oligometasis, including but not limited to hepatic, pulmonary, musculoskeletal, retroperitoneal nodal metastasis, pelvic side wall disease. It is a less invasive treatment as compared to surgical lymphadenopathy, and the procedure is repeatable. Cryoablation could also be applied on those patients with radiation failure since cryoablation and radiotherapy have different mechanism.

In this presentation, we will review the current reference of percutaneous imaging-guided cryoablation for oligometastatic tumors. Ablation technique, complication, treatment effect and the multidisciplinary collaboration will be addressed.

Application of cryoablation on musculoskeletal system

冷凍治療在骨骼肌肉系統的應用：最新發展

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Percutaneous computer tomography (CT)-guided ablation has been performed to treat bone and soft tissue tumors, with advantages of mini -invasiveness, high success rate, short recovery time, and low morbidity.

Bone is quite different from liver, kidney, and lung, with harder structure, lower temperature conductivity. Ablation tract necessitates the guidance of bone biopsy needle. Bone tumor ablation management can be curative or palliative applying to osteoid osteoma and bone metastases. This management is very helpful in patients with failed conventional therapies and thus can improve patient's life quality.

Cyroablation is among one of the best ablation modalities. The strengths of cyroablation include real time monitoring, visualization of ablation zone, and less post procedure pain. Nevertheless, cyroablation requires relatively high cost and longer procedure time.

To protect neurovascular bundle and adjacent vital organs during ablation procedure is very critical in avoiding complications. Hydrodissection, pneumodissection, thermosensor , and nerve evoked potential monitoring technique is helpful to minimize the risk of vital organ injury. Weigh bearing lesions can be supplemented by cement augmentation or vertebroplasty.

In summary, successful ablation is a multidisciplinary team work. CT guided local tumor ablation surgery is valuable in tumor treatment, especially in patients with failed conventional therapies.

Current status of hepatic ablation

肝臟腫瘤消融現況

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Surgical resection has long been considered the gold standard for the local treatment of primary and secondary liver tumors. Until recent years, the scenario has changed, and thermal ablation was accepted as a first-line option for the treatment of liver tumors and was reserved for patients who were unsuitable for surgery, as the patients with small (< 2 cm) hepatocellular carcinoma (HCC), who are not potential liver transplant candidates, and in patients with up to three 3 cm or smaller nodules with associated diseases. Ablation can also be considered in patients with larger tumors (3–5 cm) and advanced liver disease. Similarly, the European Society for Medical Oncology (ESMO) also includes thermal ablation as part of the treatment algorithm for oligometastatic colorectal disease. Most authors agree that ablation is considered for small (< 3 cm) colorectal liver metastasis (CRLM) in patients who are unsuitable for resection.

Radiofrequency ablation (RFA) has been shown to be both safe and effective for treating liver nodules. Microwave ablation (MWA) uses the most advanced devices to obtain shorter ablation times, higher ablation temperatures, larger ablation zones, and a weakened heat-sink effect than RFA and can reduce the risk of Local Tumor Progression (LTP). Meanwhile, cryoablation has emerged as an alternative option for local control of liver tumors and irreversible electroporation (IRE); due to this non-thermal mechanism of action, it can be applied to the tumors which are inoperable or are located near the vital structures where another thermal ablation modality is not possible.

Recently, advancements in immunotherapy have been proven effective in treating solid tumors, including liver tumors. The above thermal ablation techniques have the particularity to induce immunomodulation by destroying tumors, although this may not be sufficient to raise an effective antitumor immune response. Research on the interest that ablative therapies combined with immunotherapies could act synergistically to enhance antitumor immunity is under investigation. This talk will cover the current techniques and applications of percutaneous thermal ablation for liver tumors.

Current application of Irreversible Electroporation (IRE) on tumor ablation

奈米刀在腫瘤消融的發展與現況

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黃凱文

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Irreversible electroporation (IRE) is a predominantly non-thermal ablative technology that uses high-voltage DC current pulses to induce cell death through permanent damage of cell membrane. IRE has established a clinical niche as an alternative to thermal ablation for the eradication of unresectable tumors, particularly those near critical structures, and for that thermal ablative technologies such as radiofrequency ablation, microwave ablation, and cryoablation have limitations. Unlike thermal ablation modalities, IRE does not require significant consideration for dissipation of thermal energy, or heat sink, and has less complications relating to damage of normal soft tissue, eliminating a major cause of treatment failure. Additionally, IRE treatment time is significantly shorter than traditional thermal ablation modalities, in low minute ranges, and may allow for treatment of considerably larger lesions than thermal ablation modalities

IRE has shown clinical success when used as a standalone treatment and as a single component within combinatorial treatment paradigms, and proven to be safe and effective when performed on tumors in the brain, liver, kidneys, pancreas, and prostate that are located near critical blood vessels and nerves. Here, the speech will present the basics of the technology, patient selection, clinical applications, practical pointers, and the future developments.

Imaging-guided targeted biopsy and focal therapy in prostate cancer

攝護腺癌的影像導引目標切片與局部治療

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Systematic biopsy of the prostate using transrectal ultrasound (TRUS) is the conventional method for diagnosis for prostate cancer prior to treatment. This standard practice has changed in recent years following advancement of magnetic resonance imaging (MRI). Multiparametric MRI with T2-weighted images, diffusion-weighted images, and dynamic contrast-enhanced images, can effectively detect and localize prostate cancer. Hence, targeted biopsy of the lesion detected by MRI has become a clinical demand to acquire a pathological diagnosis and guide further management. However, targeting of the lesion depicted by MRI is not always possible by using TRUS guidance, since the lesions detected by MRI are not always visible by ultrasound. To overcome this limitation, imaging fusion technology has emerged and become increasingly utilized for targeted biopsy of the prostate gland.

Targeted biopsy with imaging fusion has superior specificity and sensitivity for the diagnosis of prostate cancer when compared with systematic biopsy. Targeted biopsy has a relatively higher detection rate for clinically significant prostate cancer, and a lower detection rate for clinically insignificant prostate cancer, suggesting that targeted biopsy can find more prostate cancers that need to be treated.

Targeted prostate biopsy has also triggered the conceptual changes of cancer treatment. For example, for those with solitary tumor focus or local recurrence, imaging-guided focal therapy can become a treatment of choice. In summary, novel imaging modalities not only lead to refinement of diagnosis of prostate cancer, but also provide more options for its treatment. These changes are currently under way.

The application of CAScination navigation system on CT-guided ablation of hepatic tumors

可視靈導航系統在電腦斷層導引肝臟腫瘤消融的應用

Lukas Luerken

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In recent years, percutaneous tumor ablations have gained more and more importance for the treatment of primary and secondary hepatic malignancies. In the internationally accepted Barcelona Clinic Liver Cancer classification (BCLC) for the classification and treatment of hepatocellular carcinoma (HCC) as well as in newest international and national guidelines, hyperthermic percutaneous ablations as radiofrequency ablation (RFA) and microwave ablation (MWA) are considered equivalent to surgical resection and are even suggested as first-line treatment for patients with very early (BCLC 0) and early (BCLC A) HCC with impaired liver function. In the treatment of oligometastatic colorectal carcinoma (CRC) with hepatic metastases, percutaneous hepatic ablations are suggested as alternative treatment, if a surgical resection of the hepatic metastases is not possible. Technical advances in the already existing and established ablation techniques as well as newer ablation methods like multiantenna MWA, irreversible electroporation (IRE) and electrochemotherapy (ECT) enable interventional radiologists to treat increasingly large tumors at complex and hard to reach locations. To achieve successful ablation of such large and complex tumors, various navigation devices have been developed to support interventionalists in planning and performing ablations as well as to verify ablation-success. Aim of this lecture is to introduce the CAScination CasOne IR stereotactic system, to explain how it works and to show, by means of case studies, the possibilities offered by the use of such a stereotactic navigation system in the ablation of liver tumors. In addition, this lecture aims to provide an overview of the functionality and possibilities of the latest ablation methods.

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人工植牙元宇宙

Metaverse of Dental Implant

時　間：111年7月17日　08:30~12:00

Time：July 17, 2022　08:30~12:00

地　點：臺北榮民總醫院 致德樓第四會議室

Place：The Fourth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

人工植牙元宇宙
Metaverse of Dental Implant

Metaverse and Dentomniverse

元宇宙及牙科全宇宙

Wen-Liang Lo

羅文良

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臺北榮民總醫院 口腔醫學部

The metaverse is an extension of the internet that allows users to interact with each other and the environment around them. This is achieved using various types of technologies including virtual reality (VR) and augmented reality (AR). These scenarios may seem far from our daily teaching activity or segregated to research labs only. While virtual education spaces such as Zoom, Teams and Google Meet are the new norm, the creation of digital laboratories is also a reality: real online players are challenged to solve difficult scientific problems.

The use of artificial intelligence (AI) is now a reality in dentistry. A significant advancement is the use of haptic gloves that would let dental students feel virtual objects while practicing suturing or giving a nerve block – this can significantly improve the students' technique over time and give them, for example, immediate feedback with respect to needle point insertion. While initial costs for such systems might seem high now, the hardware is proven to be cost-effective in the long term.

Currently, some medical schools have been trying out VR goggle setups or using anatomical models controlled via tablet; however, both have significant limitations compared to working directly within VR using haptic technology. Presence (the student's sense of being there) has always been considered necessary for successful learning and for appropriate patient care. In light of the last two years of forced social distancing, should we perhaps upgrade the 'old' telemedicine to a more immersive experience?

Dentistry too will evolve in the near future, taking a cue from medical health practices in their exploration of the metaverse. Soon, we might have dental telehealth conversations in a virtual metaverse with our avatars indulging in dental health consultation with patients. Imagine doing a root canal with x-ray or 3D images of canal morphology in your live view, placing an implant, seeing the exact position of implant and bone at the time of surgery, or removing a tumor growth with a live feed of anatomical tumor extension in your vision. A brand new "Dentomniverse" era is approaching!

All on four rational and success rate

從傳統到數位的歷程：數位化 All on 4 植牙規劃設計與治療

Liang-Ji Huang

黃良吉

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The term All-on-Four was first introduced by Portuguese dentist, Dr. Paulo Malo, in 1988. Patients can receive immediate function with graftless procedure of their teeth to get full mouth rehabilitation. Until now, the success rate of All-on-Four can be compatible with traditional implant treatments.

We can finish All-on-Four surgery both by freehand and by traditional surgical guide. Without reference points or accurate surgical guide, the above methods cannot help to put the fixtures precisely. Furthermore, the traditional methods may cause iatrogenic complications. Also, that may cause the prosthesis fabrication time-consuming.

Nowadays, All-on-Four surgery can be done fast and precisely by the use of the digital equipment. We can place the fixtures with CAD/CAM surgical guides and the dynamic guide equipment. Before surgery, prosthodontics can help complete the temporary denture. After surgery, patients can bring their provisional denture with them. The innovation can make All-on-Four surgery precisely, fast, safe, and most of all, can reduce the chair time.

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遠距醫療和災難醫學的新發展

New Developments in Telemedicine and Disaster Medicine

時 間：111年7月17日 08:30~12:00

Time: July 17, 2022 08:30~12:00

地 點：臺北榮民總醫院 致德樓第十會議室

Place：The Tenth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

遠距醫療和災難醫學的新發展

New Developments in Telemedicine and Disaster Medicine

Real time emergent consultation without time difference : Telemedicine program in Veterans General Hospital & Veterans Home

即時緊急會診沒有時差：榮家榮總遠距醫療計畫

Hsien-Hao Huang, David Hung-Tsang Yen

黃獻皞 顏鴻章

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臺北榮民總醫院 急診部

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak was first discovered in December 2019, and then rapidly spread to the world in early 2020, evolving into a global pandemic. At present, Taiwan is facing the rapidly changing development of coronavirus pandemic, and the following situations will occur. When the coronavirus pandemic intensifies and Taiwan enters a period of severe community infection, it will put on lockdown, including city and traffic, which will make many Veterans home susceptible to medical problems including chronic diseases and emergent disease (acute myocardial infarction, cerebral infarction, major trauma).

Telemedicine is rapidly being adopted by some of the largest health care providers in the United States. The proper application of telemedicine technology will improve access to health care and provide high-quality care at reduced costs. The use of telemedicine in emergency rooms will speed up counselling services such as stroke, trauma and mental health screenings and increase the accessibility and availability of expertise in remote areas.

At this moment, Taiwan's effective prevention in coronavirus pandemic has been known in the worldwide. Now is the best time to implant "Veterans Medical System Telemedicine". Via video software and health information organization will optimize the chronic and emergent medical demand for the elderly in Veterans home.

To sum up, this plan is to jointly optimize the long-distance video connection between the Veterans General Hospital and Veterans Home by telemedicine. Chronic diseases, geriatric syndromes (frailty and sarcopenia, etc.) and emergent severe diseases (such as myocardial infarction, cerebral infarction, etc.) will be established in sequence. Using advanced technology to improve the quality of medical care for the elderly in the Veterans Home is a major goal of Veterans General Hospital.

Medical group of USAR (Urban Search and Rescue) Teams: Experience sharing of national accreditation process of heavy rescue team

特搜隊裡的醫療組：重型救援隊國家認證經驗分享

Yu-Long Chen

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新北市政府消防局 特搜大隊

Urban Search and Rescue Teams was established for the first-line emergency rescue and management in response to disaster events. In response to future trends of disaster and learning from world experience, cities in Taiwan had established USAR teams. The initial training and planning of USAR teams focused on search and rescue, and was mainly responsible for locating the patient at the disaster site, extrication and initial stabilization. The United Nations established the International Search and Rescue Advisory Group (INSARAG) in 1999, an intergovernmental humanitarian aid agency under the UN framework, composed of disaster managers, government officials, non-governmental organizations (NGOs) and USAR team members to effectively deliver humanitarian assistance services to save lives through established international coordination networks in the event of natural or man-made disasters. As a programmatic document for international search and rescue operations, the INSARAG Guidelines were officially adopted and released in December 2002 in Resolution 57/150 of the United Nations General Assembly. The guide comprehensively discusses the framework of the international search and rescue response system, guides the capacity building of international search and rescue teams to promote the effective development of rescue operations, and is also the reference basis for the evaluation of search and rescue teams in various countries.

The National Fire Agency, Ministry of the Interior also started last year, referring to the INSAREG Guideline to release the National Accreditation Process for search and rescue teams, hoping to integrate the capabilities of these teams in various cities, to be able to dispatch appropriately competent teams to participate in a timely manner.

The USAR Team, Fire Department, New Taipei City Government took advantage of this evaluation process to strengthen the search and rescue functions that had been emphasized in the past, and also combined with the medical staff of the hospitals within the jurisdiction to establish and construct the function of a medical team. According to the recommendations of the guidelines, not only to meet the relevant minimum requirements, but also to reorganize and train three times the number of medical staff in order to make the team go smoothly in the future, including on-site medical treatment, medical treatment in confined spaces, and medical care training for K9. In order to strengthen the on-site functions of the medical team, relevant attendance procedures and a list of medicines have also been formulated. It is hoped that through the sharing of experience in New Taipei City, it can drive the development of the national special search medical ancestors, and have the opportunity to pass international certification in the future, so as to contribute to the international disaster relief affairs together.

Medical group of USAR (Urban Search and Rescue) teams: The collaboration between Taipei City urban search and rescue team and Taipei Veteran General Hospital

特搜隊裡的醫療組：北榮與北市搜救隊的合作經驗

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In recent years, Urban Search and Rescue Teams (USAR teams) established the crucial position in disaster management. Learning from the previous experiences, USAR teams in Taiwan gradually improved the abilities and formed a more comprehensive framework. Taipei City Urban Search and Rescue Team, founded in 2000, is one of the best USAR team among Taiwan. During 22 years, the team has carried out numerous abroad and domestic rescue missions. Taipei USAR teams also grew through those experiences. Not only focusing on search and rescue, USAR team also had six divisions including command, search, rescue, medical, engineer and logistics divisions now.

In order to strategically organize resources of medical sector, Taipei Veteran General Hospital (VGHTPE) ER department had collaborated with Taipei City USAR team in recent 3 years. The interdisciplinary training course also developed and conducted in these three years. Through those courses and realistic on-site trainings and exercises, a tight cooperation between VGHTPE ER and Taipei City USAR team had been established. And VGHTPE ER doctors and nurses are included into the medical sector of Taipei City USAR team. Following International Search and Rescue Advisory Group (INSARAG) Guideline, Taiwan held the National Accreditation Process for USAR teams in Taiwan since 2021. Taipei City USAR team is the first team to pass the Heavy Rescue Team accreditation.

The mission of medical sector in USAR teams included primary health care of all team members, on-going medical screening for the team, hazmat control, medical evacuation coordination. This year, we aimed to strengthen the ability to deal with acute stress disorder, from prevention, on-site surveillance to acute stress management. This speech, we will share the experience of Taipei City USAR team and the collaboration between VGHTPE ER and Taipei City USAR team.

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精準醫療與全人照顧於骨科之應用

Precision Medicine and Holistic Health Care in Orthopedics

時　間：111年7月17日　08:30~12:00

Time：July 17, 2022　08:30~12:00

地　點：臺北榮民總醫院 長青樓護理館會議室

Place：Nursing Arts Laboratory, Evergreen Building, Taipei Veterans General Hospital

精準醫療與全人照顧於骨科之應用

Precision Medicine and Holistic Health Care in Orthopedics

TKA for Posttraumatic OA with deformity: From freehand to 3D simulation correction

合併關節外變形之膝關節退化治療：從徒手到 3D 列印輔助全人工膝關節置換

Pai-Han Wang , Cheng-Fong Chen

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3D printing is an emerging technology and its use in orthopedics is being explored. We discuss the role of computed tomography-based 3D printed patient specific jigs in total knee replacement. Extraarticular deformity includes < 20° femoral deformity and < 15° tibial deformity can be corrected with intra-articular bone resection. However, severe deformity should consider simultaneously corrective osteotomy and total knee arthroplasty. Otherwise, the collateral ligament could be violated, or excessive bone resection would happen.

The advantage of computer assisted simulation includes 1. 3D model easy to access and surgical planning, 2. Multiple try and real time verification until surgeons satisfied, 3. Individualized surgical plan, 4. PSI cutting jig may reduce x ray exposure 5. Reduced surgical time. The disadvantage of computer assisted simulation includes 1. The excess time and expense cost, 2. The inconvenient of software acceptability, 3. The learning curve of the surgeon and engineer, 4. Soft tissue balance is hard to be accessed during simulation 5. The jig is difficult to apply during minimal invasive surgery.

The 3D printed simulation correction in total knee arthroplasty provide the precise and preoperative planning for the patient with difficult post-traumatic osteoarthritis. The predictive outcome through simulation can reduce the surgical time and possibility of outlier alignment production.

Innovation in biological reconstruction of bone tumors

骨腫瘤生物重建的創新

Po-Kuei Wu

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Background: Biological reconstruction of limbs affected by osteosarcoma is frequently assisted by liquid nitrogen cryoablation of resected tumor-bearing bones. The conventional free-freezing method requires the excision of tumor-bearing autograft, have longer time-to-union and low union rate; pedicle-freezing could be utilized to minimize the number of osteotomies in cryoablation. In the present study, we have adopted an appropriately designed freezing tank with increased flexibility in positioning to assist pedicle freezing. We aim to compare the peri-surgical improvements and complications between free-freezing and freezing tank-assisted pedicle freezing.

Question/Purpose: Our research questions for the present study are: (1) Is there a difference in the number of required osteotomies between free-freezing and freezing tank-assisted pedicle-freezing for treating high-grade osteosarcoma in the limbs? (2) Is there a difference in the non-union rate between the group receiving free-freezing and freezing tank-assisted pedicle-freezing after surgery? (3) Is there a difference in the incidence of graft-related complications between patients receiving free-freezing and freezing tank-assisted pedicle-freezing? (4) Is there a difference between the graft-derived recurrence rate of the two techniques?

Methods: A retrospective review of our hospital database was conducted to screen for eligible patients (n=114) who received adjunctive limb salvage treatments for osteosarcoma during June 2017 to January 2019. After excluding patients who received treatments other than cryoablation and autograft biological reconstruction, a total of 41 patients had received free-freezing (n=20) or freezing tank-assisted pedicle freezing (n=21) were deemed eligible. Patient baseline demographics were comparable between the free-freezing and the freezing tank-assisted pedicle-freezing groups.

Results: The number of osteotomies received was 1.55 per patient (31 osteotomies in 20 patients) in the free-freezing group, whereas it was 0.43 per patient (9 osteotomies in 21 patients) in the freezing tank-assisted pedicle-freezing group. The total number of graft-derived complications including soft tissue failure and structural failure were comparable between the two groups at 1 year after surgery. Three incidences of atrophic nonunion (9.7% of osteotomies) were observed in the free-freezing group, and none occurred in the freezing tank-assisted pedicle freezing group. Tumor progression and early infection occurred in 5% of patients treated by free freezing, and none was observed in those treated by freezing tank-assisted pedicle-freezing.

Conclusion: Freezing tank-assisted pedicle-freezing and free-freezing demonstrated comparable oncological outcome, but pedicle-freezing was associated with, shorter time-to-union, lower non-union rate, an improved trend of osteotomy healing and functional recovery.

Application of 3D printing, computer simulation, and precision medicine in bone tumor surgery

3D 列印、電腦模擬、精準醫療在骨腫瘤手術中的應用

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Surgical excision of complicated bone tumor is very challenging. Among different kinds of medical images, CT and MRI are most commonly applied in accessing bone tumor. CT images are very useful in demonstrating surface and counter of the target bone, while MRI is superior in accurate assessment of tumor border. Therefore, we have developed advanced tumor image management by fusion of CT and MRI and simulate tumor excision before surgery for patients with complicated bone sarcoma. Herein, we would like to report our clinical experiences in advanced image management for malignant bone tumor preoperatively. The fine-cut CT and MRI was obtained before the surgery and fusion of MRI and CT image was carried out with Surglass Orthofuse image processing software. We then simulated tumor resection surgery on computer and the PSI tumor cutting jig was designed accordingly. The fused tumor images allowed us to simulate tumor excision before surgery in a more straight-forward way. With PSI tumor cutting jig, we could excise bone tumor more easily without unnecessary soft tissue damage. Our experiences have shown that the safe margin of PSI assisted tumor resection surgery could be comparable to the conventional methods and no tumor contamination was found on normal bone area. The fused image combined both advantages of CT and MRI and allowed surgeons to make surgical planning and simulation more efficiently. The fused image and PSI-aided tumor excision might be a practical way to excise complicated bone tumor in a more precise and less-invasive manners and preserve more function for the patient.

3D printed ulnar shortening osteotomy cutting guide: From idea to reality

3D 列印尺骨縮短截骨截切瞄準器：化空想為現實

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Background: Ulnar shortening osteotomy has demonstrated good outcomes for patients with ulnar impaction syndrome. To optimize the outcome and minimize non-union, precise osteotomy and firm fixation are warranted. Despite various ulnar shortening systems have been developed, current technology does not meet all needs. Tackling this challenge, our team reported successful results in standardized free-hand USO technique. However, it's still technical demanding and requires sufficient experience and confidence to excel. Therefore, our team designed an ulnar shortening system based on our free-hand technique principle, using metal additive manufacturing technology. The goal of this study is to describe the development process and report the performance of the system.

Methods: Using computer-aided design, through series of iterations, our team produced an ulnar shortening system that requires minimal exposure, assists in precise cutting, and allows easy placement of fixating plate. For performance testing, two surgeons with different level of experience in ulnar shortening procedure was included. One fellow-trained hand and wrist surgeon and one senior resident performed USO using ulna sawbones, by free-hand technique and USO system-assisted technique, three times each. The time-to-complete-osteotomy, total procedure time, chip diameter, shortening length, maximum residual gap and deviation angle were recorded.

Results: For the hand and wrist fellow, with USO system, the time-to-complete osteotomy was significantly reduced. (468.7±63.6 to 260.0±5 seconds, $p<0.05$). Despite the preop goal was shortening 3 mm, the average shortening length was significantly larger in the free-hand group (5±0.1 vs 3.2±0.2 mm, $p<0.05$). Both maximum residual gap and deviation angle reported no statistical difference between the two techniques. For the senior resident, the maximum residual gap was significantly reduced, using the USO system (2.9±0.8; 0.4±0.4 mm, $p=0.02$). Between two surgeons, significant larger maximum residual gap and deviation angle were observed on the senior resident doctor, in the free-hand technique group, not in the USO system group.

Conclusion: The USO system developed may be a useful tool, assisting in reliable precise cutting and fixation for patients receiving ulnar shortening osteotomy using small dynamic plate, even for less experienced surgeons.

Recent trends in geriatric acetabular and pelvis fracture

老年髖臼骨盆骨折的最新進展

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With the progress of Taiwan's aging society, more and more advances in medical development. Many elderly people still maintain a certain degree of activity and physical function. However, with the progress of the aging society, many osteoporosis-related fractures will inevitably occur. Among them, pelvic and acetabular fractures in the elderly are one of osteoporotic related fractures. In the past these fractures were not taken seriously, One of the reasons is that in the past, older people were less active and less advanced in medical technology. However, with the advancement of technology and surgical skills, we are more and more able to stabilize patients' fractures in less invasive measures. In nearly five decades of orthopedic development, we have learned the importance of early stabilization of fractures for patients and the benefits of allowing patients to move early. Therefore, the main purpose of this study is to report on the new development of pelvic and acetabular fractures in the elderly. Report the benefits of early fixation in these patients. We will share our experience and report on how to reduce the risk of many patients who were considered too high risk for surgery in the past.

Artificial intelligence-assisted diagnosis of anterior cruciate ligament tears from magnetic resonance images: Algorithm development and validation study

人工智慧輔助判讀磁振造影檢查診斷膝前十字韌帶斷裂

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Background: Anterior cruciate ligament (ACL) injuries are common and critical knee injuries that require prompt diagnosis. Magnetic resonance imaging (MRI) is a strong, noninvasive tool for detecting ACL, which requires training to read accurately. Clinicians with different experiences in reading MRIs require different information for the diagnosis of ACL tears. Artificial intelligence (AI) image processing could be a promising approach in the diagnosis of ACL tears. This study sought to use artificial intelligence to (1) diagnose ACL tears from complete MRI images, (2) identify torn ACL images from complete MRI images with a diagnosis of ACL tears, and (3) differentiate intact ACL and torn ACL MRI images from selected MRI images.

Methods: Sagittal MRI images of torn ACL and intact ACL from 800 cases and complete knee MRI images of 200 cases (100 torn ACL and 100 intact ACL cases) between 20 and 40 years of age were retrospectively collected. An AI approach using a convolutional neural network was applied to build models for the objective. MRI images of 200 independent cases (100 torn ACL and 100 intact ACL) were used as the test set for the models. MRI images of 40 randomly selected cases from the test set were used to compare the reading accuracy of ACL tears between the trained model and clinicians with different levels of experience.

Results: The model differentiated between torn ACL, intact ACL, and other images from complete MRI images, with an accuracy of 0.9946. The accuracy for ACL tear diagnosis was 0.96. The model showed a significantly higher reading accuracy than less experienced clinicians. The second model identified torn ACL images from complete MRI images with a diagnosis of ACL tear with an accuracy of 0.9943. The third model differentiated torn and intact ACL images with an accuracy of 0.9691.

Conclusion: This study demonstrated the feasibility of using an AI approach to provide information to clinicians who need different information from MRI to diagnose ACL tears.

CT Hounsfield units: An alternative tool for diagnosing opportunistic osteoporosis and predicting spinal surgery outcome

CT 亨氏單位：診斷伺機性骨質疏鬆症和預測脊椎手術預後的替代工具

Yu-Cheng Yao, Po-Hsin Chou, Shi-Tien Wang, Ming-Chau Chang, Chien-Lin Liu

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Assessing bone quality before spine surgery is an essential step of preoperative planning. Dual energy X-ray absorptiometry (DXA) is the most widely used modality in bone mineral density (BMD) screening. However, for patients receiving DXA of the lumbar spine, severe degenerative conditions, deformed curvature, atherosclerotic great vessels, or prior fusions can lead to overestimation of BMD and an underdiagnosis of osteoporosis. DXA is not recommended as a routine preoperative exam for every patient receiving spinal surgeries. An alternative screening tool for assessing osteoporosis gained interest recently using Hounsfield unit (HU) measurements obtained from computed tomography (CT) scans and may help in detecting undiagnosed osteoporosis in patients receiving spinal surgery. The HU method was described as a reliable and accurate technique for assessing osteoporosis and regional BMD as well. HUs used to evaluate regional BMD were reported to correlate with surgical outcomes, such as screw loosening, cage subsidence, adjacent fracture, and proximal junctional kyphosis after adult spinal deformity surgeries. Using a high specificity threshold of 110HU for detecting osteoporosis and 135HU for detecting osteopenia (90% specific), patients should be directed toward treatment of low bone density or undergo further testing with DXA. Patients with HU values under 120 are at risk for screw loosening, subsidence, and pseudarthrosis of interbody fusion. Spine surgeons were recommended to measure HU values for all patients with an available CT scan.

Application of artificial intelligence in spine fields

人工智慧在脊椎領域之運用

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Recent advances in artificial intelligence (AI) and deep learning (DL) have shown great performance in identifying non-medical images, and the technology is thought to be the next technological revolution in the clinical application. Based on the current published papers, three main categories of clinical application by AI and DL in the spine fields are (1) automatic measurement (2) diagnosis in medical images (3) prognosis outcome prediction. Some of these published papers also provide Uniform Resource Location (URL) for open access algorithm in clinical applications. Regarding our current AI model for vertebral fracture detection in the plain lateral radiographs of spine, the framework of AI deep learning model included object detection, data pre-processing of PLRs, and classification to detect VFs. The accuracy, sensitivity and specificity for the performance of AI model were 91.88%, 90.94% and 92.83%, respectively. However, false positive and false negative rates were inevitably occurred. The factors of lung markings at thoracolumbar junction, X-ray technique, bean-can effect, normal variance of bi-concave appearance in the osteoporotic vertebral body and osteoporosis plays important roles in bias the performance of AI model. We also investigated that our AI model had higher accurate rate if the vertebral fracture was located at lumbar spine and patient's DXA T score ≦ -2.5. Fortunately, our novel innovation of the AI model with ensemble method got patent in Taiwan and get the 18th National Innovation Award in the Academic Research Category. The evidence suggests that AI models can be successfully used for spinal disease to manage its diagnosis, prognosis and outcome prediction. Further AI or DL algorithm retraining, generalizability of models, data standardization in neural networks, and focus on the application of AI or DL models as a tool in clinical spine practice, will augment decision-making efficacy.

New developments in orthopedics to optimize children's bone health

優化兒童骨骼健康的骨科新進展

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With Taiwan's economic development and population aging, the birth rate has declined gradually. Currently, Taiwan's average fertility rate is 1.1 births per woman, compared to 0.9 for men. Therefore, how to provide high-level and precise medical care in each child is an important issue in pediatric orthopedics. At the medical aspect, more refined treatment, more convenient methods, fewer complications, and faster recovery are the directions we pursue. In this section, we will introduce new developments in pediatric orthopedics area, how to use technology to simplify the patient journey, how to recover faster, and how to manage risks. More important than treatment is the part about prevention and how to definition Guidelines. In this section, we will discuss how we defined the systematic screening protocol for developmental hip dysplasia and the result of this guidelines in Taipei Veterans general hospital. Besides, we will take about how to improve bone healthy in the era of COVID-19 and our guidelines in common pediatric orthopedics disorders. Besides physical treatment, we will discuss the part about anxiety management in pediatric orthopedics and how to improve the quality of care. Finally, we will discussed the application of Machine Learning in pediatric orthopedics area and our preliminary results in TVGH.

「醫學研究論文獎」及
「盧致德院長獎」論文摘要

「盧致德院長獎」
(從刊登於中華醫學會雜誌上的全部論文中，選出被引用
20 次以上的作者，並以其中最多次者頒發盧致德院長獎)

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Concordance analysis of intrapartum cardiotocography between physicians and artificial intelligence-based technique using modified one-dimensional fully convolutional networks

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Abstract

Background. Cardiotocography is a common method of electronic fetal monitoring (EFM) for fetal well-being. Data-driven analyses have shown potential for automated EFM assessment. For this preliminary study, we used a novel artificial intelligence method based on fully convolutional networks (FCNs), with deep learning for EFM evaluation and correct recognition, and its possible role in evaluation of nonreassuring fetal status.

Methods. We retrospectively collected 3239 EFM labor records from 292 deliveries and neonatal Apgar scores between December 2018 and July 2019 at a single medical center. We analyzed these data using an FCN model and compared the results with clinical practice.

Results. The FCN model recognized EFM traces like physicians, with an average Cohen's kappa coefficient of agreement of 0.525 and average area under the receiver operating characteristic curve of 0.892 for six fetal heart rate (FHR) categories. The FCN model showed higher sensitivity for predicting fetal compromise (0.528 vs 0.132) but a higher false-positive rate (0.632 vs 0.012) compared with clinical practice.

Conclusion. FCN is a modern technique that may be useful for EFM trace recognition based on its multiconvolutional layered analysis. Our model showed a competitive ability to identify FHR patterns and the potential for evaluation of nonreassuring fetal status.

Keywords. Artificial intelligence; Cardiotocography; Fetal distress

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Genetic variations of three important antioxidative enzymes SOD2, CAT, and GPX1 in nonalcoholic steatohepatitis

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Abstract

Background. Nonalcoholic steatohepatitis (NASH) is closely related to reactive oxygen species (ROS). Superoxide anion radicals, the main product of ROS, can be reduced by manganese superoxide dismutase (SOD2) to hydrogen peroxide, which is further reduced by catalase (CAT) and glutathione peroxidase (GPX) to water. We aimed to investigate the association between the most important genetic variants of *SOD2, CAT*, and *GPX1* and susceptibility to NASH.

Methods. A total of 126 adults with liver tissue-verified NASH, 56 patients with liver tissue-verified nonalcoholic fatty liver (NAFL), and 153 healthy controls were enrolled. Their DNA profiles were retrieved for genotype assessment of *SOD2* 47T > C (rs4880), *CAT* -262C>T (rs1001179), and *GPX1* 593C > T (rs1050450) variation.

Results. There were statistical differences between the *SOD2* and *CAT* genotypes across the NASH, NAFL, and control groups, but not *GPX1*. The NASH group had a significantly higher frequency of subjects with *SOD2* C allele (38.8%) compared with the NASL group (25.0%) and the controls (22.9%, $p = 0.010$). Similarly, the NASH group had a significantly higher percentage of subjects with *CAT* T allele (23.0%) compared with the NAFL group (10.7%) and the controls (7.2%, $p = 0.001$). For subjects with both the *SOD2* C allele and *CAT* T allele, 88.2% were in the NASH group. After adjusting for confounders, the *CAT* mutant T allele and *SOD2* mutant C allele were still the highest independent risk factors for NASH (odds ratio [OR] 3.10 and 2.36, respectively). In addition, there was a synergistic effect for those two alleles and the occurrence of NASH with an adjusted OR of 8.57 ($p = 0.030$).

Conclusion. The genetic variations of *CAT* and *SOD2* may increase the risk of NASH, which may aid in the screening of patients who are at high risk of NASH, and offer a potential anti-oxidant targeting route for the treatment of NASH.

Keywords. Catalase; Glutathione peroxidase; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Superoxide dismutase

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Hepatoma upregulated protein and Ki-67 expression in resectable hepatocellular carcinoma

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Abstract

Background. Hepatoma upregulated protein (HURP) and Ki-67 have been identified as cancer-related genes involved in cell growth and proliferation. Previous experimental studies have suggested an essential role for HURP expression in liver carcinogenesis. However, data regarding HURP expression in hepatocellular carcinoma (HCC) and its correlation with patient outcomes are limited. In this study, we examined the clinicopathologic features associated with HURP expression in HCC, and compared them to the results of the Ki-67 study.

Methods. Eighty-seven resected HCC at tumor, node, metastasis (TNM) stages I (n = 28), II (n = 29), and III (n = 30) were evaluated. HURP and Ki-67 expression were assessed by immunohistochemistry. Multivariate analysis was used to examine the prognostic significance of HURP and Ki-67 expression.

Results. HURP expression in HCC tissue was observed in 59% of patients and associated with female sex, low white blood cell count, and low platelet count. Ki-67 expression was observed in 67% of patients and associated with younger age, higher serum α-fetoprotein (AFP) levels, and frequent microvascular invasion. Univariate analysis showed that factors related to overall survival were: age >55 years, AFP > 20 ng/mL, indocyanine green retention rate at 15 minutes (ICG-15) > 15%, tumor size > 5 cm, multiple tumors, macrovascular invasion, microvascular invasion, Ki-67 expression, and serum vascular endothelial growth factor > 170 pg/ mL. HURP expression was not associated with postresection survival. Multivariate analysis indicated that macrovascular invasion, multiple tumors, ICG-15 > 15%, and Ki-67 expression were independent factors for overall survival. Multiple tumors and Ki-67 expression were independent factors related to recurrence-free survival.

Conclusion. In our study, HURP expression in HCC tissue was not associated with post-resection survival. Ki-67 expression was an independent prognostic factor for survival. Our results suggest that the effect of HURP activity on growth, invasion, and postresection outcome of HCC in actual patients is less than previously demonstrated in experimental studies.

Keywords. Hepatic resection; Hepatocellular carcinoma; Hepatoma upregulated protein, Ki-67; Prognosis

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Adherence to healthy lifestyle improved clinical outcomes in coronary artery disease patients after coronary intervention

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Abstract

Background. Lifestyle modification is suggested for patients with coronary artery disease (CAD), but the impact of adherence to a healthy lifestyle remains undetermined. The aim of this study is to investigate the association of adherence to a healthy lifestyle with future outcomes and biochemical markers in CAD patients.

Methods. The Biosignature CAD study examined 716 CAD patients who underwent a percutaneous

coronary intervention (PCI). Information was collected on whether these patients adhered to a healthier lifestyle after PCI, including healthy diet, not smoking, and exercise. The clinical outcomes included major cardiovascular events and unplanned revascularization procedures, hospitalization for refractory or unstable angina, and other causes

Results. The average follow-up period was 26.8 ± 8.1 months, during which 175 (24.4%) patients experienced at least one event. The combination of healthy lifestyle factors was associated with lower risk, and the maximum risk reduction reached 50% (hazard ratio: 0.50, 95% confidence interval: 0.25-0.99). As the number of healthy lifestyle factors increased, there were decreases in inflammatory markers, C-reactive protein, waist circumference, low-density lipoprotein cholesterol, and the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol ($p < 0.05$). The benefits of modifiable healthy lifestyle factors were especially observed in the younger population, males, patients with HDL <40 mg/dL, those with reduced left ventricular ejection fraction, and those receiving statin therapy.

Conclusion. Adherence to a healthy lifestyle is independently associated with a lower risk of future adverse events in CAD patients and plays an important role in secondary prevention in the era of interventional cardiology.

Keywords. Coronary artery disease; Lifestyle modification; Secondary prevention

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Role of the kisspeptin/*KISS1* receptor system in the testicular development of mice

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Abstract

Background. Kisspeptin and its receptor KISS1R have been found to be essential regulators of reproductive function. Previous data have revealed the presence of *Kiss1* and *Kiss1r* mRNAs in the hypothalamus and the testis of humans and rodents. However, the precise location and possible physiological role of the kisspeptin/KISS1R system in the testis remain ambiguous.

Methods. We first produced an anti-KISS1R immunoglobulin Y antibody for KISS1R identification. To detect the exact sites of KISS1R and kisspeptin expression in the testis, we conducted immunohistochemistry assays on sections of testes. We used real-time polymerase chain reactions to identify *Kiss1r* in mice and to determine the expression levels of testicular genes. Finally, to verify the upstream regulation on the Kisspeptin/*KISS1* receptor system, we treated primary mouse Leydig cells and MA-10 cells with luteinizing hormone (LH) and Br-cAMP, respectively, and examined *Kiss1* and *Kiss1r* mRNA expression.

Results. Immunohistochemistry assays revealed that kisspeptin was expressed in Leydig cells and *KISS1R* was localized in the seminiferous tubules. With real-time polymerase chain reactions, we found *Kiss1r* mRNA was constitutively expressed in the mouse testis from birth until the postnatal fourth week. Furthermore, mRNA expression of *Kiss1* was synchronized with that of *Insl3* and *Cyp19a.* However, the expression of the LH receptor-encoding gene increased 1 week earlier than did *Kiss1* expression. This indicated that the kisspeptin/*KISS1R* system in the testis may be controlled by LH and cAMP signaling pathways. Finally, we confirmed that *Kiss1* mRNA expression was increased in both LH-treated primary Leydig cells and Br-cAMP-treated MA-10 cells ($p < 0.05$). On the other

hand, cotreatment of both cell lines with Br-cAMP and a protein kinase A inhibitor RP-cAMP significantly suppressed 50% of Br-cAMP-induced *Kiss1* expression ($p < 0.05$).

Conclusion. We discovered that *Kiss1* expression in mouse Leydig cells was induced by LH through the cAMP/PKA pathway. Based on the presence of kisspeptin receptors on spermatids, we inferred that kisspeptin- and development-related factors have synergistic effects on spermatogenesis. Nevertheless, more studies are required to elaborate the role of the kisspeptin/*KISS1R* system in testicular development.

Keywords. Kisspeptin; KISS1R; Luteinizing hormone; Spermatogenesis; Testicular development

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TRIM72 mediates lung epithelial cell death upon hyperoxia exposure

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Abstract

Background. Premature infants often require oxygen (O2) therapy for respiratory distress syndrome; however, excessive use of O2 can cause clinical conditions such as bronchopulmonary dysplasia. Although many treatment methods are currently available, they are not effective in preventing bronchopulmonary dysplasia. Herein, we explored the role of tripartite motif protein 72 (TRIM72), a factor involved in repairing alveolar epithelial wounds, in regulating alveolar cells upon hyperoxia exposure.

Methods. In this *in vivo* study, we used Sprague–Dawley rat pups that were reared in room air or 85% O2 for 2 weeks after birth. The lungs were excised for histological analyses, and TRIM72 expression was assessed on postnatal days 7 and 14. For *in vitro* experiments, RLE-6TN cells (i.e., rat alveolar type II epithelial cells) and A549 cells (i.e., human lung carcinoma epithelial cells) were exposed to 85% O2 for 5 days. The cells were then analyzed for cell viability, and TRIM72 expression was determined.

Results. Exposure to hyperoxia reduced body and lung weight, increased mean linear intercept values, and upregulated TRIM72 expression. *In vitro* study results revealed increased or decreased lung cell viability upon hyperoxia exposure depending on the suppression or overexpression of TRIM72, respectively.

Conclusion. Hyperoxia upregulates TRIM72 expression in neonatal rat lung tissue; moreover, it initiates TRIM72-dependent alveo-lar epithelial cell death, leading to hyperoxia-induced lung injury.

Keywords. Alveolar epithelial cells; Cell survival; Hyperoxia; Lung injury; Newborn respiratory distress syndrome

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Etiology and risk factors of intracranial hemorrhage and ischemic stroke in young adults

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Abstract

Background. Young stroke incidence has increased worldwide with lifestyle changes. Etiology and risk factors for both ischemic and hemorrhagic stroke in young Asians remain underexplored.

Methods. We retrospectively reviewed consecutive acute stroke patients aged 16–45 years admitted to the Taipei Veterans General Hospital between 2009 and 2019 to analyze etiologic subtypes, risk factors, and serial modified Rankin Scale scores for 1 year and compare the age groups of 16–30 and 31–45 years.

Results. Among 670 young Taiwanese patients (mean age at onset 37.5 ± 7.0 years; male 65.1%), there were 366 nontraumatic spontaneous hemorrhagic stroke (including 259 intracerebral hemorrhage [ICH] and 107 subarachnoid hemorrhage, SAH), 292 ischemic stroke and 12 cerebral venous thromboses. Notably, ICH was more prevalent in patients aged 16–30 than in those aged 31–45 (54.8% vs 36.8%). Specifically, structural vasculopathy (e.g., arteriovenous malformation, cavernoma) was the most common etiologic subtype in patients aged 16–30 ($p < 0.001$), whereas hypertensive ICH was the most common subtype in patients aged 31–45 ($p < 0.001$). On the other hand, the top ischemic subtype for both age groups was other determined diseases (e.g., arterial dissection, autoimmune diseases, moyamoya disease, etc.) rather than large artery atherosclerosis. Hyperlipidemia, diabetes, and cigarette smoking were more common risk factors for infarction than ICH. Familial stroke patients whose first- or second-degree relatives had a stroke by age 80 (n = 104, 15.5%) had more infarctions than those without a familial stroke history. In multivariate analyses, initial stroke severity, and infarction type were important predictors of favorable

outcomes after 3 months. At the 1-year follow-up, patients with ICH and SAH had worse functional outcomes and survival rates than those with infarction.

Conclusion. An aggressive approach to elucidate the etiology of stroke is indicated because structural vasculopathy-induced ICH and other determined infarction are distinctively prevalent in young adults, particularly those aged 16–30.

Keywords. Etiology; Outcome; Risk factor; Stroke; Subtype; Young adult

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Combination of pembrolizumab and lenvatinib is a potential treatment option for heavily pretreated recurrent and metastatic head and neck cancer

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Abstract

Background. Immunotherapy has become the current standard of care for recurrent and metastatic head and neck squamous cell carcinoma (R/M HNSCC). One potential approach to improve immunotherapy efficacy is to combine pembrolizumab, an anti-PD-1 agent, with lenvatinib, a potent multikinase inhibitor. In this study, we presented our up-to-date experience with pembrolizumab/lenvatinib combination therapy in heavily pretreated R/M HNSCC.

Methods. Patients who had R/M HNSCC, were ineligible for curative treatment, progressed after at least two lines of systemic treatment and had received pembrolizumab/lenvatinib combination therapy were enrolled in this study. The primary endpoint was the objective response rate. The secondary endpoints included the disease control rate, overall survival, progression-free survival, and the duration of response.

Results. A total of 14 patients were enrolled in this study. All the patients had received at least two lines of systemic treatment and radiation therapy, and 71% of patients had failed previous anti-PD-1 treatment. The objective response rate of pembrolizumab/ lenvatinib combination therapy was 28.6% (95% confidence interval [CI], 5.0%-52.2%). The disease control rate was 42.9% (95% CI, 17.0%-68.8%). The overall survival and progression-free survival were 6.2 months (95% CI, 2.9-9.6) and 4.6 months (95% CI, 0.05-0.9.2), respectively. Of those who had failed previous anti-PD-1 therapy, partial responses were observed in two patients. All the patients with partial responses were in the tumor proportion score <50 and combined positive score 1 to 19 groups.

Conclusion. Our study provided up-to-date evidence that pembrolizumab/lenvatinib combination therapy achieved objective responses in both heavily pretreated and anti-PD-1 refractory R/M HNSCC patients. This study supported the use of pembrolizumab/lenvatinib combination therapy in R/M HNSCC patients without standard of care.

Keywords. Head and neck cancer; Lenvatinib; Pembrolizumab; Programmed cell death 1

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Characterization of Androgen Receptor Complex Associated Protein (ARCAP) in hepatocellular carcinoma and liver

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Abstract

Background. Hepatocellular carcinoma (HCC) ranks many tasks in clinical oncology due to possibly developing a general tumor in men and, usually lead to malignant to death within years. Researches had reported about major factors for being HCC was male sex and HCC associated with cirrhosis in childhood was found more common in males than females. In certain mouse strains as studied, breeding with testosterone significantly increases the development of HCC. Furthermore, castration of male mice diminished the frequency of the development of liver tumors. Meanwhile male hepatitis B virus transgenic mice have a greater occurrence of HCC than females.

Methods. We apply degenerate priming PCR to observe the expression of various steroid receptors in livers. Yeast-two hybrid screening to search a novel RNA fragment helps to find a new full-length gene by RACE experiment. RT-PCR is applied to detect various expressions in tissues and cell lines. In situ hybridization detects DNA in Chromosome mapping. GFP-constructs transfection proves the gene localization in cells. Immunoprecipitation pulldown assay verifies protein interaction. Gene transfection followed with luciferase assay demonstrates the interaction of genes within cellular signaling. Genomic alignment analysis for observing sequences data perform from NCBI database website (http://www.ncbi.nim.nih.gov/genebank/).

Results. The androgen receptor (AR) expression level is found at the highest level among the steroid

receptors families detected in liver tumors. By yeast-two hybrid screening, we cloned an Androgen Receptor Complex Associated Protein (ARCAP), of 95 Kd in molecular weight and its cDNA. ARCAP locates at Chromosome 1. Our findings indicate ARCAP is highly expressed in hepatoma cell lines and liver tumors and their adjacent tumors as observed. Yeast two-hybrid assay and in vitro immunoprecipitation assays demonstrated an interaction between AR and ARCAP.

Conclusion. We aim to search for different types and levels of steroid receptors expressed within human HCCs and in the adjacent liver tissues. To verify possible molecular mechanisms by which AR might affect hepatoma cells, we had characterized a novel protein ARCAP which functions as a coregulator to interact with AR within liver. The ligand-dependent AR with its cofactor, ARCAP, can induce a signal cascade by transactivation.

Keywords. Androgen receptor; Androgen Receptor Complex Associated Protein; Hepatocellular carcinoma; Protein interaction; Transactivation

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Wound healing

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Abstract

Wound healing is an important physiological process to maintain the integrity of skin after trauma, either by accident or by intent procedure. The normal wound healing involves three successive but overlapping phases, including hemostasis/inflammatory phase, proliferative phase, and remodeling phase. Aberration of wound healing, such as excessive wound healing (hypertrophic scar and keloid) or chronic wound (ulcer) impairs the normal physical function. A large number of sophisticated experimental studies have provided insights into wound healing. This article highlights the information after 2010, and the main text includes (i) wound healing; (ii) wound healing in fetus and adult; (iii) pros- taglandins and wound healing; (iv) the pathogenesis of excessive wound healing; (v) the epidemiology of excessive wound healing; (vi) in vitro and in vivo studies for excessive wound healing; (vii) stem cell therapy for excessive wound healing; and (viii) the prevention strategy for excessive wound healing.

Keywords. Pathophysiology; Wound healing

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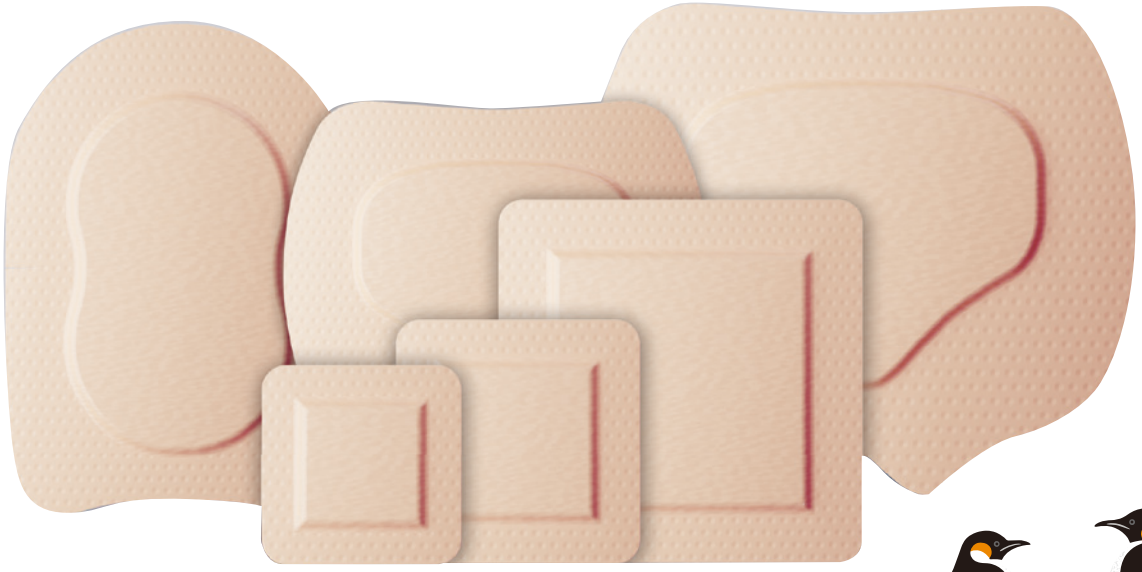

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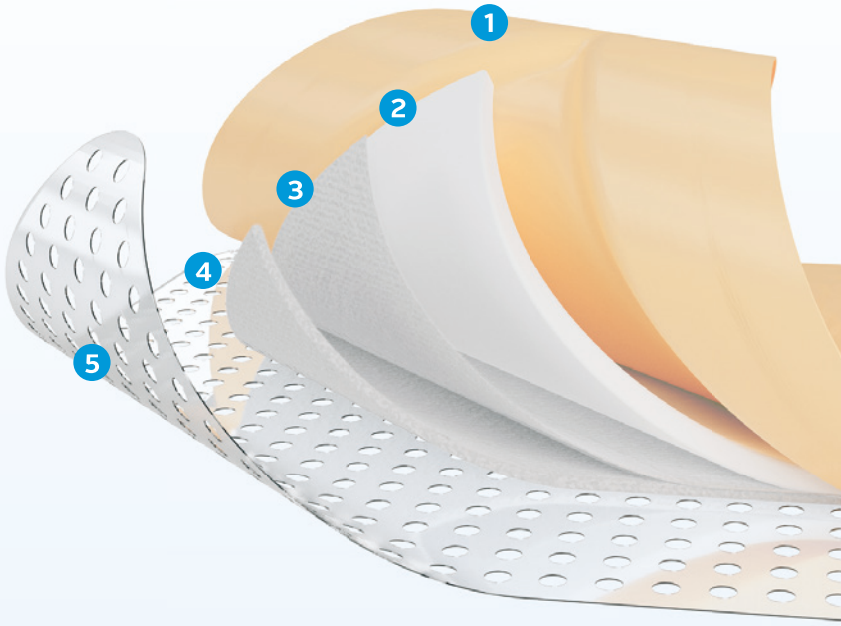

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適應症和用途 1 無法切除或轉移性黑色素瘤．適用於治療成人和小兒(12歲及以上)之無法切除或轉移性黑色素瘤。．併用 nivolumab 適用於治療無法切除或轉移性黑色素瘤病人。**2 晚期腎細胞癌** 併用 nivolumab 適用於治療中度/重度風險(intermediate/poor risk)先前未曾接受治療的晚期腎細胞癌病人。**3 高度微衛星不穩定性(MSI-H)或錯配修復缺陷(DMMR)的轉移性大腸直腸癌** 併用 nivolumab 適用於接受 fluoropyrimidine、oxaliplatin 和 irinotecan 治療後疾病惡化之具有高度微衛星不穩定性(MSI-H)或錯配修復缺陷(dMMR)的轉移性大腸直腸癌(CRC)成人病人。**4 肝細胞癌** 併用 nivolumab 適用於治療先前曾接受 sorafenib 治療的肝細胞癌 (HCC) 病人。**5 轉移性或復發性非小細胞肺癌** 併用 nivolumab 適用於帶有PD-L1(≧1%)且不具 EGFR 或 ALK 腫瘤基因異常的成年轉移性或復發性非小細胞肺 (NSCLC) 病人的第一線治療。併用 nivolumab 及 2 個週期含鉑化學治療適用於不具 EGFR 或 ALK 腫瘤基因異常的成年轉移性或復發性非小細胞肺癌(NSCLC)病人的第一線治療。**用法用量 1 無法切除或轉移性黑色素瘤的建議劑量**．YERVOY 的建議劑量爲 3 毫克/公斤連續靜脈輸注 90 分鐘，每 3 週一次，最多投予 4 次劑量。發生毒性時，可以延後給藥，但是所有治療必須在第一劑後的 16 週內投予。．．YERVOY 併用nivolumab 的建議劑量爲 nivolumab 1 毫克/公斤連續靜脈輸注 30 分鐘，隨後同一天給予 YERVOY 3 毫克/公斤連續靜脈輸注 90 分鐘，每 3 週一次，最多 4 次劑量或出現無法接受之毒性爲止，以較早發生者爲準。完成 4 次劑量的併用治療後，nivolumab 單一療法的建議劑量爲 3 毫克/公斤，連續靜脈輸注 30 分鐘，每 2 週一次，直到疾病惡化或出現無法接受之毒性爲止。Nivolumab 單一療法之首次劑量應於 nivolumab 和 YERVOY 併用治療最後一次劑量給藥後 3 週投予。請詳閱 nivolumab 處方資訊中的完整用藥及時程。**2 腎細胞癌的建議劑量** YERVOY 併用 nivolumab 的建議劑量爲 nivolumab 3 毫克/公斤連續靜脈輸注 30 分鐘，隨後同一天給予 YERVOY 1 毫克/公斤連續靜脈輸注 30 分鐘，每3週一次，共4次劑量。完成 4 次劑量的併用治療後，nivolumab 單一療法的建議劑量爲 3 毫克/公斤，連續靜脈輸注 30 分鐘，每 2 週一次，直到疾病惡化或出現無法接受之毒性爲止。Nivolumab 單一療法之首次劑量應於 nivolumab 和 YERVOY 併用治療最後一次劑量給藥後 3 週投予。請詳閱 nivolumab 處方資訊中的完整用藥及時程。 **3 大腸直腸癌的建議劑量** YERVOY 併用 nivolumab 的建議劑量爲 nivolumab 3 毫克/公斤連續靜脈輸注 30 分鐘，隨後同一天給予 YERVOY 1 毫克/公斤連續靜脈輸注 30 分鐘，每 3 週一次，共 4 次劑量。完成 4 次劑量的併用治療後，每 2 週一次給予 nivolumab 3毫克/公斤靜脈輸注 30 分鐘單一藥物治療，直到疾病惡化或出現無法接受之毒性爲止。請詳閱 nivolumab 處方資訊中的完整用藥及時程。**4 肝細胞癌的建議劑量** YERVOY 併用 nivolumab 的建議劑量爲 nivolumab 1 毫克/公斤連續靜脈輸注 30 分鐘，隨後同一天給予 YERVOY 3 毫克/公斤連續靜脈輸注 30 分鐘，每 3 週一次，共 4 次劑量。完成 4 次劑量的併用治療後，每2週一次給予 nivolumab 240mg 靜脈輸注 30 分鐘單一藥物治療，直到疾病惡化或出現無法接受之毒性或爲止。請詳閱 nivolumab 處方資訊中的完整用藥及時程。**5 轉移性或復發性非小細胞肺癌的建議劑量** YERVOY 併用 nivolumab 的建議劑量爲 nivolumab 3 毫克/公斤連續靜脈輸注 30 分鐘，每 2 週一次，以及 YERVOY 1 毫克/公斤連續靜脈輸注 30 分鐘，每 6 週一次，直到疾病惡化、或出現無法接受之毒Ω，或是最多兩年的無疾病惡化期爲止。請詳閱 nivolumab 的處方資訊。YERVOY 併用 nivolumab 與含鉑化療的建議劑量爲 nivolumab 360 毫克連續靜脈輸注 30 分鐘，每 3 週一次，加上 YERVOY 1 毫克/公斤連續靜脈輸注 30 分鐘，每 6 週一次，加上依病理組織學分類進行的含鉑雙藥化療，每 3 週一次 (化學治療共 2 個療程)，直到疾病惡化、出現無法耐受之毒性，或是最多2年的無疾病惡化期爲止。請詳閱 nivolumab 與併用之化學治療的處方資訊。**建議劑量調整方式** YERVOY 劑量調整的建議請參閱表 1 。當 YERVOY 併用 nivolumab 時，若 YERVOY 暫停使用，nivolumab 也應暫停使用。請詳閱 nivolumab處方資訊的劑量調整之建議。若病人出現輕度或中度輸注反應時，應中斷輸注或減緩輸注速率。若病人出現嚴重或危及生命的輸注反應時，應停止使用。**用藥指示**．YERVOY 不可與其他藥品混合使用或一起輸注。．每次給藥後，使用 0.9% 氯化鈉注射液(USP)或 5% 葡萄糖注射液(USP)沖洗靜脈輸注管線。．透過具有管路內過濾器(無菌、無熱原、低蛋白質吸附率)的靜脈輸注管線，以 90 分鐘的時間投予稀釋溶液。併用 nivolumab 時，需先輸注 nivolumab，接著在同一天輸注 YERVOY 。每次輸注應使用個別的輸注袋和過濾器。**警語與注意事項**．**藥物交互作用** 尚未針對 YERVOY 進行過正式的藥物動力學藥物交互作用研究。**過量** 目前尚無 YERVOY 使用過量的資訊。**作用機轉** CTLA-4 是 T 細胞活性的負向調節因子。Ipilimumab 是單株抗體，可以與 CTLA-4 結合，阻斷 CTLA-4 與配體 CD80/CD86 的交互作用。目前已知阻斷 CTLA-4 可增強 T 細胞的活化及增生，包含腫瘤浸潤 T 作用細胞的活化和增生。抑制 CTLA-4 訊號傳遞也會降低調節性T細胞的功能，促使T 細胞的反應性全面增加，包括抗腫瘤免疫反應。**包裝/儲存與處理** 請將 YERVOY 冷藏於2°C-8°C (36°F-46°F)。請將 YERVOY 保存在原始包裝盒內避光，直到使用時爲止。請勿冷凍或搖晃。**免疫相關不良反應** 告知病人免疫相關不良反應的風險，可能因此需要皮質類固醇治療以及暫停或中斷使用 YERVOY，包括：．腸炎/結腸炎：建議病人發生腹瀉或嚴重腹痛時，應立即與他們的醫療照護提供者聯繫。．肝炎：建議病人發生黃疸、嚴重噁心或嘔吐、腹部右側疼痛、嗜睡或容易淤青或流血時，應立即與他們的醫療照護提供者聯繫，．皮膚不良反應：建議病人發疹時，應立即與他們的醫療照護提供者聯繫。．神經病變：建議病人發生神經病變時，應立即與他們的醫療照護提供者聯繫。．內分泌病變：建議病人出現腦下垂體炎、腎功能不全、甲狀腺功能低下、甲狀腺功能亢進及糖尿病的徵象或症狀時，應立即與他們的醫療照護提供者聯繫。．肺炎：建議病人出現咳嗽、胸痛或呼吸急促或是原有以上症狀惡化時，應立即與他們的醫療照護提供者聯繫。．腎炎和腎功能不全：建議病人出現包括尿量減少、血尿、足踝腫脹、食慾不振等腎炎的徵象或症狀或是腎功能不全的其他症狀時，應立即與他們的醫療照護提供者聯繫。．腦炎：建議病人出現腦炎的徵象或症狀時，應立即與他們的醫療照護提供者聯繫。**輸注反應**．告知病人輸注反應的可能風險。**具有生育能力的女性**．告知女性病人 YERVOY 可能造成胎兒傷害。建議具有生育能力的女性應在 YERVOY 治療期間及最後一次投藥後3個月內使用有效的避孕方法。**哺乳**．建議女性在 YERVOY 治療期間及最後一次投藥後3個月內不要哺乳。 CCDS04Sep2018[B]+CCDS12Dec2018[C]+CCDS12Jul2019[C]+USPI May 2020 USPI

使用前請詳閱說明書、警語及注意事項 詳細處方資訊備索
北市衛藥廣字第 110050103 號
衛部菌疫輸字第 000958 號

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針對NSCLC

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2 mUC 二線新選擇
單用免疫新希望[1, 2]

5 NSCLC 五年有成
免疫治療
降低48%復發風險[1, 4, 5]

1 ES-SCLC 一線選擇
免疫合併化療
治療大突破[1, 3]

抑癌寧注射劑 IMFINZI Injection 50 mg/ml
【適應症】 1.1泌尿道上皮癌治療下列患有局部晚期或轉移性泌尿道上皮癌病人：●接受含鉑化療期間或治療結束後病情惡化。●於使用含鉑化療進行術前輔助治療，或輔助治療12個月內病情惡化。本適應症為根據腫瘤反應率及反應持續時間獲得加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。1.2局部晚期非小細胞肺癌(NSCLC)治療患有局部晚期、無法手術切除的非小細胞肺癌，且接受放射治療合併含鉑化療後病情未惡化的病人。1.3小細胞肺癌併用etoposide以及carboplatin或cisplatin兩者之一，適用於擴散期小細胞肺癌 (ES-SCLC) 病人的第一線治療。【 用法用量】●2.1建議劑量IMFINZI靜脈輸注給藥時間為 60分鐘。IMFINZI單一藥物治療及IMFINZI併用化療，建議劑量如下：泌尿道上皮癌及局部晚期非小細胞肺癌(NSCLC)，建議劑量10 mg/kg，每 2 週一次，直到疾病惡化或發生無法耐受的毒性為止；擴散期小細胞肺癌(ES-SCLC)，每3 週一次(21天)1500 mg1 併用化療2，共4個週期之後每4週一次1500 mg 單一藥物治療，直到疾病惡化或發生無法耐受的毒性為止。1. 病人體重若為 30 kg 以下，必須依體重調整適當劑量，相當於 IMFINZI每3週一次(21天)20 mg/kg 併用化療，共4個週期，之後接受每4週一次20 mg/kg 單一藥物治療，直到體重增加至30kg 以上為止。2.同一天內必須先施用IMFINZI，再進行化療。IMFINZI 與化療合併施用時，用藥劑量請參閱 etoposide和carboplatin或cisplatin的處方資訊。【 禁忌】無。【 警語及注意事項】免疫介導性肺炎，IMFINZI可能引起免疫介導性肺炎，免疫介導性肝炎，IMFINZI可能引起免疫介導性肝炎，其定義為需要使用皮質類固醇者。已有致死病例之報導。免疫介導性結腸炎，IMFINZI可能引起免疫介導性結腸炎，其定義為需要使用皮質類固醇者。免疫介導性內分泌病變，IMFINZI 可能引起免疫介導性內分泌病變，包括甲狀腺疾病、腎上腺功能不全、第一型糖尿病和腦下垂體炎/腦下垂體低能症。免疫介導性腎炎，IMFINZI可能引起免疫介導性腎炎，其定義為有腎功能不全的證據，需要使用皮質類固醇者。已出現致死病例。免疫介導性皮膚反應，IMFINZI可能引起免疫介導性皮疹；使用本類藥物其他產品曾經發生大皰性皮炎(bullous dermatitis)，史帝文生－強生氏症候群(SJS)/性表皮溶解症(TEN)；其他免疫介導性不良反應：IMFINZI可能引起嚴重和致死的免疫介導性不良反應。感染，IMFINZI可能引起嚴重的感染，包括致死病例。輸注相關反應，IMFINZI可能引起嚴重或危及生命的輸液相關反應。胚胎-胎兒毒性,根據其作用機制和來自動物研究的數據，當給予孕婦時，IMFINZI可能導致胎兒危害。【常見不良反應】PACIFIC研究，最常見的不良反應(20%的病人發生)為咳嗽、疲勞、肺炎(pneumonitis)或放射性肺炎、上呼吸道感染、呼吸困難和皮疹。試驗1108，最常見的不良反應(15%)為倦怠(39%)、肌肉骨骼疼痛(24%)、便秘(21%)、食慾降低(19%)、噁心(16%)、周邊水腫(15%)、泌尿道感染(15%)。CASPIAN研究，最常見的不良反應(20% 的病人發生)為噁心、疲倦/虛弱和掉髮。【 使用前詳閱說明書警語及注意事項，詳細仿單資料備索】【僅限醫藥專業人員參考；處方藥物請參考衛生福利部核准仿單說明書】

Ref：1. 抑癌寧注射劑50 mg/ml 衛福部核准仿單說明書 2. Powles T et al. JAMA Oncol. 2017;3(9):e172411. 3. Paz-Ares L et al. Lancet. 2019;394(10212):1929-1939. 4. Antonia SJ et al. NEJM. 2018;379:2342-2350. 5. Spigel DR, Faivre-Finn C, Gray JE, et al. 5-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC-an update from the PACIFIC trial. Poster presented at: 2021 ASCO Virtual Annual Meeting; June 4-8, 2021. Poster 8511.

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【成分含量與劑型】持續性藥效硬膠囊劑，每膠囊含 2、4 毫克的 tolterodine tartrate。**【適應症】**治療伴有急尿、頻尿或急迫性尿失禁症狀的膀胱過動症。**【用法與用量】**口服使用，除了肝功能受損以及嚴重腎臟功能受損 (GFR ≤ 30 ml/min) 病患的建議劑量是每次 2 毫克、一天一次外，一般的建議劑量是每次 4 毫克、一天一次。持續性藥效膠囊可伴隨或不伴隨食物服用。但是必須整顆吞服。**【禁忌事項】**Detrusitol SR 禁用於對 tolterodine 或本品中之賦形劑過敏、尿液滯留、未控制的狹角性青光眼病患。**【警語與注意事項】**於下列之病患應謹慎給予 Tolterodine：尿液滯留之危險群；胃腸道蠕動力減少之危險群；腎臟功能損傷；肝臟功能受損；重症肌無力症；先天或後天已證實 QT 延長之病人；病人正在服用 Class IA (如：quinidine, procainamide) 或 是 Class III (如 amiodarone, sotalol) 的抗心律不整藥；併用其他 CYP3A4 抑制劑之患者。**【不良反應】**藥物相關不良反應: 鼻竇炎、過敏反應、困惑、暈眩、頭痛、思睡、不正常視力、乾眼症、眩暈、皮膚發紅、口乾、腹痛、便秘、消化不良、脹氣、胃與食道逆流症、皮膚乾燥、排尿困難、尿滯留、胸痛、疲倦、體重增加。**【備註】***此為簡易處方資訊，完整處方資訊請詳閱仿單。

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與Aspirin併用，與Clopidogrel相比，Brilinta可以降低心血管死亡、心肌梗塞風險

心肌梗塞病史

與Aspirin併用，可減少有心肌梗塞病史合併有高風險發生動脈血栓事件病人之心血管死亡、心肌梗塞或中風發生率

急性缺血性腦中風或暫時性腦缺血（TIA）

與Aspirin併用，用於降低急性缺血性腦中風(NIHSS 分數 ≤5) 或高風險暫時性腦缺血病人之中風風險。

百無凝膜衣錠60毫克，90毫克 BRILINTA™（ticagrelor）Film-coated Tablets 60 mg, 90 mg

北市衛藥廣字第111060144號

衛部藥輸字第027145號，衛署藥輸字第025691號

【適應症】1.急性冠心症或心肌梗塞病史 2.急性缺血性腦中風或暫時性腦缺血【用法用量】Brilinta與Aspirin併用時，Aspirin之每日維持劑量不可超過100 mg。急性冠心症：Brilinta的預載劑量（loading dose）為單劑180 mg（兩顆90 mg錠劑），接著每次90 mg，每日兩次，建議治療持續12個月，除非臨床上有需要停藥。使用Brilinta加上 Aspirin 每日維持劑量 75-100 mg。心肌梗塞病史：Brilinta 60 mg每日兩次建議在有一年以上MI病史合併有高風險發生動脈血栓事件的病人，需要延長治療時使用。具高風險動脈血栓事件的ACS病人，使用Brilinta 90 mg 或其他二磷酸腺苷（ADP）受體抑制劑療法初步一年治療之後，Brilinta 60 mg每日兩次可作為接續療法而無須中斷。治療亦可在發生MI後2年內、或停用先前ADP受體抑制劑治療後1年內開始。Brilinta作為延長治療超過3年的療效和安全性資料有限。急性缺血性腦中風或暫時性腦缺血 (TIA) ：Brilinta與Aspirin併用治療：開始治療時，Brilinta的預載劑量為單次口服180 mg，後續則每日兩次、每次口服90 mg持續30天，療效在療程初期顯現；Aspirin的預載劑量為單次口服300至325 mg，後續則每日一次，每次口服75-100 mg。如果需要更改藥物，第一劑Brilinta應於最後一劑其他抗血小板藥物後24小時給予。如果病人錯過一劑Brilinta，應於下次服藥時間僅服用一顆錠劑（即下一次劑量）。無法吞嚥錠劑之病人可將Brilinta膜衣錠壓碎後混入水中並喝下。該混合藥液亦可透過鼻胃管（CH8或更大）給藥。【禁忌症】顱內出血病史、活動性出血、過敏反應、重度肝功能不全。【警語和注意事項】出血風險：抑制血小板功能的藥物會增加出血風險。Brilinta不可使用於活動性病理性出血或顱內出血病史者。急性缺血性腦中風或暫時性腦缺血 (TIA) 之病人：NIHSS 分數 >5之病人以及接受血栓溶解治療(thrombolysis)之病人被排除在THALES試驗之外，且不建議這類病人使用Brilinta。可能的話，處理出血不要停止使用Brilinta。停止使用Brilinta可能增加隨後心血管事件的風險。治療ACS病人時併用之Aspirin每日維持劑量：在治療ACS病人時，Brilinta與每日維持劑量超過100 mg的Aspirin併用會減低Brilinta的有效性。在這類病人中，給予Aspirin預載劑量後，與Brilinta併用時，除非有特殊禁忌，Aspirin每日維持劑量應為75-100 mg。呼吸困難(Dyspnea)：如果病人有新發生、長時間或惡化性的呼吸困難且確定與Brilinta相關，無須特別治療，如果可能的話，繼續使用Brilinta不要中斷。若病人發生難以承受之呼吸困難時，應考慮停止投予Brilinta並採取其他抗血小板藥物。ACS病人停用Brilinta之考量：ACS之病人如停用Brilinta可能會增加心肌梗塞、中風和死亡的風險。如果必須暫時停用Brilinta，要儘快重新開始。可能的話，在有重大出血危險的手術前五天中斷Brilinta治療；一止血就恢復Brilinta治療。緩脈型心律不整 (Bradyarrhythmias)：Brilinta會造成心室停歇(ventricular pause)。主要發生於ACS病人，心因性缺血和併用藥物減少心跳或影響心臟傳導等潛在干擾因素所致。肝功能不全：Ticagrelor目前尚未在重度肝功能不全病人進行試驗，因此這些病人禁止使用。與強效CYP3A抑制劑併服：Ticagrelor會被CYP3A4/5代謝，避免與強效CYP3A抑制劑併用。 血栓性血小板低下性紫斑症 :有極少數案例使用ticagrelor時出現血栓性血小板低下性紫斑症TTP。其特徵是有神經系統異常、腎功能不全或發燒症狀的血小板減少與微血管病變溶血性貧血。TTP具有潛在致命危機須立即進行包括血漿分離術等治療。以血小板功能干擾試驗診斷肝素引起血小板低下症(heparin-induced thrombocytopenia, HIT)：HIT血小板功能試驗 (包括但不限於HIPA試驗)的偽陰性結果出現在服用ticagrelor的病人。中樞神經性睡眠呼吸中止症 (central sleep apnea) : 使用Brilinta之病人在上市後被報導發生中樞神經性睡眠呼吸中止症，包含陳-施氏呼吸(Cheyne-Stokes respiration)。如有中樞神經性睡眠呼吸中止症之疑慮，應考量進一步臨床評估。【特殊族群使用】老年人：老年人無須調整劑量。腎功能不全：腎功能不全病人無須調整劑量。肝功能不全：Ticagrelor 目前尚未在重度肝功能不全病人進行試驗，因此這些病人禁止使用。中度肝功能不全病人只有有限資訊。未建議調整劑量，但使用 ticagrelor 時應特別謹慎。輕度肝功能不全病人不需要調整劑量。懷孕：從使用Brilinta懷孕婦女個案報告可獲取的數據，並未發現有重大出生缺陷、流產、對母親或胎兒有副作用等與藥物有關的風險。授乳婦女：未有資料指出ticagrelor或其代謝物是否存在於人乳、對哺育中嬰兒或乳汁製造的影響。在Brilinta治療期間不建議哺乳。兒童族群：目前尚未確立 18 歲以下兒童使用 ticagrelor 的安全性及療效。目前尚無可用資料。【不良反應】出血及呼吸困難。

【使用前詳閱說明書警語及注意事項，詳細仿單資料備索。】

【僅限醫藥專業人員參考，處方藥物請參考衛生福利部核准仿單說明書。】

BRILINTA™ ticagrelor tablets

臺灣阿斯特捷利康股份有限公司 台北市敦化南路二段207號21樓
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VOYAGER Study

降低LDL-C效果

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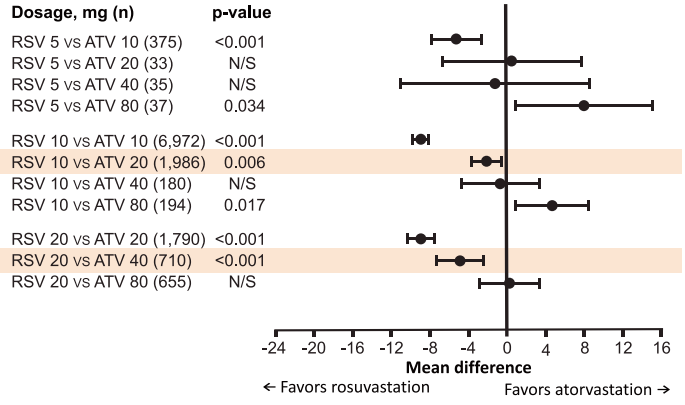

Adapted from Karlson, Björn W., et al. *Am J Cardiol. 2016 May 1;117(9):1444-8.*

冠脂妥® 膜衣錠5，10，20毫克 CRESTOR® 5, 10, 20 mg Film-Coated Tablets

【適應症】高膽固醇血症，高三酸甘油酯血症。【用法用量】CRESTOR 每天服用一次，服藥時間早晚不拘，隨餐或空腹均可。高膽固醇血症（異型接合子家族型及非家族型）及混合型高脂血症 （Fredrickson IIa 型及IIb 型）：CRESTOR 的劑量範圍是 5-20 mg 每天一次，並應根據治療目標及患者的反應，個別調整劑量。CRESTOR 的一般建議起始劑量是 10 mg 每天一次。需要降低低密度脂蛋白膽固醇較少程度的患者，應考慮以 5 mg 每天一次開始治療，這些患者包括有肌病促發因子者和下列特殊族群，例如服用 cyclosporine 者、亞裔患者及重度腎功能不全的患者。有顯著高膽固醇血症（低密度脂蛋白膽固醇 > 190 mg / dL）且有積極血脂目標值的患者，可考慮以 20 mg 開始治療。開始 CRESTOR 治療及/或調整劑量之後，應在 2-4 週內檢查血脂濃度並依照結果調整劑量。開始statin類藥物治療或由另一種 statin 改為 CRESTOR 時，首先應使用適當的 CRESTOR 起始劑量，然後才可以根據患者個別的治療目標調整劑量。患有異型接合子家族型高脂血症的小兒患者（10-17歲）：CRESTOR 的一般劑量範圍是每天 5-20 mg，最大建議劑量是每天 20 mg。劑量應按照治療的建議目標個別調整。應以4週或更久的時間調整劑量。同型接合子家族型高膽固醇血症：建議劑量是 20 mg 每天一次。CRESTOR 應作為其他降血脂治療（例如低密度脂蛋白血漿析離術）的輔助治療，或不能利用此類治療時的輔助治療。應從施行血漿析離術之前的低密度脂蛋白膽固醇濃度估計對治療的反應。亞裔患者的劑量：對亞裔患者宜考慮以 5 mg 每天一次開始。對於用 5 或 10 mg 每天一次的劑量無法適當控制高膽固醇血症的患者，考慮提高劑量時，必須注意亞洲人的 rosuvastatin 暴露量可能比白種人高。與Cyclosporine、Atazanavir/Ritonavir、Lopinavir/Ritonavir 或 Simeprevir 併用：對於使用cyclosporine的患者，CRESTOR 的劑量應以 5 mg 每天一次為限。對於使用 atazanavir 及 ritonavir, lopinavir 及 ritonavir 或 simeprevir 的患者，CRESTOR 的劑量應以 10 mg 每天一次為限。併行降血脂治療：與膽汁結合樹脂併用時，CRESTOR 降低低密度脂蛋白膽固醇及總膽固醇的療效會增加。若與 gemfibrozil 併用，CRESTOR 的劑量應以 10 mg 每天一次為限。腎功能不全患者的劑量：輕度至中度腎功能不全患者無須調整劑量。對於有重度腎功能不全（CLcr < 30 mL/min/1.73 m^2）而未接受血液透析的患者，CRESTOR 應以 5 mg 每天一次開始治療，不可超過 10 mg 每天一次。【禁忌症】已知對本品任何成分過敏之患者；有活動性肝疾病之病患；懷孕或可能懷孕的婦女；授乳婦。【警語和注意事項】骨骼肌效應：HMG-CoA 還原酶抑制劑(包括CRESTOR)曾有肌球蛋白尿(myoglobinuria)引起之橫紋肌溶解(rhabdomyolysis)、肌病(myopathy)及急性腎衰竭的案例報告，這個風險可能發生在任何一個用藥劑量之下，但在高劑量下(40 mg)風險會升高。肝酵素異常和監測：使用本品可能引起病人肝轉氨酶的持續升高，建議在開始治療之前，及在開始治療和每次調高劑量後 12 週都要做肝功能檢查，此後還要定期監測(例如每半年檢查一次)。併用 Coumarin 類的抗凝血劑：開始 CRESTOR 治療前應測量其 INR，在治療初期也應常常監測 INR。蛋白尿和血尿：對於在例行尿液檢查中，有不明原因、持續性蛋白尿及/或血尿之患者，應該要考慮降低 CRESTOR 的劑量。內分泌效應：醣化血色素(HbA1c)上升。當 CRESTOR 和可能會降低內生性類固醇荷爾蒙濃度或活性的藥品併用時(例如ketoconazole、spironolactone、cimetidine)，需謹慎小心。可逆性認知障礙：曾有少數上市後研究顯示，使用statin類藥品與認知功能障礙(如:記憶力減退、健忘、記憶障礙、認知混亂等)可能有關。該等認知功能問題通常是不嚴重的，且於停藥後可恢復，其症狀發生及緩解時間不定。【不良反應】常見不良反應（發生率≧2%）：頭痛、肌肉疼痛、腹痛、衰弱無力、噁心、便祕。可能嚴重不良反應：橫紋肌溶解伴隨肌球蛋白尿、急性腎衰竭及肌病（包括肌炎）、肝臟酵素異常。【使用前詳閱說明書警語及注意事項，詳細仿單資料備索。】【僅限醫藥專業人員參考，處方藥物請參考衛生福利部核准仿單說明書。】

衛署藥輸字第024597、024131、024129號
北市衛藥廣字第110060015號
TW-20320_CRE_24/06/2022

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OLYMPUS TERUMO BIOMATERIALS　TERUMO

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Terudermis
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品號	尺寸 (cm x cm)
TD*M006SJ	2.5 x 2.5
TD*M013SJ	2.5 x 5
TD*M025SJ	5 x 5
TD*M100SJ	10 x 10

- 熱脫水架橋
- 高生物相容性
- 減少疤痕攣縮率
- 促使肉芽組織生長
- 適用深度傷口(骨,肌,腱外露)

日本元祖再生醫療

產品結構

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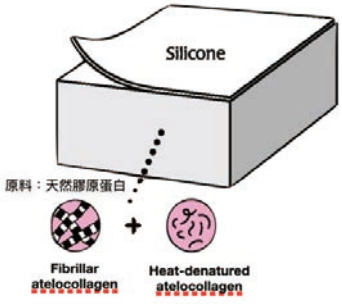
  防止乾燥和污染。
- 膠原蛋白
  促進血管浸潤、細胞攀附，
  建構類真皮組織。



使用說明

將傷口處清潔並去除感染和壞死組織，完成止血。
置於傷口上縫合，兩週後拆線，進行分層植皮。

聯絡資訊:

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乳癌治療領域中 第一個

雙標靶皮下注射劑型 5-8分鐘 完成雙標靶治療

正式取得台灣適應症

早期乳癌(EBC)

與化學治療藥物合併使用於：

- 術前輔助療法適用於 HER2 陽性，局部晚期、發炎性或早期乳癌(腫瘤直徑大於 2 cm 或淋巴結陽性) 之病人，作為早期乳癌完整治療處方之一部分。
- 術後輔助治療適用於 HER2 陽性且具有高復發風險之早期乳癌病人。

說明: 根據 Aphinity 臨床試驗結果，在術後輔助治療中，具有高復發風險之HER2 陽性早期乳癌病人定義為其乳癌呈淋巴結陽性。

轉移性乳癌(MBC)

與docetaxel併用於治療轉移後未曾以抗 HER2 或化學療法治療之 HER2 陽性轉移性乳癌病人。

Reference:
1.PHESGO 最新版仿單
2.Tan AR, et al. Lancet Oncol 2020
3.Joyce O'Shaughnessy, et al. Eur J Cancer 2021

賀雙妥® 皮下注射劑
Phesgo® Solution for Subcutaneous Injection (pertuzumab/trastuzumab)
衛部菌疫輸字第001172號 1200/600毫克
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適應症:早期乳癌(eBC)及轉移性乳癌患者(mBC)。
用法用量:
依據腫瘤檢體的HER2蛋白過度表現或HER2基因放大來篩選病人。PHESGO僅可以皮下施打於大腿。請勿施打到靜脈。
・起始劑量: 15毫升溶液中含1,200毫克pertuzumab、600毫克trastuzumab與30,000單位玻尿酸酶(hyaluronidase) 以約8分鐘皮下施打。
・維持劑量: 10毫升溶液中含600毫克pertuzumab、600毫克trastuzumab與20,000單位玻尿酸酶，每3週以約5分鐘皮下施打。
・乳癌的術前輔助治療: 在早期乳癌治療療程中，每3週施打PHESGO一次，為期3至6個週期。手術後，病人應繼續接受PHESGO以完成1年的治療(最多18個週期)，或直到疾病復發或出現無法處置的毒性為止，以先發生者為準。
・轉移性乳癌: 當docetaxel和PHESGO併用治療時，docetaxel的起始建議劑量為75 mg/m2，以靜脈輸注的方式給予。若起始劑量耐受性良好，則可提高劑量至100 mg/m2每3週一次。施打PHESGO直到疾病復發或出現無法處置的毒性為止，以先發生者為準。
・延遲或遺漏劑量: 針對延遲或遺漏的PHESGO劑量，若兩劑接續注射之間的時間短於6週，則施打600 mg、600 mg與20,000單位/10 mL之維持劑量。若兩劑接續注射之間的時間為6週或以上，則重新施打起始劑量1,200 mg、600mg與30,000單位/15 mL，之後給予每3週一次的維持劑量600 mg、600 mg與20,000單位/10 mL。
禁忌症: PHESGO禁用於已知對Perjeta (pertuzumab)或Herceptin (trastuzumab)或玻尿酸酶(hyaluronidase)或任何賦形劑過敏的病人。
警語: PHESGO可能會導致無臨床症狀與有臨床症狀之心臟衰竭。在有出現臨床上左心室功能顯著降低的情況下，接受輔助治療的病人應停止PHESGO之治療，對轉移性乳癌病人則應暫停PHESGO之治療。PHESGO曝藥可能導致胚胎-胎兒死亡與先天缺陷，請告知病人這些風險，以及有效避孕措施的必要。PHESGO給藥可能導致嚴重且致命的肺部毒性。應考量哺乳對於發育和健康的利益，以及母親對於PHESGO治療的臨床需求，和PHESGO或潛在母體情況對於哺乳嬰兒的任何潛在不良作用。此項考量也應將pertuzumab的排除半衰期及trastuzumab清除期為7個月納入考量。尚未確立小兒病人使用PHESGO的安全性與療效。
副作用: 由於臨床試驗進行的條件變異很大，在藥物臨床試驗中觀察到的不良反應率無法直接與另一項藥物臨床試驗中的不良反應率相比較，且無法反映實際觀察到的不良反應率。靜脈輸注之Perjeta (pertuzumab)與Herceptin (trastuzumab)給藥後曾通報下列不良反應：腹瀉、禿髮、噁心、疲倦、嗜中性白血球減少症、嘔吐、周邊神經病變、便秘、貧血、無力、黏膜發炎、肌痛和血小板減少症。

產品詳細資訊，請參考完整仿單。

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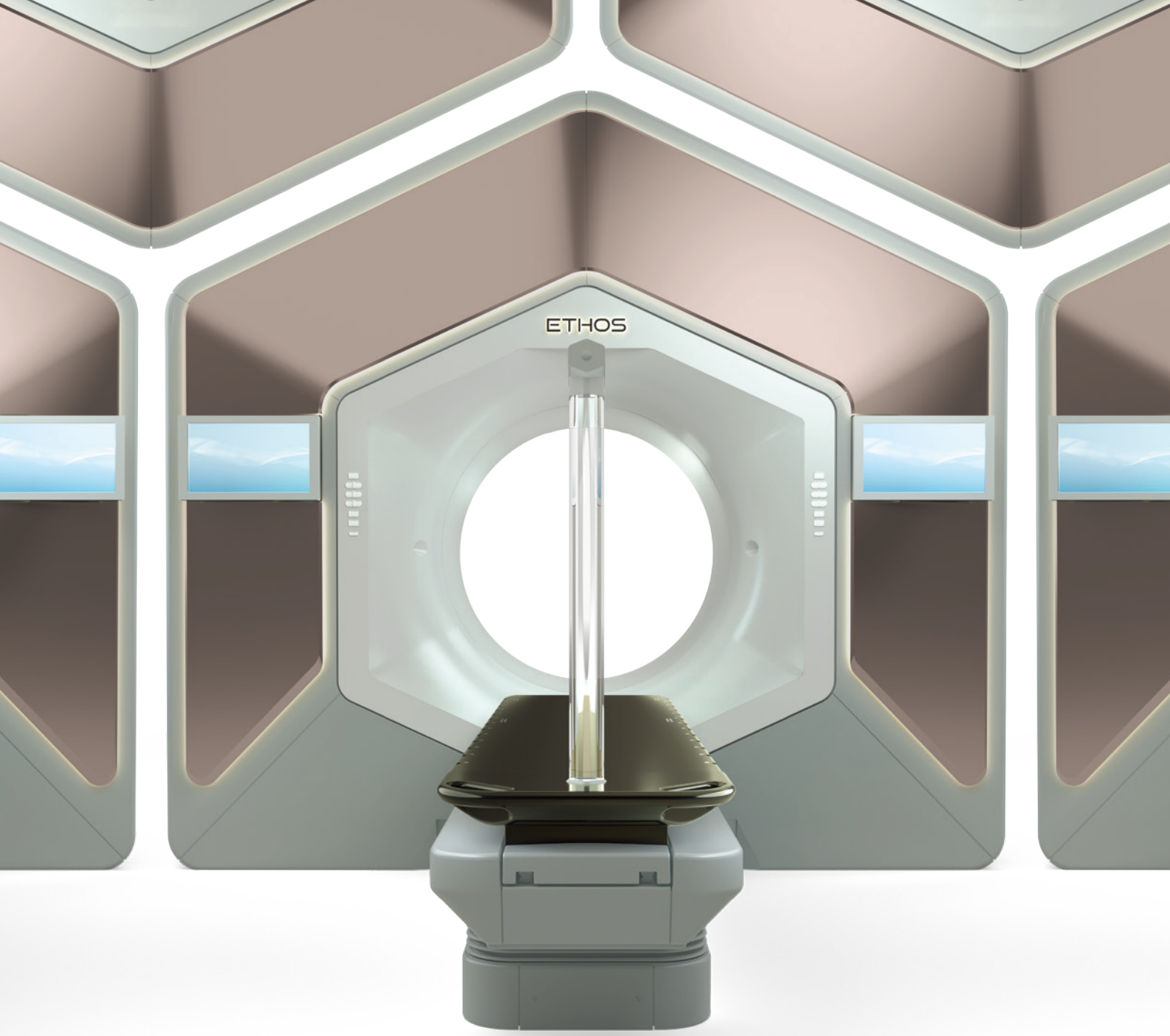

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[適應症]6個月型注射劑，用於已使用1個月型paliperidone palmitate持續性藥效注射用懸浮液充分治療至少4個月後，或已使用3個月型paliperidone palmitate持續性藥效注射用懸浮液治療至少一次3個月週期療程後之思覺失調症病人。

[禁忌症]INVEGA HAFYERA®禁用於已知對paliperidone 或risperidone 過敏，或是對INVEGA HAFYERA®配方中之任一賦形劑過敏的病人。在使用risperidone 及使用paliperidone 治療的病人中曾有發生過敏反應的報告，包括嚴重過敏性反應與血管性水腫。Paliperidone palmitate 會轉化成paliperidone，而paliperidone 也是risperidone 的代謝物之一。

[用法用量]INVEGA HAFYERA®應每6個月注射一次。每次注射都必須由醫療專業人員施行。

從INVEGA SUSTENNA® (1個月型paliperidone palmitate持續性藥效注射用懸浮液)轉換成INVEGA HAFYERA®

應於預定投予下一劑INVEGA SUSTENNA® (1個月型paliperidone palmitate)的時間開始使用INVEGA HAFYERA®，並依據先前的1個月型paliperidone palmitate注射劑量來決定INVEGA HAFYERA®的劑量，如表1所示。可於預定投予下一劑1個月型paliperidone palmitate之時間點的前後1週內投予INVEGA HAFYERA® 。

表1. 對已使用INVEGA SUSTENNA®充分治療之成人病人改用INVEGA HAFYERA®的劑量

如果最後一劑 INVEGA SUSTENNA®的劑量為：	以下列劑量開始 使用 INVEGA HAFYERA®：
156 毫克	1092 毫克
234 毫克	1560 毫克

目前並無與 39 毫克、78 毫克或 117 毫克劑量之 INVEGA SUSTENNA®等效的 INVEGA HAFYERA®劑量，也尚未進行過相關的研究。

從INVEGA TRINZA® (3 個月型paliperidone palmitate 持續性藥效注射用懸浮液)轉換成INVEGA HAFYERA®

應於預定投予下一劑 3 個月型paliperidone palmitate 的時間開始使用INVEGA HAFYERA®，並依據先前的 3 個月型paliperidone palmitate 注射劑量來決定INVEGA HAFYERA®的劑量，如表 2 所示。可於預定投予下一劑 3 個月型paliperidone palmitate 之時間點的前後 2 週內投予INVEGA HAFYERA®。

表 2. 對已使用INVEGA TRINZA®充分治療之成人病人改用INVEGA HAFYERA®的劑量

如果最後一劑INVEGA TRINZA® 的劑量為：	以下列劑量開始 使用 INVEGA HAFYERA®：
546 毫克	1092 毫克
819 毫克	1560 毫克

目前並無與 273 毫克或 410 毫克劑量之 INVEGA TRINZA ®等效的 INVEGA HAFYERA®劑量，也尚未進行過相關的研究。

[特殊警語及注意事項]會升高失智症相關精神病老年病人的死亡率、發生於失智症相關精神病老年病人的腦血管不良反應，包括中風、抗精神病藥物惡性症候群(Neuroleptic Malignant Syndrome) 、QT間期延長、遲發性運動異常 (Tardive Dyskinesia) 、代謝改變、直立性低血壓與暈厥、跌倒、白血球減少症、嗜中性白血球減少症、以及顆粒性白血球缺乏症、高泌乳激素血症、認知與行動能力可能會減弱、癲癇發作、吞嚥困難、陰莖異常勃起、干擾體溫調節 。

[副作用]臨床試驗的經驗 常見的不良反應：在INVEGA HAFYERA®臨床試驗中最常見的不良反應(在雙盲階段的發生率至少為5%)為上呼吸道感染、注射部位反應、體重增加、頭痛、以及帕金森氏症。

[使用前請詳閱說明書警語及注意事項]

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Better Health, Brighter Future

武田是一家以價值為基礎，以研發為導向的全球生物製藥領導者，總公司位於日本，我們致力於研發並提供改善人類健康的創新治療，並依據我們對病患、員工和全球環境的承諾為準則。

武田聚焦研發在四大治療領域，包括**腫瘤學**、**罕見遺傳**和**血液學**、**神經科學**和**胃腸病學**，我們也針對**血漿衍生療法**和**疫苗**進行策略性研發的投資，我們專注在研發高度創新性藥品，透過開拓創新治療的研究領域、利用我們深厚的研發基礎及動能，打造強大且形態多樣化的新藥研發，有助於為人類健康帶來改變。

在武田全球據點約 **80** 個國家中，我們的員工致力於改善患者的生活品質並與醫藥產業的夥伴攜手努力。

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