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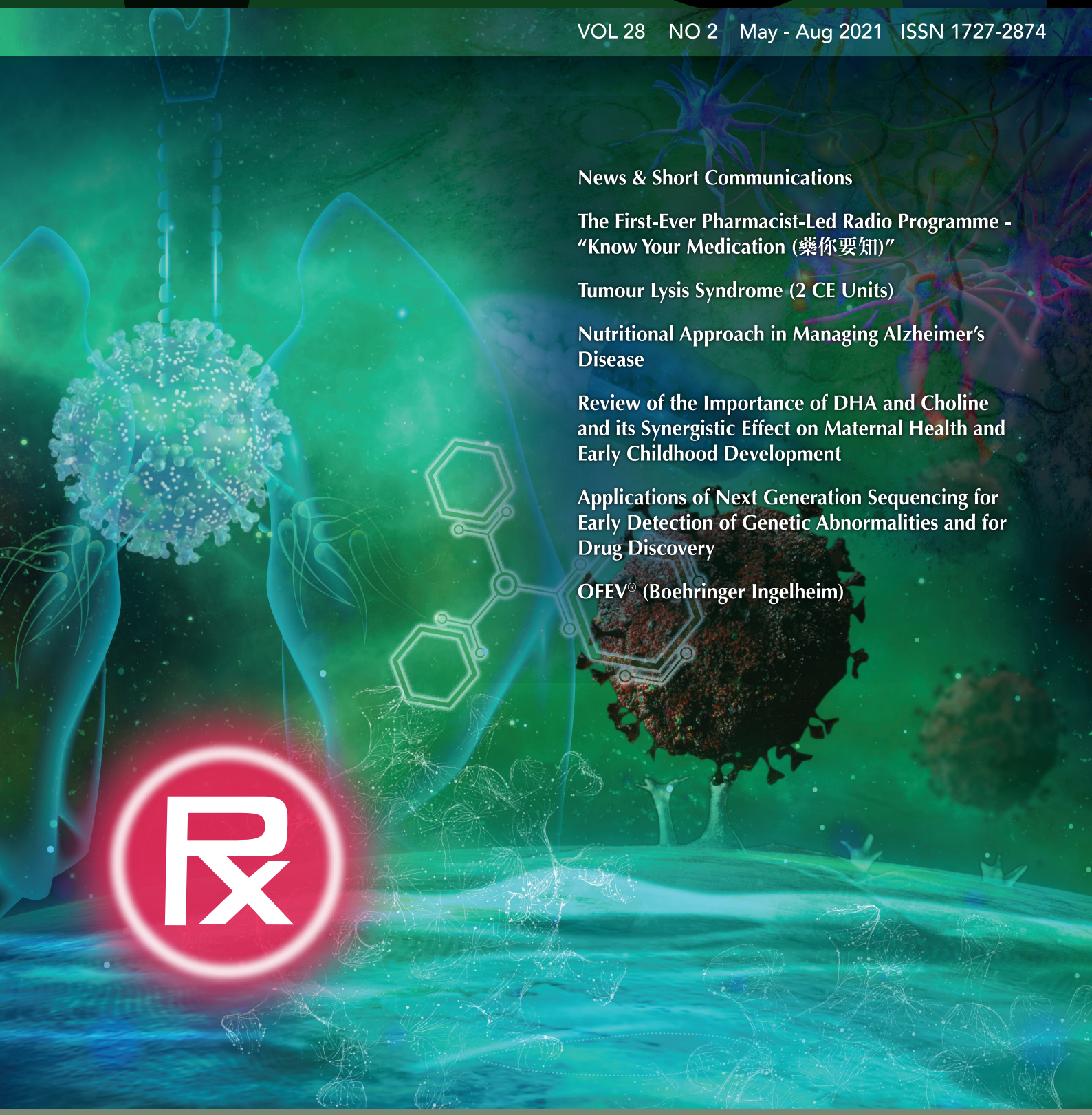

News & Short Communications

The First-Ever Pharmacist-Led Radio Programme - "Know Your Medication (藥你要知)"

Tumour Lysis Syndrome (2 CE Units)

Nutritional Approach in Managing Alzheimer's Disease

Review of the Importance of DHA and Choline and its Synergistic Effect on Maternal Health and Early Childhood Development

Applications of Next Generation Sequencing for Early Detection of Genetic Abnormalities and for Drug Discovery

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INSTRUCTIONS FOR AUTHORS

The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
- Drugs & Therapeutics
- Primary Care
- OTC & Health
- Pharmaceutical Techniques & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- New Products

Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

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For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

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Primary Care and Advances in Medical Technology

The most effective way to combat the Covid-19 Virus is by vaccination and to prevent its spread by personnel hygiene and wearing of face masks. In Hong Kong, as of 13 September 2021, total population with 1st Covid 19- vaccine dose administered is 4,350,857(64.6%) and with 2nd vaccine dose administered is 3,831,270(57%). The Government has announced (page 49) in view of the supply of vaccines and the demand and pace of vaccination, the operation of 21 Community Vaccination Centres(CVCs) will be extended to the end of this year. These CVCs will continue to provide the first-dose vaccination services in October and November, and will only provide the second-dose vaccination services in December. Let's hope that at the end of December, total population with vaccine dose administered can reached at least 80%.

In this issue, "The First-Ever Pharmacist-Led Radio Programme - Know Your Medication (藥你要知)" written by CHENG, Celia Sin-Man, CHOW, Tiffany Hoi-Yee, HAU, Melody Wing-Kei*, CHONG, Donald Wing-Kit (page 50) is a RTHK (Radio Television Hong Kong) programme led by a group of pharmacists. The programme covered topics such as common health issues, drug regulatory affairs, and drug development processes, with an aim to enhance public health knowledge, and to promote the image of pharmacists in Hong Kong. It was successfully broadcasted throughout July to October in 2020.

The article on "Tumour Lysis Synrome" written by CHAN, Tsz Yue Pauline (page 53), describes the principle of managing tumour lysis syndrome is prompt identification of patients at risk and provision of appropriate prophylaxis. Hydration is the mainstay of management followed by therapeutic interventions, such as allopurinol and rasburicase. Correction of electrolyte disturbance is also vital.

Alzheimer's disease is an age-related neurodegenerative disease which affects more than 20-30% of the elderly population aged 80 years or older. In the article on "Nutritional Approach in Managing Alzheimer's Disease" written by LIN, Hinson Hin Sang (page 60), he describes that nutritional approach with better side effect profile has been widely studied. It is able to target the well-established neuro-degeneration cascade of Alzheimer's disease and provides favourable clinical outcome. A nutritional drink containing predominantly polyunsaturated fatty acids has demonstrated clinical benefit in managing early Alzheimer's disease. Different dietary patterns which might be effective in primary prevention of Alzheimer's disease are also described.

The article on "Review of the Importance of DHA and Choline and its Synergistic Effect on Maternal Health and Early Childhood Development" (page 64) written by LEE, Annie Hang Yue; LEE, IHsuan; LUI, Tsz Yan; TANG, Sara Suet Yee and YAU, Edward Fook Wing , describes that DHA has beneficial effects on not only fetal growth but also maternal health, recent findings show synergistic implications of DHA and choline in supporting brain and eye development. It is suggested that pregnant and lactating women should seek dietary advice from nutritionists and other healthcare professional to ensure adequate consumption of DHA and choline during the critical time frame of fetal growth.

The article on "Applications of Next Generation Sequencing for Early Detection of Genetic Abnormalities and for Drug Discovery" (page 72) written by CHAN, Alfred and CHEUNG, Hon-Yeung describes New Generation Sequencing (NGS) technology is an automated and high-throughput DNA sequencing method allows people to simultaneously analyze large numbers of nucleotides. This method can carry out an enzymatic sequential addition of nucleotides to immobilized DNA templates and significantly reduces sequencing cost with improved accuracy. NGS technology has been applied to sequence circulating tumor DNA (ctDNA) in liquid biopsy or extract of target tissue in oncology. It can identify mutation and aberrations in DNA that render tumors exquisitely sensitive to certain therapies, resulting in real time exceptional responses. Hence, it has opened a broad new era of clinical applications for prompt screening of genetic diseases, cancer and for development of precise personalized medicine.

I hope you will take time to read and enjoy the articles. Let's hope with increase of vaccinated population, our borders can be opened and life can get back to normal as soon as possible.

Mary Catherine Cheng
Managing Editor
13 September 2021

Prepared by Branson Fok and Chloe Ip

Donanemab in Early Alzheimer's Disease

Date: May 6, 2021

The accumulation of amyloid-B (AB) peptide plaques in the brain is an indicator of Alzheimer's disease. Donanemab is a humanized IgG1 antibody that specifically targets epitopes present in established plaques. A phase 2 clinical trial was conducted to evaluate the safety and efficacy of donanemab in patients with early symptomatic Alzheimer's disease who had tau and amyloid deposition on positron-emission tomography (PET).

TRAILBLAZER-ALZ is a multicenter, randomized, double-blind, placebo-controlled phase 2 trial conducted across 56 sites in the United States and Canada. Patients were randomly assigned in a 1:1 ratio to receive donanemab (700 mg for the first three doses and 1400 mg thereafter) or placebo intravenously every 4 weeks for up to 72 weeks. The primary outcome was the change from baseline in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS; range, 0 to 144, with lower scores indicating greater cognitive and functional impairment) at 76 weeks. Secondary outcomes included the change in scores on the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB), the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog13), the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL), the Mini–Mental State Examination (MMSE), and the change in the amyloid and tau burden on PET.

Of the 257 enrolled patients, 131 received donanemab and 126 received placebo. The baseline iADRS score was 106 in both groups. The change from baseline in iADRS score at 76 weeks was -6.86 with donanemab and -10.06 with placebo (difference, 3.20; 95% confidence interval, 0.12 to 6.27; P=0.04). No substantial difference was found in most of the secondary outcomes.

Donanemab exhibited a better composite score for cognition and the ability to perform activities of daily living than placebo at 76 weeks. However, larger trials are necessary to consolidate the findings on donanemab in early Alzheimer's disease.

Source: www.nejm.org

US FDA Approves Oral Dabigatran for Children with Venous Thromboembolism

Date: June 21, 2021

Pradaxa (dabigatran etexilate) oral pellets was approved by the US FDA for the treatment and recurrence prevention of venous thromboembolism in children with 3 months to 12 years of age in condition that they have received injection of blood thinner for at least 5 days. The use of Pradaxa capsule was also approved for children with 8 years of age in the same condition as above.

Pradaxa is the first oral anticoagulant that has been approved for paediatric use. The supporting study with 267 participants aged below 18 showed that 45.8% of the study group had their blood clots resolved after treatment of Pradaxa. In contrast, 42.2% of the study population who received standard of care also met the same composite endpoint. For the safety endpoints, comparable results in recurrence of blood clots, major bleeding events, and death was observed between the two groups.

The approval of Pradaxa provided another choice of medication for children with potentially fatal blood clots caused by cancer or heart problems. Complications of venous thromboembolism like edema, angina or pulmonary diseases could also be prevented. Yet, Pradaxa is still contraindicated in patients with bioprosthetic heart valves or triple-positive antiphospholipid syndrome. It is also important to monitor for side effects such as gastrointestinal problems and bleeding and prevent early treatment discontinuation which possibly leads to spinal complications.

Source: www.fda.gov

Sustained Response Observed in Patients with Dementia-Related Psychosis Treated by Pimavanserin

Date: July 22, 2021

Pimavanserin is a selective inverse agonist and antagonist of 5-HT_{2A} receptor. With less activity at dopamine, histamine and muscarinic receptors, this new generation of atypical antipsychotic drug may achieve a better efficacy and safety for dementia treatment.

The phase 3, double-blind, randomized, placebo-controlled discontinuation HARMONY trial enrolled 392 patients with dementia and at least 2 months of psychotic symptoms. Initially, eligible participants entered the open-label phase to receive a daily dose of pimavanserin 34mg. 61.8% (217 out of 351) of the participants had at least 30% reduction from baseline in the total score of Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions (SAPS–H+D) and a Clinical Global Impression–Improvement (CGI-I) score of 1 or 2 comparing to baseline at both weeks 8 and 12. Among the patients who achieved sustained response, 194 of them along with 23 additional participants entered the double double-blind phase to receive either pimavanserin or placebo. The primary endpoint was the time for psychosis relapse with at least 30% increase in the SAPS–H+D total score and a CGI-I score of 6 or 7, hospitalization, trial withdrawal or addition of antipsychotics due to treatment failure.

Interim data analysis showed that the frequency of relapse was 13% and 28% in the pimavanserin group and the placebo group respectively (hazard ratio, 0.35; 95% confidence interval, 0.17 to 0.73; P=0.005). The mean reduction in the ESRS-A score at week 26 during the double-blind phase in the pimavanserin group (−0.9±0.6) was also larger than the placebo group (−0.4±0.3). Yet, adverse events like urinary tract infection (6.4%), QT prolongation (1.3%), and even death due to myocardial infarction (0.3%) posed safety a big concern.

Patients with pimavanserin showed a lower risk of relapse than those discontinued in this study. The efficacy of pimavanserin on treating dementia-related psychosis is still a question that requires further investigation.

Source: www.nejm.org

Abelacimab for Prevention of Venous Thromboembolism

Date: August 12, 2021

Enoxaparin, an inhibitor of factor Xa and thrombin, is administered postoperatively to reduce the risk of venous thromboembolism (VTE) for patients undergoing total knee arthroplasty. However, it is often associated with adverse events like bleeding. Emerging evidence suggests that targeting factor XI attenuates thrombosis with mild disruption of haemostasis. A trial was conducted to evaluate the safety and efficacy of Abelacimab, a fully human monoclonal antibody that targets factor XI.

In this phase 2, prospective, randomized, open-label, parallel-group trial, 412 patients who had undergone total knee arthroplasty were randomly assigned in a 1:1:1:1 ratio to receive abelacimab (30 mg, 75 mg, or 150 mg) or enoxaparin (40 mg). The regimens of abelacimab were administered postoperatively in a single intravenous dose and enoxaparin was administered subcutaneously once daily until venography was performed. The primary efficacy outcome was VTE as detected by mandatory venography of the leg involved in the operation or objective confirmation of symptomatic events. The principal safety outcome was a composite of major or clinically relevant non-major bleeding up to 30 days after surgery.

VTE occurred in 13 of 102 patients (13%), 5 of 99 patients (5%), 4 of 98 patients (4%) and 22 of the 101 patients (22%) in the 30 mg, 75 mg and 150 mg abelacimab group as well as the 40 mg enoxaparin group respectively. As a result, the 30 mg abelacimab regimen was non-inferior to enoxaparin, and the 75 mg and 150 mg abelacimab regimens were superior to enoxaparin ($P<0.001$). Bleeding only occurred in 2% of the patients in the 30 mg and 75 mg abelacimab groups.

In conclusion, this trial showed that the postoperative initiation of factor XI inhibition was important in reducing the risk of developing venous thromboembolism, meanwhile associated with a low risk of bleeding.

Source: www.nejm.org

FDA Grants First of its Kind Indication for Chronic Sleep Disorder Treatment

Date: August 12, 2021

The U.S. Food and Drug Administration (FDA) has approved a new indication for Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution for the treatment of idiopathic hypersomnia (IH) in adults. The existing approved indication of Xywav is the treatment of cataplexy or excessive daytime sleepiness in patients seven years or older with narcolepsy. IH is an uncommon chronic sleep disorder that causes difficulty in waking up and excessive daytime sleepiness despite a well-rested night. It is suggested that the approval of Xywav will be crucial in treating symptoms of IH, thus effectively managing this debilitating disorder.

The safety and efficacy of Xywav was evaluated in a double-blinded, placebo-controlled, randomized-withdrawal study in 154 adult patients (aged 19 to 75 years) with IH. Results revealed that patients who were randomized to switch from Xywav to placebo had experienced worsening of IH symptoms such as sleepiness compared to patients randomized to continue treatment with Xywav.

The most common adverse events observed in this clinical trial were nausea (21.4%), headache (16.2%), dizziness (11.7%), anxiety (10.4%) and vomiting (10.4%). Additionally, central nervous system depression and abuse and misuse are the boxed warning for Xywav. The active moiety of Xywav is oxybate, commonly known as gamma-hydroxybutyrate (GHB). The abuse or misuse of illicit GHB has been associated with seizures, trouble breathing, changes in alertness, coma, and death.

Source: www.fda.gov

Operation arrangements of Community Vaccination Centres after October

Date: September 9, 2021

The COVID-19 Vaccination Programme has been implemented for 196 days since February 26, 2021. By the end of September, Community Vaccination Centres (CVCs) will have operated continuously for seven months.

The Government announced on September 9 that, in view of the supply of vaccines and the demand and pace of vaccination, it has decided to make following arrangements for the operation of CVCs:

1. Five CVCs will be closed from November. They are the CVCs at Hong Kong Sanatorium & Hospital (HKSH), HKSH Eastern Medical Centre, St Paul's Hospital, Tai Po Hui Sports Centre and Tsuen King Circuit Sports Centre.

2. The operation of 21 CVCs will be extended to the end of this year. These CVCs will continue to provide the first-dose vaccination services in October and November, and will only provide the second-dose vaccination services in December.

3. Starting from November 1, the opening hours of the 21 CVCs will be adjusted. The opening hours of the CVCs on Saturdays and Sundays will remain unchanged, i.e. from 8am to 8pm. They will operate from 10am to 6pm on Mondays, Tuesdays, Thursdays and Fridays and will be closed on Wednesdays. All CVCs will close between 1.30pm and 2.30pm on working days for cleaning.

"We have endeavoured to maintain as much as possible the operation of the CVCs with the more popular time slots to facilitate the vaccination of members of the public. Starting from November, the number of CVCs will be decreased by eight to 21 from the peak of 29," a Government spokesman said.

"Starting from November, the CVCs will serve a total quota of 27,000 people being vaccinated daily on weekdays, comprising 21,000 people receiving the BioNTech vaccine and 6,000 people receiving the Sinovac vaccine. On weekends, the CVCs will provide daily vaccination quotas of 32,000 and 9,000 for the BioNTech and Sinovac vaccines respectively. Together with the vaccination services of the Sinovac vaccine provided by over 1,000 private doctor clinics, we believe the demand of the public can be met."

Source: https://www.info.gov.hk/gia/general/202109/09/P2021090900301.htm?fontSize=1

The First-Ever Pharmacist-Led Radio Programme - "Know Your Medication (藥你要知)"

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ABSTRACT

"Know Your Medication" (藥你要知) is a RTHK (Radio Television Hong Kong) programme which was led by a group of enthusiastic pharmacists and healthcare professionals. It was successfully broadcasted throughout July to October in 2020. The programme covered a wide range of topics such as common health issues, drug regulatory affairs, and even drug development processes, with an aim to enhance public health knowledge, and to promote the image of pharmacists in Hong Kong.

Keywords: *Know Your Medication, 藥你要知, Pharmacy, Pharmacists, Radio Programme*

INTRODUCTION TO "KNOW YOUR MEDICATION" (藥你要知)

Led by a diverse group of pharmacists and healthcare professionals, the 13-episode radio programme, namely "KNOW YOUR MEDICATION", was broadcasted under every Friday between 10 July and 2 October 2020 via RTHK. The duration of each episode was 30 minutes. Each episode was divided into three main sessions: (1) a role-play session/skit to bring out the theme of that episode; (2) a content session addressing relevant drug information of that episode; and (3) a summary to conclude the main points of the episode. This arrangement could provide a relaxing atmosphere to attract audiences' attention while delivering useful health messages to the public.

Aiming to enhance drug knowledge of the public and to promote the roles of pharmacists, the programme included a wide variety of drug-related topics, such as discussions on some common diseases and their treatment options, introduction of vaccines and the concept of clinical trials, drug regulatory affairs and development processes. Acting as a bridge between drugs and the public, the program can help deliver appropriate drug knowledge based on the expertise of a diverse group of pharmacists. Misunderstandings about drugs will also be addressed, which can be helpful for the public to make correct judgements later in their daily lives.

INTRODUCTION TO MR. DONALD CHONG

Mr. Chong, currently the Regulatory Affairs Director of Consumer Health at GlaxoSmithKline, graduated from the University of British Columbia with a pharmacy degree in 1994 and obtained a Master's degree in Health Services Management from the University of Hull in 2001. Mr. Chong is a registered pharmacist in both Canada and Hong Kong, as well as a member of the Appeal Board Panel for Consumer Goods Safety Ordinance since 2019.

With over 20 years of experience in the multinational pharmaceutical industry, Mr. Chong has a wide-ranging leadership experience specializing in regulatory affairs and medical affairs.

Initiated by Mr. Chong, he gathered a group of enthusiastic pharmacists and healthcare professionals, preparing the whole series. As a pharmacist, he hopes to bring more positive impacts to society and the public would recognize the roles of pharmacists.

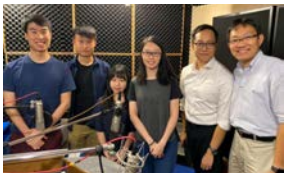

Figure 1. *Some of the crew members from the radio programme (from left to right): Jason, Justin, Rita, Melody, Kelvin, Donald*

INTERVIEW WITH MR. DONALD CHONG

Q: Why did you choose to initiate a drug-related radio programme, but not through other channels?

Mr. Chong: In 2018, I saw an advertisement of CIBS (Community Involvement Broadcasting Service) from RTHK on the MTR, which was calling for applicants to establish social gains in the community. Participating in a radio programme has always been a childhood dream of mine, as tuning into radio programmes was a form of entertainment when I was young. I would even make a call to the radio station and appoint songs for my family and friends to listen to! Therefore, I thought that this would be a great chance for me to make my childhood dream come true. As a pharmacist, I wanted to make this an opportunity to enhance the public image of pharmacists in Hong Kong, and share my experiences and knowledge with others.

Figure 2. *Interview at RTHK building during programme selection phase*

Q: What are the aims of the programme?

Mr. Chong: The primary objectives are to promote the image of pharmacists, provide drug education as per our expertise, and reach out to the public on topics that they might want to know more about.

Radio broadcasting could get access to people from different backgrounds, so I thought it would be a good platform

to educate the audience on drug safety and basic drug knowledge/information.

Q: How does this programme benefit society?

Mr. Chong: As mentioned earlier, we would like to educate the public and clarify the queries that they might have regarding drugs/medications through our radio show.

We conducted a survey after the programme as a performance evaluation. Over 60% of the audience stated that the programme helped them gain a better understanding of drugs. Some of the audience had even listened to five out of thirteen episodes, which was encouraging to us!

Radio is now highly accessible, fitting the role of providing sustainable education to the public. Nowadays, RTHK records all the episodes and uploads them onto the internet. The audience can revisit any episodes that they may have missed whenever they want, or share them with their family and friends. In general, we had really good and positive preliminary feedback from the audience, and I believe the social impact of "Know Your Medication" could last for a long time.

Q: Are there any unforgettable memories or lessons learnt from running the radio programme that you would like to share with us?

Mr. Chong: I am lucky to have this opportunity to work with a group of pharmacists and healthcare professionals who play important roles in different sectors across the industry.

One of the lessons learnt is trying to coordinate the schedules between all team members. As we work in different sectors, some members have a regular schedule, while some are on shift duty. Thus, it was quite challenging to conduct a team briefing or have a discussion with all members at times. It was also my first time finding a studio, completing paperwork up to standards, and brainstorming the topics and format of the radio show. Filling in paperwork and submitting record samples to RTHK 1 week before each episode publication was also time consuming. These may sound tedious, but I found this experience very memorable as it's very different from my normal job.

Figure 3. *Technician at the recording studio.*

In addition, getting to know the recording technician was a big blessing, as he gave us lots of useful tips on how to improve the programme or recording. He would listen to our content, and give us feedback from the perspective as a layman. Being medical professionals, we might use medical jargon that may not be understood by the general public. The feedback from our recording technician helped us immensely in ensuring that the general public understands the information that we are trying to convey.

Figure 4. *For the full interview with Mr Donald Chong from RTHK, please refer to the link (Photo credits to RTHK Community Involvement Broadcasting Service): https://www.facebook.com/watch/?v=2728866607381689*

This was an unforgettable experience for me. It was an amazing opportunity to carry out a pharmacist-led radio programme in Hong Kong, and we were so happy to see that the audience enjoyed it so much!

INTERVIEW WITH OTHER PARTICIPATED PHARMACISTS

The following section of the interview was conducted with the following pharmacists: **CHENG Humphrey** (Principal Pharmacist at CUHK Medical Centre), **CHENG Kwan Wa Tommy** (Former Regulatory Affairs Executive at GSK), **CHEUNG Nigel Coleman** (Pharmacy Intern at Kwong Wah Hospital), **CHEUNG Sum Yi Rita** (Former Pharmacy Intern at GSK), **HAU Melody Wing-Kei** (Pharmacist), **HO Chun Ting Justin** (Former GSK Intern), **LEUNG Win Kin Philip** (Resident Pharmacist in the Hospital Authority), **TONG Jason** (President of Pharmacists Connect), and **WONG Kelvin** (Associate Director of Medical Affairs at Astellas Pharma Hong Kong Co., Ltd.).

Figure 5. *Meeting up with CIBS coordinators from RTHK (i.e. the two people on the left) at the recording studio.*

Q: Why did you choose to participate in the programme?

Interviewees: Being healthcare professionals, we always wanted to share our experiences and knowledge of drugs and diseases to the public.

Through our participation in the radio programme, we hoped that the general public would gain more understanding about the role of a pharmacist, and know that no matter where we work (i.e. hospital, community pharmacy, pharmaceutical companies), our skills and tasks involve far more than just dispensing medications. We also thought that it would be a fun and once-in-a-life-time experience to run a radio program on our own!

Q: How did the experience differ from your regular job?

Interviewees:

[Member working in a pharmaceutical company]:
As a Biochemist who works in the Medical/Regulatory Affairs Department, I am constantly exposed to a lot of research and information regarding medications. I have to liaise with the Department of Health or stakeholders through emails or phone calls very often. Thus, I have less opportunities to partake in patient education. "Know Your Medication" is the first radio programme that I've ever taken part in, and I had a very positive experience!

[Members working in local hospitals]:
When working as a pharmacist in the local hospitals, we could always have two-way communications with our patients and other healthcare professionals such as pharmacists, doctors and nurses. Take patient counseling as an example, we could give immediate response by reading others' facial expressions or address instant queries from patients through one-on-one interactions. However, tuning a radio programme is completely different. It is more like a one-way communication because the audience can only tune in and listen to our voices. Therefore, we have to avoid jargons to ensure that the general public will understand the topics that we are introducing while we also incorporate some interesting elements, such as drama into our show to attract the audience's attention. Having appropriate pronunciation and speech rate is also the key to success.

[Members working in a multinational pharmaceutical company]:
As a pharmacist that works in a multinational pharmaceutical company that focuses on drug registration, I mainly communicate with other pharmacists and customers through email or phone calls. The recording format of the radio programme is thus very different from my daily job. Instead, we used the radio channel to deliver drug knowledge to the public. I hope that this form of mass media will be able to educate the public and help clarify some myths or misleading information that can be found on the internet.

Figure 6. *Pharmacists Philip (Left) and Jason (Right) during the recording session.*

Q: How will the radio programme impact the pharmacy profession?

Interviewees: Hospital and community pharmacists are more accessible to the public as they are mainly involved in the frontline duties that interact the most with the general public.

One of the biggest impacts of the radio programme is promoting the various roles of pharmacists in our society. We could let the public know that pharmacists also support the profession in many other areas beyond hospitals and community pharmacies e.g. drug registration, drug import and export and academic research and development.

Figure 7. *Pharmacists Tommy (Left) and Rita (Right) during the recording session.*

Q: How do you think the radio programme impacted/ helped the audience?

Interviewees: As pharmacists, we usually explain different treatments of some common illnesses to the patients, e.g. hypertension, diabetes and cold and flu. In some of the episodes, we also addressed some common misunderstandings and drug queries that the public may have (e.g. should the medicines be stored in the fridge, whether the drugs can be mixed with juices to cover the flavour, and difference between generic and branded drugs). Besides, we also tackled any misinformation or myths that are found on the internet.

Figure 8. *Behind the scenes of a promotion video on the roles of hospital pharmacists.*

We believe that the radio programme could help the audience by enhancing their knowledge on drugs and diseases.

Q: What was your favorite topic covered? Any reasons why?

Interviewees: We have a lot of crew members that are experts on different topics. One of our favorite episodes was "臨牀實證係真唔係?". For some of the topics that we have covered such as hypertension and cold and flu, the audience might already have some ideas about them before listening to our show. As for 'Clinical Research', especially when we are talking about the stages that are involved in a clinical trial, we believe that most of the people seldom hear of it in daily life. That's why we believed this topic is worthy of being included in the radio show.

Apart from the topics on some common diseases and drugs, we also addressed how a drug is developed, from the initial research stages to its final form which could be a tablet, or a solution. By having a Biochemist on our team, we were able to educate the general public on how long it takes for a drug to be developed from basic raw materials, and the corresponding investment required to help secure drug safety and efficacy.

Q: Any unforgettable broadcasting experience you could share with us?

Interviewees: The experience was definitely a 'first' to most of us we have not had the opportunity to participate in a radio programme before. It was thus a good and meaningful experience for us to practice how to apply and relate all the knowledge to people's daily lives.

Figure 9. *For the promotion video published from RTHK, please refer to the link (Photo credits to RTHK Community Involvement Broadcasting Service): https://www.facebook.com/RTHK.HK/posts/4867312716627430/*

In addition, we have also designed a specific flow for our show (i.e. short drama → content → summary) so that every episode created an enjoyable listening and learning environment.

Another unforgettable experience would be planning and participating in the role-play segment of the radio programme. We got the chance to put down our professional side to act as an 80-year-old lady, a van driver or even a worrying mother who is nervous about the kid's medicines. The programme was really a good opportunity and an eye-opening experience for our personal growth.

Q: Will there be another series of the programme (藥你要知 2.0)?

Interviewees: We received a lot of positive comments from the people from CIBS and from our audience. For instance, there were people commenting on our Facebook posts saying that they would like to hear more about psychiatric drugs (which is not covered in season 1) in the future!

Of course we do hope to start working on the new series soon, but there are still a lot of factors that we need to consider. If we do choose to move forward with a second series, we would like to introduce topics that are in trend right now, such as COVID vaccines, to help the audience gain understanding on how vaccines are made, how long they generally take to be approved, and any concerns the audience should have when they choose which vaccine to receive. We would also like to introduce topics that match the audiences' preferences, such as psychiatric drugs, or even simpler topics such as the stimulant effect of coffee. We believe that by including a wide range of topics, we can arouse the public's attention and meet their expectations.

We also hope to increase the diversity of our programme by inviting pharmacists from different sectors to share their working routines and experiences, so that the general public can continue to learn more about our roles in the industry.

CONCLUSION

We believe the programme has brought positive impacts to society and public health, and these effects could be long-lasting. Educating the public with common drug knowledge and rectifying false perceptions on medication use could also enable them to make suitable decisions on their own in the future.

Moreover, the roles of pharmacists are becoming more known by the public, and are expanding within the industry. Pharmacists from various sectors are involved in different parts of a complete drug production chain: from drug formulation and development, to where it is registered and dispensed to the patients.

We sincerely hope the radio programme could benefit the public by raising their knowledge towards drugs, and help them understand more about the role of pharmacists. We hope we can proceed with the next series of the programme soon. Stay tuned!

For more details or episodes of the programme, please visit https://www.rthk.hk/radio/pth/programme/p0934_know_your_medication.

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Tumour Lysis Syndrome

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ABSTRACT

Tumour lysis syndrome is a complex metabolic disturbance involving abnormally high levels of uric acid, potassium, phosphorus and low level of calcium. In severe cases, it can lead to clinical manifestations, including cardiac arrhythmias, neurological and neuromuscular abnormalities and acute kidney failure. If it is left untreated, tumour lysis syndrome can deteriorate to life-threatening multi-organ failure. The principle of managing tumour lysis syndrome is prompt identification of patients at risk and provision of appropriate prophylaxis. Hydration is the mainstay of management followed by therapeutic interventions, such as allopurinol and rasburicase. Correction of electrolyte disturbance is also vital. This article summarises diagnostic criteria, risk factors, prevention and treatment options for tumour lysis syndrome.

Keywords: *Tumour lysis syndrome, Chemotherapy-induced metabolic syndrome, Allopurinol, Rasburicase*

INTRODUCTION

Tumour lysis syndrome (TLS) is a metabolic syndrome caused by rapid tumour cell lysis. The abrupt release of intracellular contents into the peripheral blood results in electrolyte imbalances in the body and is considered a life-threatening complication in cancer treatment.[1] TLS is usually observed within 12 to 72 hours after initiation of chemotherapy but can also occur at any time due to spontaneous cellular death of rapidly dividing cancer cells (spontaneous TLS).[2,3] It can be fatal if unrecognised and left untreated. Risk factors associated with the development of TLS include malignancies with a high tumour burden and high sensitivity to chemotherapy, rapidly proliferative or aggressive malignancies, initiation of cytotoxic chemotherapy and pre-existing renal impairment.[4,5] Although it can occur in any tumour type, TLS is most frequently observed in patients with non-Hodgkin lymphoma (NHL), acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML).[4,6] Due to the potential severity of complications resulting from TLS, risk stratification and appropriate medical interventions are important in preventing and managing it.[4,5]

PATHOPHYSIOLOGY and CLINICAL PRESENTATION

When malignant cells lyse spontaneously or secondary to therapy, their intracellular contents are expelled to extracellular fluid and mediate the pathophysiology of TLS and its clinical complications.[7] The metabolic derangements resulting from the failure of homeostatic mechanisms in the body are associated with impaired organ function and morbidity.

A large number of nucleic acids from the disintegration of malignant cells are catabolised to hypoxanthine, then xanthine and finally to uric acid causing hyperuricemia.[8] **(Figure 1)** If not already in existence at presentation, hyperuricemia usually develops 48 to 72 hours after anti-cancer treatment initiation.[9] Since uric acid has poor solubility in water, particularly in an acidic environment, crystal precipitation is likely to occur in the renal tubules.[7] When uric acid accumulates and precipitates in the renal tubules, it can cause uric acid nephropathy and acute kidney injury.[10] It is the main cause of renal failure.[1] When renal function is compromised, the kidneys are unable to excrete large amounts of phosphorus and potassium from cell lysis, leading to hyperphosphataemia and hyperkalaemia.

Hyperkalaemia is another metabolic abnormality related to TLS due to the rapid release of intracellular potassium. It is usually the first sign of TLS and can develop as quickly as 6 hours after anti-cancer treatment initiation.[5,11] Hyperkalaemia can manifest as muscle weakness and cardiac arrhythmias, which can progress to cardiac arrest in severe cases.[4,11]

In malignant cells, the level of phosphorus can be up to four times greater than normal cells.[1,11] Therefore, rapid lysis of tumour cells results in a significant increase in serum phosphorus level. Initially, the renal transport system responds by increasing phosphorus excretion and decreasing resorption until this mechanism becomes overwhelmed. Acute kidney injury caused by hyperuricemia may further exacerbate hyperphosphatemia, causing symptoms like nausea, vomiting, diarrhoea and lethargy.[4] Significant hyperphosphataemia may develop 24 to 48 hours after commencing cancer treatment.[11] In addition, calcium phosphate precipitates can be formed when serum phosphate binds with calcium, especially when phosphorus is in excess. This results in secondary

hypocalcaemia in which cardiac arrhythmias, muscle cramps and hypotension can occur in severe cases.[1,4] When the precipitate deposits in the renal tubules, it will further worsen kidney injury.[7,12]

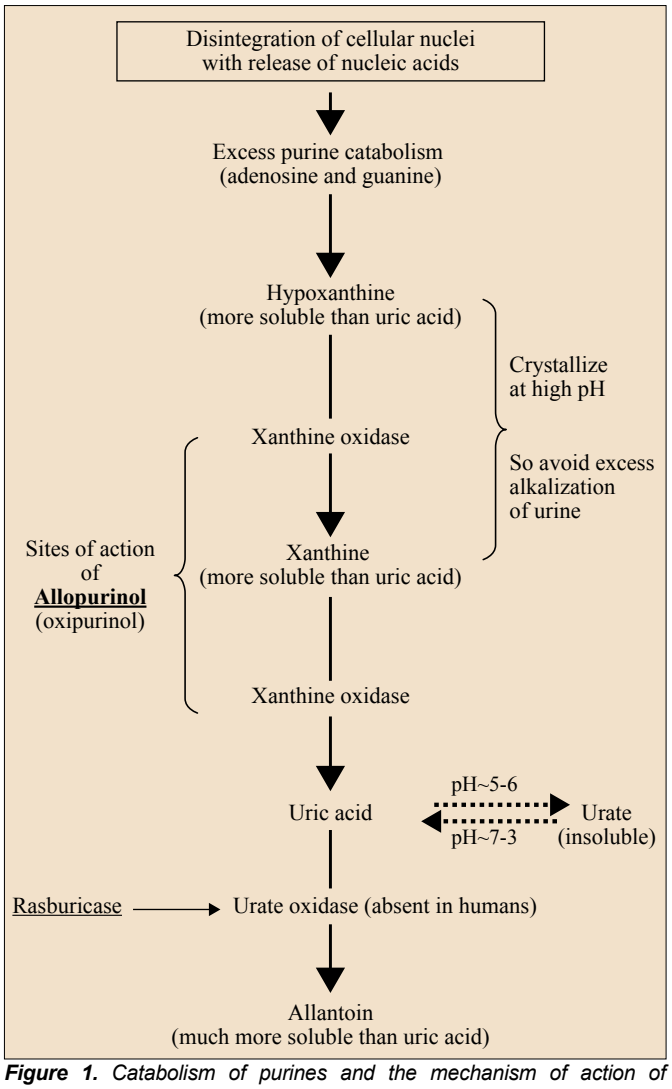

Figure 1. *Catabolism of purines and the mechanism of action of allopurinol and rasburicase[8]*

CLASSIFICATION and RISK STRATIFICATION

In 2004, Cairo and Bishop proposed specific criteria for the diagnosis of TLS, classified as laboratory TLS (LTLS) and clinical TLS (CTLS) with a grading system.[12] LTLS is defined as the co-occurrence of two or more of the four metabolic derangements (hyperuricemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia) at presentation or if they change by 25% from baseline up to three days before or seven days after the start of chemotherapy.[12] CTLS is defined as LTLS plus one or more of the following clinical manifestations: increased serum creatinine level to more than 1.5 times upper limit normal (ULN), cardiac arrhythmias, seizure or sudden death.[12] It is graded from Grade 0 to Grade 5 depending on the level of serum creatinine, the severity of cardiac arrhythmia and types of seizures.[12] This grading system helps to identify patients with laboratory abnormalities but does not require interventions from those who are experiencing life-threatening conditions that require specific therapeutic interventions. It was also considered more useful than the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), which only grades TLS as present (grade 3), life-threatening (grade 4), or death (grade 5).[13]

The risk of developing TLS is influenced by a number of factors, which can be patient-related and tumour-related. The use of aggressive chemotherapy may also contribute to the risk.[14] Older age is considered a risk factor for developing TLS because it is related to decreased renal function with a reduction in the glomerular filtration rate.[1,4] It leads to higher concentration of metabolites in the bloodstream. Elevated white blood cell (WBC) counts and lactate dehydrogenase (LDH) levels were found to be independent risk factors and predictors of TLS.[1,4] Many studies reviewing TLS incidence identified that patients with LDH higher than ULN or WBC counts ≥ 20 x 10^9/L had a higher incidence of TLS.[15,16] With regards to tumour-related factors, malignancies with a high tumour burden and high sensitivity to chemotherapy are more prone to develop TLS.[4,5] Increased tumour burden can be reflected by large tumour size, elevated LDH, increased WBC counts and extensive bone marrow involvement[1,6] Acute leukaemia and high-grade lymphoma are haematological malignancies with a high potential of cell lysis. They were found to have higher tendency in developing TLS than other cancer types.[6,14]

Later in 2010, an international expert panel published a panel consensus on recommendations for the risk evaluation of TLS. It provides a model of low-, intermediate- and high-risk TLS classification with prophylaxis recommendations.[14] **(Table 1 and 2)** For example, multiple myeloma and most solid tumours are classified as low-risk disease (LRD) but neuroblastoma, germ cell tumour and small-cell lung cancer are classified as intermediate-risk disease (IRD) because they are bulky tumours that are sensitive to chemotherapy.[14] The panel also stratified chronic leukaemia, acute leukaemia, Hodgkin lymphoma and Non-Hodgkin lymphoma (NHL) into different risk levels according to their subtypes, WBC counts and LDH levels.

INCIDENCE of TLS

The incidence of TLS varies depending on different malignancies and different TLS criteria used in various studies. It is observed most frequently in acute leukaemia and high-grade NHL after initiation of cancer treatment but less commonly in chronic leukaemia.[4] This is supported by the findings ranging from case reports to retrospective analyses conducted in different facilities in children and adult age groups. In a retrospective study of 50 patients with haematological malignancies in 2012, the incidence of TLS was found to be 14%, 4% and 2% in acute leukaemia, NHL and chronic leukaemia respectively.[1] From an observational study of 772 adult patients with acute myeloid leukaemia (AML) who received allopurinol prophylaxis, the incidence of

Table 1. TLS risk stratification in Adults/Children with Malignancies (Recommended by Cairo et. al)[14]			
Malignancies	**Low risk disease (LRD)**	**Intermediate risk disease (IRD)**	**High risk disease (HRD)**
Solid tumours	Most solid tumours	Neuroblastoma Germ cell tumours Small cell lung cancer	
Multiple myeloma	Most cases		
Hodgkin lymphoma			
CML	Most CML (Chronic Phase)	Accelerated blast crisis	
NHL	Indolent NHL	Burkitt lymphoma early stage with LDH <2 X ULN	Burkitt lymphoma stage III/IV and/or LDH ≥2 X ULN
		Lymphoblastic lymphoma stage I/II and LDH <2 X ULN	Lymphoblastic lymphoma stage III/IV and/or LDH ≥2 X ULN
	Adult Intermediate grade NHL and LDH <2 X ULN	Adult Intermediate grade NHL and LDH ≥2 X ULN	
	Adult ACLC	Children ACLC stage III/IV	
	Children ACLC stage I/II	Childhood intermediate grade NHL stage III/IV with LDH <2 x ULN	
ALL		WBC <100 X 10^9/L and LDH <2 X ULN	WBC ≥100 X 10^9/L and/or LDH ≥2 X ULN
CLL	Most CLL (On therapy using only alkylating agents)	Treated with fludarabine, rituximab and/or WBC ≥50 X 10^9/L	
AML	WBC <25 X 10^9/L and LDH <2 X ULN	WBC 25-100 X 10^9/L WBC <25 X 10^9/L and LDH ≥2 X ULN	WBC ≥100 X 10^9/L

CML: Chronic myeloid leukaemia, NHL: Non-Hodgkin lymphoma, ALL: Acute lymphoblastic leukaemia, CLL: Chronic lymphocytic leukaemia, AML: Acute myeloid leukaemia, ACLC: Anaplastic large cell lymphoma, WBC: Which blood cell, LDH: Lactate dehydrogenase, ULN: Upper limit of normal

TLS was 17%.[16] In paediatric patients, two multicentre studies showed an overall TLS incidence of 4.4% in 1791 children and adolescents with NHL, with the incidence of 8.4% in patients with Burkitt lymphoma.[14] In another retrospective study of 327 children's medical records, an overall incidence of 5.8% was observed, within which TLS in NHL accounted for 15.9% and TLS in acute lymphoblastic leukaemia (ALL) accounted for 0.47%.[17] Moreover, in a multi-institutional study of children (n=322) and adults (n=433) with acute leukaemia or NHL, the overall incidence of LTLS and CTLS were 18.9% and 5.0% respectively.[18] In a subgroup analysis, the respective rates of TLS in children and adults were 5.2% and 21.4% in ALL, 6.1% and 19.6% in NHL, and 3.4% and 14.7% in AML.[18] Although the occurrence is rare, TLS can also occur in solid tumours.[19]

New cancer therapies are emerging in the market but the risk of TLS caused by these novel agents is not well examined. A systematic review published in 2016 highlighted that reports of TLS incidence are scarce in the literature, suspecting that it has been underreported in the current era.[20] In some clinical trials, the incidence or management of TLS was not mentioned at all. The authors, *Howard SC et al*., emphasised the importance of awareness in TLS when using contemporary treatments for haematologic malignancies.[20]

PREVENTION and MANAGEMENT

Risk stratification, recognition of risk factors and provision of appropriate interventions to prevent TLS are the mainstay in managing it.[4,5] **(Table 2)** Once TLS has developed, interventions should be made promptly to minimise the risk of progression and deterioration to a life-threatening condition.

Table 2. Prophylaxis recommendations based on TLS risk[13]		
LRD	**IRD**	**HRD**
Monitoring	Monitoring	Monitoring
Normal hydration	Increased hydration	Increased hydration
± Allopurinol*	Allopurinol	Rasburicase

*In cases of metabolic changes, bulky and/or highly proliferative diseases

Hydration

Adequate hydration and maintenance of high urine output are fundamental in preventing TLS in all patients at risk.[4] It is essential for the effective removal of excessive uric acids, phosphate and potassium. Meanwhile, it prevents uric acid crystallisation and calcium phosphate precipitation in the renal tubules in established TLS.[21]

Low-risk patients can be managed by fluid status monitoring and intravenous fluid can be given when necessary.[5] The British Committee for Standards in Haematology and the American Society of Clinical Oncology recommend fluid intake of 2-3 Litre/m^2/day in all patients with intermediate to high-risk diseases.[4,5] For paediatric patients who weigh 10kg or less, fluid delivery of 200 mL/kg/day is recommended.[4] Care should be taken to monitor for fluid overload in patients with pre-existing cardiac and renal diseases.[5] Urine output should be maintained at 80-100 mL/m^2/hr in most patients and at 4-6 mL/kg/hr in patients weighing 10kg or less.[4,5] In patients whose urine output remains low after fluid hydration, diuretics may be necessary to promote diuresis.[7] Loop diuretics are often preferred because of their property in promoting potassium excretion.[3] However, diuretics should be avoided in hypovolemic patients. The combination of hydration and

diuresis promotes renal excretion of uric acid and other electrolytes to prevent nephropathy.[6] It has been shown that adequate hydration can reduce the incidence of uric acid nephropathy.[22]

The use of intravenous sodium bicarbonate has been historically recommended to be given in the intravenous fluid for urine alkalinisation in the prevention of TLS.[23] Alkalinisation of urine aims to increase the solubility of uric acid and hence prevents any neuropathy that might otherwise result. It is because uric acid, with a pKa of 5.4-5.7, is more soluble in an alkaline pH.[4] However, xanthine and hypoxanthine do not carry the same property and have low solubility in alkaline pH instead. This can potentiate precipitation of xanthine crystals in renal tubules resulting in xanthine-obstructive nephropathy.[5] Besides, calcium phosphate tends to precipitate in an alkaline environment. Given the multiple concerns over urine alkalinisation and the lack of strong evidence demonstrating benefit, alkaline diuresis is no longer recommended.[4,5]

Allopurinol

Allopurinol is converted to its active metabolite, oxipurinol, which acts as a competitive xanthine oxidase inhibitor.[24] It prevents hyperuricemia by blocking the conversion of hypoxanthine and xanthine to uric acid.[24] Hypoxanthine is more soluble than uric acid, thus allopurinol has been shown to reduce the incidence of uric acid nephropathy by reducing the formation of uric acid crystals.[24] When being used for prophylaxis of TLS, allopurinol has been demonstrated to prevent the increase in uric acid levels in 93% of adults and in 92% of children.[25]

Yet, there are some limitations in the use of allopurinol. Although it prevents the formation of uric acid, it is ineffective in breaking down the uric acid that has already been formed. Therefore, it takes several days to lower and stabilise the uric acid levels, which explains why allopurinol should be started several days before the commencement of chemotherapy for TLS prevention.[4] Moreover, as allopurinol blocks the catabolism of xanthine to uric acid, it may result in the accumulation of xanthine, which can also form crystals in the renal tubules and cause xanthine nephropathy.[4,6] Apart from xanthine, allopurinol also inhibits the degradation of purine-based chemotherapeutic agents, such as azathioprine and 6-mercaptopurine, requiring dose reductions to one-third or one-quarter of usual doses for those purine-based agents when used concomitantly with allopurinol.[21] Lastly, allopurinol is associated with hypersensitivity reactions that can be manifested as severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[26] It is reported to occur more frequently in Han Chinese populations who carry HLA-B*5801 allele.[26]

The recommended dose of allopurinol is 100mg/m^2/dose every 8 hours for adults and 10mg/kg/day divided every 8 hours for paediatric patients.[4,8] In practice, most haematologists simply use 300 mg daily for adults and dosage has to be adjusted in the presence of renal impairment.[5] Treatment should be initiated in patients with intermediate-risk disease.[14] According to the National Comprehensive Cancer Network (NCCN) guideline, it is recommended to start allopurinol 2-3 days prior to chemotherapy and continue for up to 10-14 days or until uric acid levels become normalised.[2,4] A guideline for the management of TLS written by *Jones GL et al.* in 2015 recommended that any patients who developed TLS despite allopurinol prophylaxis should receive rasburicase.[5]

Rasburicase

Urate oxidase is an enzyme that catalyses the oxidation of uric acid to a more soluble metabolite, allantoin.[4] This enzyme exists in many mammals but not humans. Therefore, a recombinant urate oxidase, rasburicase, was developed by cloning the gene encoding urate oxidase from *Aspergillus flavus* and expressing it in a genetically modified strain of *Saccharomyces cerevisiae*.[27] Unlike allopurinol, rasburicase can break down uric acid deposits and effectively reduces uric acid levels within 4 hours of administration.[28] In an international compassionate use trial, rasburicase resulted in decreased uric acid levels in all 280 enrolled patients.[29] The mean uric acid levels decreased from 14.2 mg/dL to 0.5 mg/dL in patients with hyperuricaemia at baseline and from 4.8mg/dL to 0.4 mg/dL in the remaining patients.[29] The efficacy and safety of rasburicase were also evaluated in the GRAAL trial where 100 patients with aggressive NHL received rasburicase during their first cycle of chemotherapy.[30] Uric acid levels decreased and were maintained at the normal range for all patients throughout chemotherapy. No patients required dialysis and other metabolites, such as potassium, phosphorus, calcium, were controlled during treatment.[30]

The efficacy and safety of rasburicase were compared with that of allopurinol in adults with haematological malignancies in a prospective phase III randomised trial.[31] Patients were randomised to three arms: i) rasburicase alone, ii) rasburicase combined with allopurinol, and iii) allopurinol alone. The rate of uric acid response was 87% for rasburicase, 78% for rasburicase combined with allopurinol and 66% for allopurinol alone.[31] The incidence of LTLS was lower in the rasburicase arm compared with allopurinol alone (21% vs. 41%) but the incidence of CTLS was similar across three arms.[31] Rasburicase is generally well tolerated but severe hypersensitivity reactions, such as anaphylaxis, have been reported from case reports.[32] It is also important to note that rasburicase is contraindicated in patients with glucose-6-phosphatase dehydrogenase (G6PD) deficiency due to the risk of severe haemolytic anaemia and methaemoglobinaemia.[4,33] It is because of the production of hydrogen peroxide during the breakdown of uric acid.[4] Methaemoglobin is a form of haemoglobin that carries less oxygen, so excess amounts will result in hypoxia and require intensive care.[33]

The Food and Drug Administration (FDA)-licensed dose of rasburicase is 0.2mg/kg once daily for 5 days in paediatric and adult patients.[5] In patients with high-risk diseases, preventive rasburicase is recommended in addition to increased hydration.[14] However, the use of rasburicase is hindered by its high treatment cost. With this respect, different dosing studies attempted to look for alternate dosing of rasburicase at lower doses or for shorter duration, and the results demonstrated activity comparable to the licensed dose. Rasburicase 0.1-0.2mg/kg once daily depending on the risk of TLS was proposed by *Coiffier et al*.[4] The duration of treatment can range from 1-7 days guided by plasma uric acid levels and clinical judgment.[4] In adult setting, it has also been shown that single-dose rasburicase, ranging from 0.05mg/kg to 0.2mg/kg, was non-inferior to multiple daily dosing in terms of efficacy and is more cost-effective in the prophylaxis and treatment of TLS in high-risk patients.[34] The use of single fixed-dose rasburicase at 3mg-7.5mg has also been studied and suggested to be an effective alternative regimen.[2,5] In paediatric patients, single-dose rasburicase at 0.2mg/kg is recommended by the British Committee for Standards in Haematology in 2015.[5] With close monitoring of clinical and laboratory parameters, repeated dosing may be given when indicated.[5] Despite the favourable data from various studies, most of them were retrospective and some were conducted in small sample sizes. More comprehensive systematic analyses and clinical studies are warranted to provide clear guidance on the use of rasburicase.

Febuxostat

Febuxostat is a selective xanthine oxidase inhibitor that is hepatically metabolised, thus not requiring dose adjustment in renal impairment. Its usage in tumour lysis syndrome is not extensively studied. A meta-analysis on febuxostat administration for the prevention of TLS was conducted in 2019 aiming to evaluate the safety and efficacy of febuxostat, comparing it with allopurinol. Six studies were included in the review with 659 patients in total. The findings supported that febuxostat is an effective intervention for hyperuricaemia and no significant difference was found in TLS incidence and response rate between the two investigated groups.[35] The safety profiles were also comparable suggesting it is a promising alternative to allopurinol in the prevention of TLS, especially in patients who cannot tolerate allopurinol or when rasburicase is either not available or contraindicated.[2,35] Further randomised controlled trials should be carried out to confirm the efficacy and safety of febuxostat in TLS, as well as to define the optimal dosage in order to be applied to clinical settings.

Management of hyperkalaemia

In moderate hyperkalaemia (≥ 6mmol/L), any sources of potassium should be avoided, and cardiac monitoring is required.[4,5] The standard treatment is sodium polystyrene sulfonate.[4,12] In severe (≥ 7mmol/L) and/or symptomatic hyperkalaemia, more intensive medical treatment, such as insulin-glucose infusion, intravenous sodium bicarbonate or calcium gluconate infusion should be given to initiate the shift of potassium from the extracellular to the intracellular space.[4,21] Loop diuretics also promote potassium excretion.[3]

Management of hyperphosphatemia

The initial management should be ensuring adequate hydration and a high urine output for patients presenting with hyperphosphatemia. Also, any phosphate-containing drugs and intravenous fluids in patients' treatment profiles should be discontinued if possible. Dialysis may have to be considered if the phosphate level is uncontrolled despite vigorous hydration.[4,5] The use of aluminium hydroxide 50-150 mg/kg/day orally in divided doses as phosphate binder has been suggested.[5,12] However, due to its slow onset of action and poor tolerance in children and ill patients, it is less commonly used.[4] Calcium carbonate may be an alternative but it poses the risk of calcium phosphate precipitation.[4]

Management of hypocalcaemia

No treatment is recommended in asymptomatic hypocalcaemia because treatment can contribute to calcium phosphate precipitation, but cardiac monitoring should be offered.[12] When patient becomes symptomatic, e.g. presenting with signs of arrhythmia or seizures, intravenous calcium gluconate should be administered to treat the symptoms. Yet, the aim of treatment should not be normalisation of the laboratory values.[4,5]

Renal dialysis

When a TLS patient developed persistent and significant fluid overload with severe electrolyte imbalances, renal function will deteriorate quickly, and renal dialysis is indicated.[4,21] Haemodialysis is recommended over peritoneal dialysis (PD) because PD is slower in bringing clinical improvement.[5] Direct comparison among different types of haemodialysis is not available but both daily dialysis and continuous renal replacement therapy have been shown to be useful.[5] Dialysis should be continued until there is adequate recovery of renal function, urine output and electrolyte imbalances.[5]

CONCLUSION

TLS, either spontaneous or chemotherapy-induced, can result in significant morbidity and fatal outcomes. In the current era of novel therapy in malignancies, the development of effective chemotherapeutic agents and new combination treatments come with an uncertain risk of TLS. Clinical guidelines have been developed to heighten the awareness of TLS and emphasised the importance of its prevention with upfront risk assessment and implementation of proper preventive measures including adequate hydration and appropriate drug prophylaxis.

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units

Tumour Lysis Syndrome

1. ***Which of the following is more likely to be the first sign of tumour lysis syndrome?***
   a. Hyperkalaemia
   b. Hypokalaemia
   c. Hyperphosphataemia
   d. Hypocalcaemia

2. ***Proposed by Cairo-Bishop in 2004, clinical tumour lysis syndrome (CTLS) is defined as…***
   a. Laboratory TLS plus one or more of the clinical manifestations: increased serum creatinine level, cardiac arrhythmias, seizure or death
   b. One metabolic derangement plus one clinical manifestation
   c. One metabolic derangement plus two clinical manifestations
   d. Laboratory TLS plus two or more of the clinical manifestations

3. ***Apart from the type of malignancy, which of the following is/are also considered when evaluating the risk of tumour lysis syndrome?***
   i. Red blood cell count
   ii. White blood cell count
   iii. Lactate dehydrogenase
   a. i and ii
   b. ii only
   c. iii only
   d. ii and iii

4. ***Which of the following statement is true regarding the risk of tumour lysis syndrome in newly developed cancer therapies?***
   a. New cancer therapies are proven to be less likely to cause tumour lysis syndrome.
   b. Prevention of tumour lysis syndrome is not necessary when new cancer therapies are used.
   c. The incidence rate of tumour lysis syndrome in new cancer therapies is not well examined.
   d. Tumour lysis syndrome associated with the use of new cancer therapies is heavily reported in the literature.

5. ***In patients with intermediate risk of developing tumour lysis syndrome, which of the following preventive measures are required when chemotherapy is to be initiated?***
   a. Monitoring, hydration
   b. Monitoring, hydration, allopurinol
   c. Monitoring, hydration, rasburicase
   d. Monitoring, hydration, allopurinol, rasburicase

6. ***What medication can be given to promote diuresis when urine output remains low despite increased hydration in patients who are not volume-depleted?***
   a. Loop diuretics
   b. Potassium-sparing diuretics
   c. Sodium bicarbonate
   d. No medication should be given

7. ***Which of the following is/are considered a drawback of allopurinol in tumour lysis syndrome prophylaxis?***
   a. It can cause xanthine nephropathy.
   b. It takes several days to lower and normalise uric acid levels.
   c. It is associated with severe hypersensitivity reactions.
   d. All of the above

8. ***Which of the following is one of the rare severe adverse reactions of rasburicase?***
   a. Anaemia
   b. Methaemoglobinaemia
   c. Neutropenia
   d. Thrombocytopenia

9. ***Which of the following is/are appropriate management of hyperkalaemia?***
   i. Avoiding potassium from all medical treatment
   ii. Sodium polystyrene sulfonate
   iii. Insulin-glucose infusion
   a. i only
   b. ii only
   c. i and ii
   d. i and ii and iii

10. ***Which of the following is an appropriate approach when a patient with established tumour lysis syndrome has persistent fluid overload and electrolyte imbalances?***
    a. Loop diuretics
    b. Peritoneal dialysis
    c. Haemodialysis
    d. Kidney transplant

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 281(D&T)

Cardiovascular and Renal Benefits of SGLT-2 Inhibitors – Is It a Class Effect?

1. B 2. D 3. D 4. C 5. C 6. B 7. B 8. B 9. C 10. A

Nutritional Approach in Managing Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is an age-related neurodegenerative disease which affects more than 20-30% of the elderly population aged 80 years or older. It is characterised by the decline in memory and cognitive function, as well as behavioural and psychological changes. Current pharmacological treatment focuses on regulating neurotransmitter-induced neuronal degradation, instead of managing neurological degeneration cascade. It could possibly lead to ineffective treatment. Adverse effects of the medications may also cause early treatment termination. Nutritional approach, which offers a better side effect profile and an economic benefit, has been widely studied. It is able to target the well-established neuro-degeneration cascade of Alzheimer's disease and is proven to provide favourable clinical outcome. A nutritional drink containing predominantly polyunsaturated fatty acids has demonstrated clinical benefit in managing early Alzheimer's disease. Different dietary patterns which might be effective in primary prevention of Alzheimer's disease have also been identified. This review summarises the current evidence of nutritional management that could be provided in primary care setting to manage Alzheimer's disease.

Keywords: *Nutritional Management, Dietary Patterns, Alzheimer's Disease, Dementia, Nutritional Counselling*

INTRODUCTION

Alzheimer's disease (AD) is a progressive, age-related and neuro-degenerative disease that manifests gradual reduction in cognitive function, memory and ability of self-care.[1,2] Rising incidence of AD has been expected due to the increased life expectancy and an aging population.[3] A long-standing hypothesized pathophysiology suggested that the abnormal processing of β-amyloid, which leads to tau phosphorylation and the formation of plaque and neurofibrillary tangles, will result in neuronal death.[4] It is believed that a neurological cascade including oxidative stress, mitochondrial dysfunction and brain neuroinflammation, also takes part in the neuronal damage process.[4]

PHARMACOLOGICAL INTERVENTION

Current pharmacological therapy of AD approved by the Food and Drug Administration includes acetylcholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonist.[5] Both of them specifically target the neurotransmitter-induced neuronal degradation, but not the neurological degeneration cascade. Although they demonstrated an improvement in cognitive function, mood control, behavioural symptoms and quality of life, the effectiveness is modest and not guaranteed.[4,6] Unfavourable side effects and intolerance are possible which limit the use of these pharmacological therapies.[4] Furthermore, the new drug therapy such as monoclonal antibodies targeting the β-amyloid production and aggregation has been under investigation, yet it barely achieves adequate clinical benefits in disease modification of AD.[7,8]

NUTRITIONAL MANAGEMENT IN PATIENT WITH AD

Nutritional approach is one of the current research directions. An effective nutritional and dietary intervention can reduce financial cost and improve tolerability.[9] Different diets and nutrients have been identified with clinical benefits in primary prevention and treatment of mild cognitive impairment (MCI) and AD. They target the pathological pathway at neuronal damage, such as synaptic loss and oxidative stress.[9,10] By reducing the rate of neuron degeneration, they help delay the onset of dementia and are able to slow down the progression of AD.[4]

NUTRITIONAL THERAPY FOR TREATING EARLY AD

A nutritional drink has demonstrated clinical benefits in several randomised clinical trials (RCT)[4] and is readily accessible in community pharmacy. In a RCT consisting of 259 untreated elderly subjects with a MMSE score ≥20 (Souvenir II), the arm with a daily nutritional drink consumption showed a better modified Neuropsychological Test Battery (NTB) memory domain score (z-score), which analysed the memory function, after 24 weeks.[4,11] Moreover, no significant difference in adverse effect and intolerability when compared to

control group was observed.[4] However, it did not provide long term benefit in executive function, with insignificant difference in the Disability Assessment for Dementia and the executive function domain of the NTB.[4] Overall, it agreed on the hypothesis that the nutritional drink supported synaptic formation and improved memory function in early AD, which could be considered as one of the treatment considerations.[4] The suggested standard dose of this currently marketed nutritional drink is one bottle per day to manage early AD **(Table 1)**.[4]

Table 1. Components in the Daily Intake of the Nutritional Drink[4]

Nutritional component	Quantity per daily intake of the nutritional drink (Souvenaid®)
Fish oil	
Docosahexaenoic acid (DHA)	1200 mg
Eicosapentaenoic acid (EPA)	300 mg
Others	
Uridine monophosphate (UMP)	625 mg
Choline	400 mg
Phospholipids	106 mg
Ascorbic acid (Vitamin C)	80 mg
Vitamin E	40 mg
Pyridoxine (Vitamin B6)	1 mg
Folic acid	400 mcg
Selenium	60 mcg
Cobalamin (Vitamin B12)	3 mcg

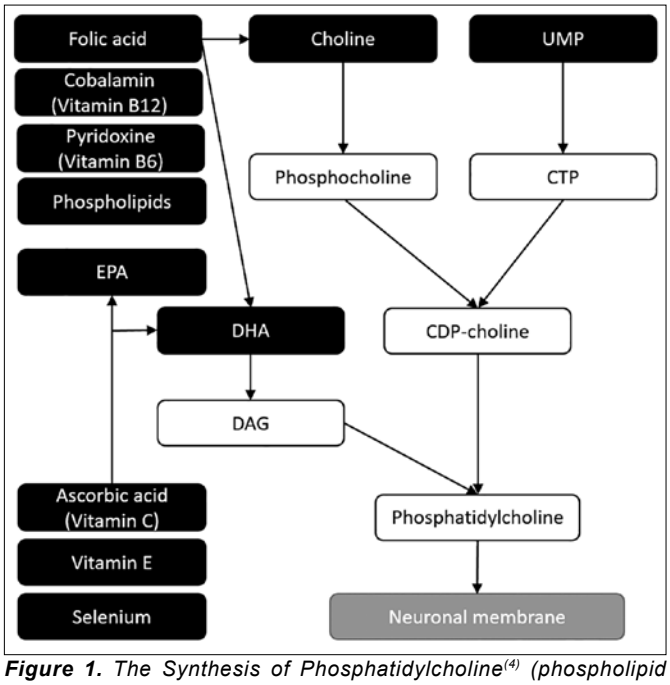

Figure 1. *The Synthesis of Phosphatidylcholine[4] (phospholipid in synaptic membranes) CDP, cytidine diphosphate; CTP, cytidine triphosphate; DAG, diacylglycerol; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; UMP, uridine monophosphate Omega-3 polyunsaturated fatty acids (EPA and DHA), choline and uridine monophosphate are the major precursors for neuronal membrane phospholipids formation; and phospholipids, folic acid and B Vitamins are co-factors to enhance bioavailability of the precursors. Vitamin C, Vitamin E and selenium have the role of protecting neuronal membrane from oxidative stress and damage. Increasing dietary supply of these precursors could enhance the production of phospholipids and synaptic membranes in the brain.*

FISH OIL

The main component in this nutritional drink is fish oil, which is composed of Ω-3 polyunsaturated fatty acids, namely docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Fish oil has been studied in clinical trials and animal studies, which showed an established beneficial effect in reducing risk of dementia and increasing attention.[4,12-14] It is believed that these components act as major precursors for neuronal membrane synthesis and subsequently new synapses formation.[4] Thus, it is able to reduce synaptic loss and slow down the progression of aging and AD **(Figure 1)**.[4] Observational study demonstrated that DHA (50-300 mg/kg/day) could increase the dendritic spine density.[4] It was believed to improve synaptic membrane and phospholipid formation within the hippocampus.[4]

DIETARY PATTERNS FOR PRIMARY PREVENTION IN AD

Studies have also investigated different dietary patterns. They are expected to show a synergistic interaction to modulate disease progression and prevent typical pathological process of AD.[9] In particular, the Mediterranean diet (MeDi), the Dietary Approaches to Stop Hypertension (DASH) diet, the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet and Intermittent Fasting (IF) have been studied for their anti-oxidant and anti-inflammatory effects.[9] These effects might be associated with brain protection property and hence help prevent MCI and AD.[9]

MEDITERRANEAN DIET (MeDi)

The MeDi, originated from Mediterranean regions, consists of a high intake of foods containing unsaturated fatty acids such as nuts, seeds, fish (polyunsaturated fatty acid), and olive oil (monounsaturated fatty acid), as well as vegetables and fruits **(Table 2)**.[9] These food components have established antioxidant and anti-inflammatory effects, which are believed to lessen oxidative stress in the neuronal damage cascade.[15] Recent multicentre RCTs reported that an increased adherence to this diet was associated with an increase in the mean Mini-Mental State Examination score and the reduction in risk in AD progression.[15,16] On the contrary, the latest two RCTs demonstrated no benefits in preventing or treating AD.[17,18] Despite of the broad heterogeneity in study design and analysis, which contributed to the contradictory results, several systematic reviews still managed to conclude that there was still a benefit from MeDi in reducing risk of neurodegenerative disease.[19-22]

Table 2. Type and Frequency of Consumption of Foods in MeDi[9]	
Mediterranean Diet (MeDi)	
Food Component	Frequency
Moderate-to-high consumption	
Whole-grain cereals	1-2 servings every main meal
Vegetables	≥2 servings every main meal
Fruits	1-2 servings every main meal
Olive oil	Every main meal
Olives / Nuts / Seeds	1-2 servings every day
Low-fat diaries	2 servings every main
Herbs / Spices / Garlic / Onions	Every day
Eggs	2-4 servings / week
White meat	2 servings / week
Fish / Seafood	≥2 servings / week
Potatoes	≤3 servings / week
Legumes	≥2 servings / week
(Red) wine	N/A
Low consumption	
Added salt	N/A
Red meat	<2 servings / week
Processed meat	<1 servings / week
Sweets	≤2 servings / week

DIETARY APPROACHES TO STOP HYPERTENSION (DASH) DIET

The DASH diet, established by the National Heart, Lung, and Blood Institute consists of a high intake of blood pressure-reducing nutrients such as lean meat, dietary fibres and low-fat dairy products **(Table 3)**.[9] It aims to reduce the intake of sodium, low-density lipoprotein cholesterol and saturated fat, in order to reduce risk factors for cardiovascular disease such as high blood pressure and cholesterol.[9] These risk factors, including insulin resistance, oxidative stress and neuronal inflammation, are postulated to be involved in the pathophysiology of AD.[9] However, studies on DASH diet are limited, with only one RCT of small sample size (124 participants) showed improvement in psychomotor function.[23,24] Observational studies suggested that the higher the adherence to DASH diet, the better the average cognitive function within 10 years.[25-27] Adhering to the DASH diet for more than 10 years was not yet proven to provide additional benefit.[23]

MEDITERRANEAN-DASH INTERVENTION FOR NEURODEGENERATIVE DELAY (MIND) DIET

The MIND diet combines the elements of both Mediterranean and DASH diets. It consists of a high amount of nuts, olive oil, fish, vegetables and fruits, similar to the Mediterranean diet, as well as a low consumption of unhealthy diet, as suggested in the DASH diet **(Table 4)**.[23] Better cognitive performance has been reported from several cross-sectional and cohort studies while there is no clinical trial published yet to study the association.[23,28,29]

Table 3. Type and Frequency of Consumption of Foods in DASH Diet[9]	
Dietary Approaches to Stop Hypertension (DASH) diet	
Food Component	Frequency
Moderate-to-high consumption	
Whole-grain products	Every day
Vegetables	Every day
Fruits	Every day
Diary products	N/A
Poultry	2 servings / week
Fish / Seafood	1-2 servings / week
Legumes	2 servings / week
Low consumption	
Saturated fats	N/A
Total fats	N/A
Salt (sodium)	N/A
Sweetened beverages	N/A
Red and processed meats	N/A

Table 4. Type and Frequency of Consumption of Foods in MIND Diet[30]	
The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet	
Food Component	Frequency
High consumption	
Whole-grain products	≥3 servings / day
Green leafy vegetables	≥6 servings / week
Vegetables	≥ 1 servings / day
Berries	≥2 servings / week
Olive oil	Primary oil used
Fish	≥1meals / week
Beans	>3 meals / week
Poultry	≥2 meals / week
Moderate consumption	
Alcohol / Wine	1 glass / day
Low consumption	
Red meat and products	<4 meals / week
Pastries and sweets	<5 servings / week
Cheese	<1 servings / week
Butter / Margarine	<1 time / day
Fast fried foods	<1 time / week

INTERMITTENT FASTING (IF) & CALORIE RESTRICTION (CR)

Another approach is IF or CR, which is postulated to be effective in promoting neurogenesis of the hippocampus and improving neuronal plasticity **(Figure 2)**.[9,31] One of the popular methods of IF is the Leangains protocol with an eating pattern of eight-hour eating and 16-hour fasting.[31] It is believed to stimulate the activation of cAMP responsive substance binding signal in neurons at hippocampus and entorhinal cortex which helps in neurotransmission and memory formation.[31] An animal study suggested a better learning and memory function whereas a human observational study involving 99 elderly subjects diagnosed with MCI demonstrated a better cognitive score and function after 3 years of

follow-up.[32,33] Studies also mentioned that in elderly patient, CR had a possibility of intolerability and chronic malnutrition, while IF did not restrict daily calories intake and was safer for implementation.[31,34]

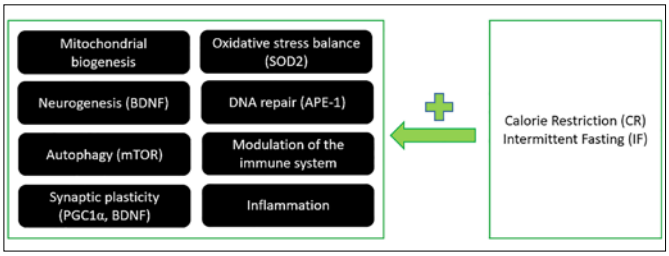

Figure 2. *Signal Pathways Involving in Neuronal Modulation Pathway[9] IF positively modulates these pathways including mitochondrial biogenesis, neurogenesis, synaptic plasticity and oxidative stress balance. These modulation provides benefits in neuroprotection.*

CONCLUSION

Nutritional intervention can be one of the strategic approaches to prevent and manage Alzheimer's disease. It improves tolerability and adherence compared to pharmacological treatment. With the current review and update, pharmacists in primary care are able to provide dietary counselling and patient education regarding the clinical benefits of the nutritional products. On the other hand, nutritional approach has not yet been included in international guidelines, nor studied in a large population. Further research is necessary to explore the role of the above-mentioned and other nutritional interventions for Alzheimer's disease. Additional research is also important to identify clinical outcome in the patients with moderate and severe Alzheimer's disease, so as to improve the quality of life in both patients and caregivers.

Author's background

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Review of the Importance of DHA and Choline and its Synergistic Effect on Maternal Health and Early Childhood Development

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ABSTRACT

DHA and Choline play an important role in brain and eye development during fetal and early childhood periods. Data from different countries have shown that the dietary intake of both DHA and Choline do not meet the recommended levels during pregnancy. Current evidence shows that DHA and choline can exert positive effect on maternal health and pregnancy outcomes. Recent studies also suggest that choline may act in synergy with DHA to maintain the structural integrity of the membrane in nervous system and support eye health and development. It is found that maternal consumption of choline and DHA could affect nutritional intake of the child through placental transmission and breastmilk. A balanced diet with food high in DHA and choline is needed to fulfil the recommended intake with supplementation a solution for those unable to obtain sufficient levels from their diet.

Keywords: *Docosahexaenoic acid (DHA); Choline; Synergistic Effects; DHA Choline Nutritional Status*

INTRODUCTION

Current evidence shows that DHA and choline may exert positive effect on maternal health and pregnancy outcomes, and that maternal DHA and choline supplementation may improve the neurodevelopment and atopic diseases of the infant.[1-3] While DHA is widely known for its importance during pregnancy and lactation, it is important to note that choline as an essential component of membrane phospholipid also plays a role in supporting the developing brain and eye.[1] In fact, recent studies suggest that choline may act in synergy with DHA to maintain the structural integrity of the membrane in nervous system and support eye health and development of the infant, in which they regulate the biosynthesis of glycerophospholipids - phosphatidylcholine and phosphatidylserine, the important components of cell membrane. This raises the importance of dietary intake of both of these nutrients during pregnancy and lactation. Epidemiology studies in different countries have shown suboptimal nutritional intake of DHA and choline among pregnant women.[4-8] Dietary modification or supplementation may hence be warranted when diet alone cannot fulfill intake needs.

FETAL DEVELOPMENT

Brain and eye developments start as early as the fetal period. The brain grows rapidly during pregnancy and early life with brain weight increasing from 100g at 30 weeks of gestation to nearly 400g at birth.[9] Its weight further rises to 1,100g at 18 months of age, indicating a more than 10-fold increase in brain size.[10] As the brain grows through processes such as neurogenesis and synaptogenesis, multiple physiological functions start to develop. For example, the ontogenesis, which builds on one another, begins with the development of senses including vision and hearing, followed by language skills and eventually higher cognitive functions. Brain development lays the foundation for subsequent functional growth, any alterations may adversely affect brain function and lead to lasting cognitive effects.[11]

ROLE OF DHA AND CHOLINE

Docosahexaenoic acid (DHA), a type of omega-3 fatty acid, plays an important role in lipid metabolism, cell signaling, supporting cell membrane function and eye development. On the other hand, according to the

National Academy of Medicine, choline is an essential nutrient which must be obtained from dietary intake. It is involved in lipid transport, supporting cell membrane structure and neurotransmission. In addition to their essential functions, DHA and choline are critical for brain and eye development of the infant.[1] DHA and choline, as a long-chain polyunsaturated fatty acid, are integral structural components of neurons.[1] They are also present in eyes which promotes retinal stem cell development, protects retinal photoreceptors from apoptosis and supports photoreceptor differentiation.[12] Hence, it is suggested that inadequate intake may result in visual and neurocognitive deficits.[1] In fact, from 30 weeks of gestation to 18 months of age, a 35-fold increase in DHA content of the brain is observed. DHA supply during this period is therefore considered vital for fetal growth and development of the brain.[10] Moreover, the importance of choline for fetal growth is evident by the rise in maternal plasma free choline during pregnancy. It is discovered that the content of choline in placenta is about 50 times higher than that in maternal blood.[13]

SCIENTIFIC EVIDENCE ON DHA SUPPLEMENTATION DURING PREGNANCY AND LACTATION

Effect on pregnancy outcomes and neonatal conditions

In a meta-analysis involving 10,806 participants, studies included showed that supplementation of n-3 fatty acids exerted a protective role in preeclampsia (Relative risk: 0.82; p = 0.024).[14]

It was shown that the postpartum depression score decreases with an increase in maternal DHA intake from seafood by another study. Kyushu Okinawa Maternal and Child Health Study was conducted to find out if there is any association between fish intake and depression (EPDS), and 1745 women were involved. It was found that women at 4th quartile (Q4) consumed 460 mg DHA daily, while 1st quartile (Q1) had 140 mg DHA daily. Compare to Q1, women at Q4 who ate much more fish had an odds ratio of 0.61 (p = 0.01) in terms of depressive symptoms in pregnancy; women at Q4 who took in much more DHA had an odds ratio of 0.64 (p = 0.007) in terms of depressive symptoms in pregnancy.[15]

The Cochrane analysis including 70 RCTs with 19,927 women compared omega-3 long-chain polyunsaturated fatty acids (LCPUFA) interventions with placebo or no supplementation. In the overall analysis, preterm birth < 37 weeks (RR 0.89, 95% CI: 0.81 to 0.97) and early preterm birth < 34 weeks (RR=0.58, 95% CI 0.44 to 0.77) were reduced in intervention arms. As for infant, a reduced risk of perinatal death (RR 0.75, 95% CI 0.54 to 1.03) and of neonatal care admission (RR 0.92, 95% CI 0.83 to 1.03), and a reduced risk of LBW babies (RR 0.90, 95% CI 0.82 to 0.99) were shown.[16]

Effect on children's brain and visual development

A randomized control trial conducted by Judge et al. recruited 48 pregnant women. They were randomized from 24th week of pregnancy until delivery to take omega-3 LCPUFA cereal bars containing 300 mg DHA an average of 5 days per week (mean daily DHA intake = 214mg) or placebo bars. The sleeping pattern of the infants were assessed in the first 48 postnatal hours. A significant difference in arousals in quiet sleeps was observed on both day 1 (p=0.006) and 2 (p=0.011) with intervention group having fewer arousals. Arousals in active sleep on day 1 were also significantly lower in intervention group (p=0.012). Moreover, the mean acuity scores were 3.8 cycles/degree in DHA group while 3.2 cycles/degree in placebo group, with the effect being significant at four months of age (p = 0.018) but not at six months.[17] At the age of nine months the Infant Planning Test was carried out. It is shown that DHA supplementation had significant effects on the performance of problem-solving tasks but no significant differences in terms of intelligence as measured by Fagan Test of Infant Intelligence.[18]

From a recent triple-blind randomized controlled trial, the daily supplementation of 120 mg DHA and 180 mg EPA beginning of second trimester up to 1 month post-delivery showed higher mean scores of neurodevelopment of the infant at the end of four and six months compared to placebo in each tested domain. However, a statistically significant difference was observed only in the communication domain at the 4th month. And no significant differences in weight, length or head circumference were observed between the two groups.[19]

Jensen et al. randomized lactating women to receive either 200 mg DHA per day or placebo four months after delivery. At four months postpartum, milk lipid and plasma phospholipid DHA contents of the intervention and placebo groups were around 75% and 35% higher respectively. DHA supplementation resulted in higher psychomotor development index at 30 months of age.[20] Five years later, the children who had been breastfed by the DHA supplemented mothers showed higher sustained attention scores, suggesting that DHA intake during early infancy confers long-terms benefits on neurodevelopment.[2]

Effect on children's risk of respiratory symptoms and allergies

A randomized controlled trial with 1094 pregnant women involved shows that taking 400 mg daily algal DHA from 18th to 22nd gestation week to delivery can reduce the incidence rate ratio (IRR) of severe respiratory symptoms for example, nasal discharge or nasal congestion (IRR=0.78; 95% CI 0.60 to 1.02) and fever with phlegm and nasal discharge or nasal congestion (IRR=0.53; 95% CI 0.29 to 0.99) for the infant of atopic mothers until 18-month-old.[21] Another randomized controlled trial showed that fish oil intake during pregnancy can reduce asthma happening on children up to 16-year-old.[3]

SCIENTIFIC EVIDENCE ON CHOLINE SUPPLEMENTATION DURING PREGNANCY AND LACTATION

Effect on risk of neural tube defects

Shaw et al. analyzed in a nested case-control study the choline serum specimens in 489 pregnant women between 15th-18th week of gestation and used a retrospective food frequency questionnaire to assess choline intake. The serum level of choline was measured. The level of total choline in cases of neural tube defects are lowered than that in controls by more than one-half standard deviation. It is discovered that elevated risks of neural tube defect were associated with lower levels of total choline and reduced risks with higher levels of choline.[22] This would support the results from animal studies which identified choline as a mandatory nutrient for normal neural tube closure in early pregnancy.[23]

Effect on children's cognitive development

Caudill et al. recruited 29 women entering their 3rd trimester and supplemented them with either 480 or 930 mg choline every day until delivery. Processing speed of their infants were analyzed at the time point of 4, 7, 10, and 13 months after birth and was found to be faster in those whose mothers had been supplemented with 930 mg of choline per day during their pregnancy until delivery. Yet, the supplementation of a smaller dose of 430 mg was also shown to be effective: there was a significant linear effect of exposure duration, in other words, infants with longer exposure showed faster reaction times. This implies that even modest increases in maternal choline intake during pregnancy may produce cognitive benefits in offspring.[8] Later follow-up showed that at the age of 7 years, children whose mothers consumed 930 mg choline per day were more likely to solve problems at the first attempt and thus providing supporting evidence that increased maternal choline intake improves child cognitive functioning in the school-age years.[24]

One observational study done by Wu et al found that increased choline status in the first half of the pregnancy (16 weeks of gestation) is associated with improved cognitive development in the infant assessed at the age of 18 months. Moreover, each 1 mcmol/L increase in maternal plasma free choline at 16 weeks gestation was associated with an increase by 2.23 points in infant cognitive test score based on the Bayley Scales of Infant Development, Third Edition (BSID-III) at 18 months of age.[25]

At present, there has only been one randomized, double-blind, controlled study performed on choline supplementation in breastfeeding women of term-infants. In this study, 750 mg of choline was supplemented per day from the 18th week of pregnancy until 3 months post-partum with no effects seen in memory, language development, and global development of the infant at age 10 and 12 month.[26]

SYNERGISTIC EFFECTS OF DHA AND CHOLINE

Maintain structural and functional integrity of the neuronal tissue

Glycerophospholipids, being the most common glycerol backbone lipid in eukaryotic cells, consist of two hydrophobic fatty acid molecules with DHA being one of the components, and a hydrophilic phospholipid, which give rise to its amphiphilicity. **Figure 1** demonstrates the structure of a glycerophospholipid and the role of DHA and choline in it. This hydrophilic head-hydrophobic tail nature makes it suitable for the formation of membranes. Diacyls are the most abundant glycerophospholipids and its classification is based on the head groups such as choline, ethanolamine, and serine. In fact, phosphatidylethanolamine (PE) accounts for nearly half of the total phospholipids in human, and more importantly, it is mainly found in nervous system tissues, for example, neural tissues, spinal cord and nerves.[27] This suggests the significant role of glycerophospholipids in supporting nervous system health and development.

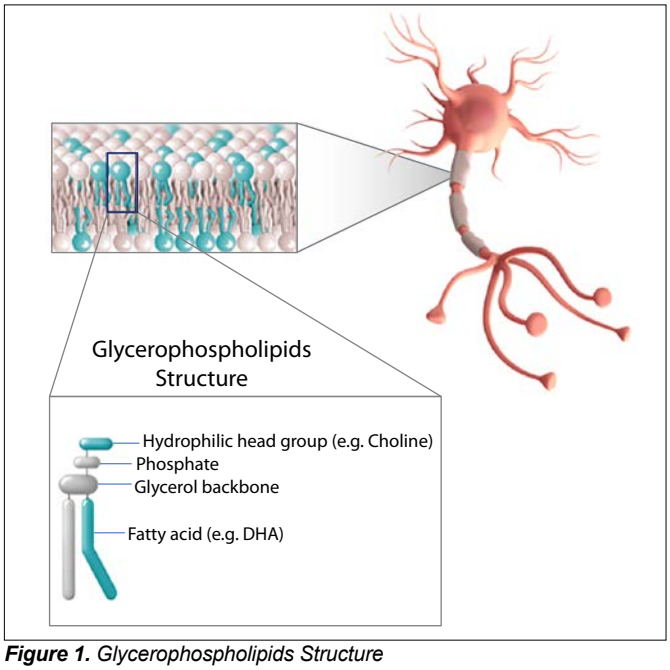

Figure 1. *Glycerophospholipids Structure*

The brain has a unique fatty acid composition with high levels DHA, but low levels of other omega-3 PUFAs, such as EPA and DPA. Brain EPA levels are in general about 300 times lower than DHA with DHA make up 50% of the total brain lipid and up to 15% of total fatty acids. Therefore, DHA, as implied by its relative abundance, is the most important omega-3 PUFA in brain.[27, 28] One of the major roles of DHA in maintaining structural integrity of eukaryotic cells is to regulate phosphatidylserine (PS) biosynthesis and accumulation, which is subject to the level of membrane DHA. It is in fact the PS species of highest abundance in brain. The biosynthesis of PS relies on serine base exchange with pre-existing phosphatidylcholine (PC) or PE.[28]

As for choline, phosphatidylethanolamine N-methyltransferase (PEMT) pathway is responsible for endogenous synthesis of PC from PE. It is discovered that a higher choline intake will support the PEMT pathway through increasing the availability of methyl donors generated from its metabolite – betaine, evidenced by the study that compared to supplementation of either choline or DHA alone, a higher choline intake together with DHA produce the greatest increase in erythrocyte phosphatidylcholine-DHA (PC-DHA), which reflects the tissue DHA content of liver, brain, retina and adipose and serves as a proxy for PEMT activity.[1,29] Bernhard et al. also conducted a randomized partially blinded trial in preterm infants to compare the effects of exclusive choline and DHA supplementation, combined supplementation, and standard feeding on their nutritional status. Results showed that choline supplementation alone cause no significant increase in PC-DHA, while DHA supplementation alone raise PC-DHA by 35%. The greatest increase is observed in combined supplementation with PC-DHA increasing by 63%.[30] These suggest that there is a metabolic synergy between DHA and choline as linked by PC and their actions are not mutually exclusive. A study on mice also found that deficiency in PEMT gene is associated with disrupted fetal hippocampal development which can be reversed by maternal DHA supplementation. As for wild type genes, DHA supplementation also reduce neural apoptosis rate by half.[1] On a clinical level, Cheatham et al. through an observational study demonstrated that DHA and choline interaction was significant for the difference in latency scores at midline, frontal and central areas, which reflected brain electrical activity. Also, higher choline and DHA content was associated with better recognition memory.[31]

These preclinical and clinical findings illustrated the synergistic effect of DHA and choline in infant neurocognitive development via different mechanisms.

Support inner retinal networks by maintaining neurotransmitter balance

DHA has been shown to stimulate choline acetyltransferase (ChAT) enzymatic activity which catalyzes the biosynthesis of acetylcholine (Ach) from coenzyme and choline. It is suggested that ChAT and acetylcholinesterase (AChE) activities will act together to maintain a suitable balance of ACh and thereby support the development of inner retinal networks.[32] The inner retinal networks consist, among others, of amacrine and ganglion cells. Amacrine cells have various functions such as allowing the detection of directional motion and modulate light adaptation. Ganglion cells transmit information from the retina to several brain regions for further processing.[33]

Table 1 summarized the synergy of DHA and Choline in supporting brain and eye growth and development.

MATERNAL NUTRITIONAL SUPPLY

Choline

Placental transmission

The Phosphatidylethanolamine N-methyltransferase (PEMT) pathway is responsible for de novo biosynthesis of phosphatidylcholine which can be incorporated into very low-density lipoprotein (VLDL) followed by releasing into circulation from liver. The liver can also synthesize apolipoprotein A-1, a lipid-poor high-density lipoprotein (HDL) which obtains other lipoproteins and phosphatidylcholine from peripheral tissues to form mature HDL. The lipoproteins generated will then be made available to the fetus after entering the placental cells via a receptor mediated process. Besides, the newly synthesized phosphatidylcholine can be hydrolyzed into free choline which is then secreted to circulation and taken up by placental. Note that dietary consumption is required to meet the high demands of fetus for choline.[13]

Breastmilk

In fact, mature human milk contains large amount of choline, ranging from 104 to 156 mg/L, in which 45% of choline exists in the form of phosphocholine, while glycerophosphocholine, sphingomyelin, free choline and phosphatidylcholine account for 29%, 10%, 9%, and 7% correspondingly. This is further supported by the findings that the serum free choline concentration in lactating women increases by up to 100%, which is believed to ensure a sufficient amount of choline will be taken up by mammary glands. Choline uptake by mammary gland is mediated by the concentration gradient and the sodium-dependent transporter under the secondary active transport system.[13] It is noticed that the concentration of free choline in breastmilk is 10-15 times higher than that in circulation and its contents are subject to individual variability with the choline levels in milk correlated with serum free choline, phospholipid-bound choline and glycerophosphocholine concentrations and lactating days.[34]

Table 1. Summary of the synergism of DHA and choline in supporting brain and eye growth and development

Component	Functions	Synergistic Effect
Choline	Hydrophilic head group to support the PEMT pathway responsible for the formation of PC through increasing the availability of methyl donors. PC is later converted to PS.	Exert metabolic synergy to maintain structural integrity of the nervous system including visual cortex
DHA	Hydrophobic fatty acids to regulate PS biosynthesis and accumulation	
Choline	Essential component of acetylcholine	Support inner retinal networks by maintaining neurotransmitter balance
DHA	Stimulate ChAT activity to facilitate acetylcholine biosynthesis from choline, which maintains neurotransmitter balance and supports retinal development	

DHA

Placental transmission

There is preferential uptake and delivery of DHA during pregnancy. Maternal total fatty acid concentration in circulation increases at the late stage of pregnancy. This can be partly attributed to the increase in estrogen levels which results in the predominance of lipid catabolism in late pregnancy phases in place of the lipid storage in early phases. The temporary hyperlipidemia raises the availability of fatty acid to placenta. The placental lipoprotein lipase and epithelial lipase residing on the microvillous membrane of the synctiotrophoblasts which faces the maternal compartment release fatty acid from triglyceride (TG)-rich lipoproteins in maternal circulation so as to allow placental uptake of non-esterified fatty acids, one of which is DHA. It is discovered that the concentration of DHA and arachidonic acids in the placental intervillous space are approximately 4 times higher than that in maternal circulation at the time of delivery, implying that placental lipase release LCPUFA from TGs in a selective manner. The activity of placental lipase also increases during the third trimester which is presumably to support placental fatty acid transmission to meet the highest fetal demand for fatty acid. It is assumed that DHA may enter placenta through passive diffusion and certain membrane-bound carrier proteins.[35]

Breastmilk

Maternal LCPUFAs are provided to the offspring via lactation after birth.[36] The maternal plasma and breastmilk fatty acid level were measured in 89 lactating women 4-6 weeks postpartum who were randomized to receive either 200 mg, 400 mg DHA or placebo for 6 weeks with no diet modifications. Breastmilk and maternal plasma DHA were significantly greater in participants taking 200 mg and 400 mg DHA compared to those without. Infant plasma omega 6:3 and arachidonic acid (AA):DHA ratios were significantly higher among placebo group when compared to DHA groups.[37]

INCREASING DEMAND DURING PREGNANCY

DHA requirement of the fetus increases across pregnancy, with the peak occurring after week 32, approaching the end of the third trimester during. This is the time when the fetal brain tissue is undergoing a significant development during which fetus accrues up to 70mg DHA per day. As mentioned above, maternal dietary intake and circulating concentration of DHA are important sources of supply of DHA to the fetus.[1,38] Hence, higher maternal DHA intakes may be required during pregnancy particularly at the late stage to meet the increasing demand.

The increase in demand for choline during pregnancy is evident by depletion of choline-derived methyl donors in pregnant women compared to nonpregnant women. A study conducted by Yan et al. has shown that pregnant women at their third trimester have lower circulating concentrations of choline-derived methyl donors, for example, 55% lower plasma betaine, 38% lower plasma dimethylglycine, and 49% lower serum sarcosine than non-pregnant women.[39] The depletion during pregnancy can be attributed to two main reasons: increase in demand for betaine as methyl donor in PEMT pathway, and decrease in betaine production from choline due to preferential supply of choline to cytidine diphosphate-choline pathway for PC biosynthesis.[40]

The rise in demand for the nutrients is supported by the increase in recommended intake during pregnancy. According to the National Institutes of Health, the adequate intake (AI) for women at the age of 19-50 is 1.1g of total omega-3 fatty acids and increases to 1.4g during pregnancy.[41] As for choline, the AI for women at the age of 19 or above is 425mg per day, while for pregnant women, the AI increases to 450mg per day.[42]

NUTRITIONAL STATUS DATA AND RECOMMENDED INTAKE

The Food and Agriculture Organization of the United Nations (FAO) have recommended that adult pregnant and lactating women to have a minimum intake of 300mg per day of EPA+DHA, or which 200mg per day of DHA for optimal adult health and fetal and infant development.[43] Meanwhile, for choline, according to the National Academy of Medicine, the adequate intake for choline during pregnancy and lactation are 450mg and 550mg per day respectively.[42]

Table 2. The mean dietary intake of DHA and choline of pregnant women in relation to the recommended dietary intake

Nutrients	Region	Mean Intake [mg/d]	Recommended dietary intake (RDI) [mg/d]	Percentage of RDI [mg/d]
DHA	China	38.3[4]	200	9.45%
	Taiwan	143[5]		46.50%
	US	67.5[6]		33.75%
Choline	Australia	252.91[7]	450	56.20%
	US	300-350[8]		66.67%-77.78%

Table 2 illustrates the mean intake of DHA and choline of the concerned populations in China, Taiwan and the US. None of the regions meet half of the RDI of DHA, among only 27% of pregnant women at the age of 20-40 years in Taiwan reached the recommended intake of 200mg per day.[5] In China, significant difference in choline consumption across regions is observed: coastland region (28.6 mg/day) has the highest consumption, preceding lake land region (22.3 mg/day) and inland region (9.1 mg/day).[4] A global survey on omega-3 fatty acids also indicates that Japan and regions where people have yet to fully adapt to Westernized food habits in general have high EPA and DHA blood levels.[44] Therefore, it is presumed that dietary habit plays a vital role in their nutritional status. Taking Japan as an

example, fish, the richest source of DHA, composes a majority of their diet. When compared to western diet consisting of mainly meat, Japanese typically has better DHA status. This also applies to China where coastal areas have better accessibility to seafood, vice versa. It is worth noticing that China overall has poorer DHA intake than western population, which is probably attributed to infrequent consumption of fatty fish by Chinese.[4] Although there is no local data available currently, it is logical to assume that Hong Kong as a culture hub under the influence of both Asian and Western cultures might have nutritional status in between mainland China and the US, but is still below the RDI.

As for choline, although no data during pregnancy or lactation is available, it is observed that female at child-bearing age in general does not consume adequate choline. Hence, dietary modifications are warranted during pregnancy and lactation to meet the increasing need of choline.

DIETARY SOURCES OF DHA AND CHOLINE

DHA can be found in marine food, especially cold water and fatty fish, such as wild salmon, tuna, sardines, mackerel, oyster and mussels (see **Table 3**). For example, a single serving of cooked salmon can already fulfill the RDI. Plant sources, such as walnuts, flaxseeds, whole grains, only contain ALA, which can convert in human body to EPA and then to DHA, but only in very small amount. In fact, the DHA content of non-marine food is generally low, taking egg as an example, one boiled egg contains only 30mg DHA, accounting for 15% of the RDI; while nuts like almonds and walnuts contain no DHA.

Table 3. DHA Content of Selected Foods[45]

Food	Serving Weight (g)	DHA per serving (g)
Fish oil, salmon, ½ cup	109	19.9
Mackerel, baked or broiled, no added fat, ½ large fillet	170	2.7
Fish, salmon, Atlantic, wild, cooked, dry heat. 0.5 fillet	154	2.2
Fish, sardine, Pacific, canned in tomato sauce, drained solids with bone, ½ can	185	1.6
Fish, tuna, white, canned in water, without salt, drained solids, 1 can	172	1.2
Pompano, steamed or poached, ½ medium	170	0.8
Mussels, steamed or poached, 1 cup	150	0.8
Sea bass, baked or broiled, no added fat, ½ large fillet	128	0.7
Oysters, raw, 3 pacific oysters	144	0.2
Egg, whole, boiled or poached	50	0.03
Chicken breast, roll, oven-roasted	56	0.015
Milk, whole, 1 cup	244	0
Almonds, unsalted	28	0
Pork steak or cutlet, breaded or floured, broiled or baked, 1 small steak/cutlet	164	0

Choline can be found in most animal organs, including liver and stomach, also in poultry, beef, chicken meat, milk and dairy products. Choline can also find in plant sources, including beans, cruciferous vegetables, and whole grains. In general, meat and vegetables contain a certain amount of choline; yet, its content in bread, cheese and cereal, which are some common options for breakfast, are very low. (see **Table 4**)

Table 4. Choline Content of Selected Foods[46]

Food	Weight (g)	Milligrams (mg) per serving
Pork kidney, cooked, 1 kidney	142	723
Wheat germ, plain, 1 cup	113	202
Egg, whole, cooked, hard-boiled, 1 large	50	147
Salmon, raw, 3oz	85	80.4
Beef, roast, roasted, lean and fat eaten, 3oz	85	67.2
Chicken breast, baked, coated, skin / coating not eaten, 3oz	85	64.5
Almonds, unsalted, 3oz	85	42.9
Broccoli, cooked, boiled, drained, without salt, 0.5 cup, chopped	78	31.3
Milk, whole, 1 cup	244	43.4
Corn, sweet, yellow, frozen, kernels cut off cob, boiled, drained, without salt, ½ cup	82.5	18.2
Lettuce, cooked	86	10.1
Cheese, Cheddar, 1 slice	21	3.5
Kiwifruit, green, raw, 1 fruit	69	5.38
Bread, sour dough, toasted, 1 slice, snack-size	9	0.79
Cereal, frosted corn flakes, 1 serving box	32	0

CONCLUSION

While DHA has long been a nutrient of concern particularly during pregnancy for its beneficial effects on not only fetal growth but also maternal health, recent findings on the synergistic implications of DHA and choline in supporting brain and eye development raises our awareness in the potential benefits of concomitant consumption of the two nutrients (see **Table 5**). According to the Food and Agriculture Organization of the US, the minimum intake of EPA and DHA for maternal health and infant development during pregnancy and lactation is 0.3 g/d in total, among which DHA should comprise at least 0.2 g/d. Studies on the nutritional status of people living in different regions reveals that the consumption of DHA and choline is inadequate when comparing to the recommended intake level, which suggests that dietary modification or supplementation may be required. In light of the increasing demand for DHA and choline during pregnancy and lactation and the suboptimal nutritional status, it is suggested that pregnant and lactating women should seek dietary advice from nutritionists and other healthcare professional to ensure adequate consumption of DHA and choline from diet, with or without the help of supplements, during the critical timeframe of fetal growth.

Table 5. Summary of Clinical data on DHA and choline supplementation

Reference	Design	Setting; Participant	Intervention	Results
Judge et al, 2007[17] Judge et al, 2007[18]	Double blinded, placebo control, RCT	United States; hospital n = 48 pregnant women	Period: 24th week of pregnancy until delivery Form: cereal bar omega-3 LC- PUFAs/d: 240 mg DHA/d: average of 214 mg	Sleep patterning: Fewer arousals in quiet sleeps in DHA group on day 1 (2.7 vs 5.89, p=0.006) and 2 (3.55 vs 5.44, p=0.011) Fewer Arousals in active sleep in DHA group on day 1 (17.41 vs 20.41, p=0.012) Visual Acuity: Higher mean acuity scores in DHA group at 4 mos of age (3.7 vs 3.2, p=0.018) Intelligence: Better problem-solving at 9 mos of age: total average intention score (8 vs 6.7, p=0.017), total intentional solutions (2.5 vs 1.7, p=0.11)
Ostadrahimi et al, 2017[19]	Triple blinded, placebo control, RCT	Public healthcare centres in Tabriz, Iran n = 150 pregnant women	Period: 20th week of pregnancy until 30 days after delivery Form: capsule DHA+EPA/d: 120 mg DHA + 180 mg EPA (1'000 mg fish oil capsule)	Neurodevelopment was assessed with ASQ-2 (5 domains: gross motor, fine motor, problem solving, personal-social, and communication) Higher mean scores in intervention group in only communication domain at 4th month (adjusted difference=2.63, p=0.02)
Jensen et al, 2005[20] Jensen et al, 2010[2]	Double blinded, placebo control, RCT	United States, Texas hospital n = 227 breastfeeding mothers n = 160 breastfeeding mothers	Period: 5 days after delivery until 4 mos after delivery	At four months postpartum: Milk lipid and plasma phospholipid DHA contents of the intervention and placebo groups were approximately 75% and 35% higher respectively. DHA supplementation resulted in 8.4 points higher in Bayley psychomotor development index at 30 months of age. (p=0.005) Five years later: Children who had been breastfed by the DHA supplemented mothers showed higher sustained attention scores, as assessed by Sustained Attention Subscale of the Leiter International Performance Scale. (46.5 vs 41.9, p=0.008)
Shaw et al, 2009[22]	nested case-control study	USA, California (Orange, San Diego, and Central valley counties) n = 489 pregnant women	No choline supplementation. Measurement of serum specimens (incl. choline) the 15th-18th week of pregnancy	Elevated NTD risk was associated with the lowest decile of total choline (<2.49 mmol/L; OR=2.4, 95% CI 1.3 to 4.7) and reduced risk was seen in the highest decile of total choline (≥3.50 mmol/L; OR=0.14, 95% CI 0.02 to 1.0).
Caudill et al, 2018[8] Nevins et al, 2018[24]	Single centre, double blinded, RCT	USA, Cornell University n = 29 pregnant women	Period: 14th week of pregnancy until delivery Form: solution mixed with cranberry-grape juice Choline/d: 480 mg or 930 mg	Infant's processing speed Processing speed of their infants is 22.6 ms (p=0.03) faster in those with 930 mg/d than 480mg/d maternal choline dose. Significant linear dose-response showing that faster infant processing speed was associated with a greater number of days of fetal exposure to the 480 mg/d maternal choline dose (p<0.001). At the age of 7: Problem-solving Children whose mothers consumed 930mg/d choline were more likely to solve problems at the first attempt (OR=1.9, P = 0.03) when compared to those whose mothers consumed 480mg/d.
Cheatham et al, 2012[26]	Double blinded, RCT	USA, North Carolina, Raleigh-Durham-Chapel Hill n = 40 pregnant women	Period:18th week of pregnancy until 90 days after delivery Form: gel cap Choline/d: 750 mg Placebo (corn oil)	No effect on short-term visuospatial memory, long-term episodic memory, language development, global development at age 10 and 12 month.

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Applications of Next Generation Sequencing for Early Detection of Genetic Abnormalities and for Drug Discovery

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ABSTRACT

New Generation Sequencing (NGS) technology is an automated and high-throughput DNA sequencing method allows people to simultaneously analyze large numbers of nucleotides. This method can carry out an enzymatic sequential addition of nucleotides to immobilized DNA templates and significantly reduces sequencing cost with improved accuracy. There are several designs of NGS platform available in market. NGS technology has been applied to sequence circulating tumor DNA (ctDNA) in liquid biopsy or extract of target tissue in oncology. It can identify mutation and aberrations in DNA that render tumors exquisitely sensitive to certain therapies, resulting in real time exceptional responses. Hence, it has opened a broad new era of clinical applications for prompt screening of genetic diseases, cancer and for development of precise personalized medicine. This review paper addresses its principle of screening and discusses its applications in various biomedical fields.

Keywords: *next generation sequencing, genetic disease screening, cancer prevention, ctDNA, precise personalized medicine, drug discovery, COVID-19 vaccines*

INTRODUCTION

Genetic abnormality is a common problem in adult.[1] By 25 years of age, approximately 5% of individuals will suffer from a genetic disease. However, if disorders that have a genetic component in their causation are included, approximately 60% of the population will suffer from abnormality with a major or minor genetic contribution during their lifetime.[2-4] Cancer arises because of some genetic disorders taken place in cellular DNA. It is the second leading cause of death globally and is responsible for about 10 million deaths per year of the contemporary world. Globally about 1 in 6 deaths is due to cancer.[5] As shown in **Table 1** based on World Health Organization, the most common causes of cancer death in 2020 were lung (1.80 million cases), colon and rectum (935,000 cases), liver (830,000 cases), stomach (769,000 cases) and breast cancer (685,000),[6] while the order of incidence in Hong Kong was slightly different,[3] pattern of both reported incidence and mortal cases were roughly similar.

Table 1. Reported cancer incidence and cancer that causes death of human beings

Type of Cancer	No of Reported Cases			No of Mortal Cases		
	Global (milliom)[a]	Hong Kong[b]		Global Death (million)[a]	Hong Kong[b]	
		2010	2018		2010	2018
Lung	2.206	4,480	5,252	1.800	3,696	3,853
Colorectal	1.880	4,370	5,634	0.935	1,864	2,314
Liver	0.906	1,863	1,742	0.830	1,530	1,487
Stomach	1.089	1,107	1,277	0.769	686	687
Breast	2.261	3,025	4,645	0.685	566	756
Prostate	1.414	1,492	2,204	0.375	319	468
Skin	0.324	816	1,107	0.057	--	--
Leukaemia	0.474	--	--	0.312	--	349
Nasopharynx	0.737	858	--	0.724	652	311
Lymphoma	0.544	779	1,008	0.259	362	375
Corpus uteri	0.417	713	1,165	0.097	--	--
Total	19.292	26,390	34,028	9.958	13,076	14,594

Source: [a] **Year 2020** Data of Globocan,[6] accessed March 3, 2021; [b] Data of Hong Kong Cancer Registry, 2018[7]

Figure 1 is the distribution of Hong Kong's reported cancer in 2018. Four types of cancer, namely, colorectal, lung, breast and prostate cancers shared more than 50% of all incidences in Hong Kong.[7]

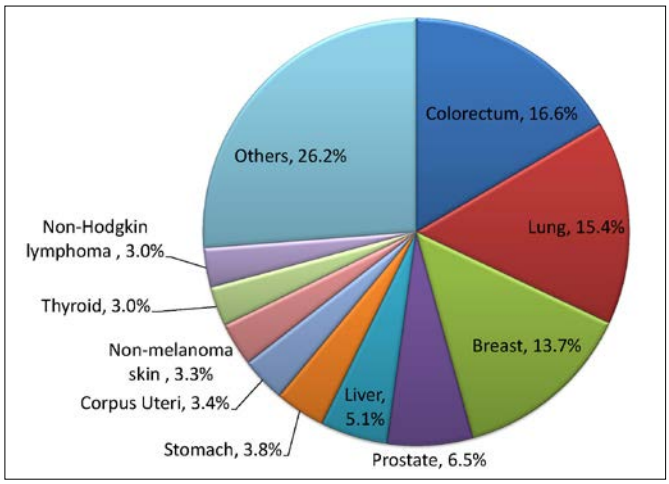


Figure 1. *Distribution of Hong Kong New Cancer Cases Registered in 2018.*[7]

WHAT CASUES CANCER?

Cancer is basically a disease of uncontrolled cell division. It arises from accumulations in cell of DNA alterations that are beyond repair.[8] When cells acquire a series of mutations that make them divide more quickly, escape internal and external controls on division, and avoid programmed cell death.[9,10] If someone inherits an aberrated gene from their parents, they prone to have higher incident rate of cancer at certain stage of their life. This explains why members from the same family quite often to have the same type of cancer in life because they all bear the same damaged gene.[11]

Cancer could occur whenever a normal cell transforms into an uncontrollable growing one in a multi-stage process that generally progresses from a pre-cancerous lesion to a malignant tumor. These changes are the result of interaction between a person's DNA materials and three categories of external agents in daily life.[12-15] They are, namely, (1) physical agents, such as ultraviolet light and ionizing radiation; (2) chemical carcinogens, such as asbestos, components of tobacco smoke, aflatoxins in contaminated foods due to growth of fungi or persistently consumption of water contaminated with arsenic *etc*; (3) biological carcinogens, such as infections from some viruses, bacteria, or parasites.[14]

Besides, environmental carcinogens mentioned above, cancer could also arise when people get old; most likely due to a build-up of mutations that increase with age in DNA.[16] It is now almost very sure that one out of a million cells may have mutation during proliferation. Under normal situation mutation of a gene could be repaired or fixed by some build-in repair mechanism, such as the involvement of DNA polymerases.[9,10] Nevertheless, the overall risk of aberrations in gene is combined with the tendency of less effective cellular repair mechanism as a person grows older. By 25 years of age, approximately 5-7% up to 50% of individuals will suffer from a genetic disease.[11,16,17]

Risk factors for cancers

Worldwide, an estimation of 28.4 million new cancer cases (including NMSC, except basal cell carcinoma) are projected to occur in 2040; *i.e.* a 47% increase from the corresponding 19.3 million cases in 2020, assuming that national rates estimated in 2020 remain constant. The relative magnitude of increase is most striking in countries with low Human Development Index (95%) and in medium HDI countries (64%). In terms of the absolute burden, the high HDI countries are expected to experience the greatest increase in incidence, with 4.1 million new cases more in 2040 compared with 2020.[5] This projection is solely due to the growth and aging of the population and may be further exacerbated by an increasing prevalence of risk factors in many parts of the world.

Overall speaking, tobacco use, alcohol consumption, unhealthy diet, physical inactivity, air pollution and perhaps some other noncommunicable disease, such as blockage in lung due to fine dust, are regarded the risk factors contributing to a high incidence of developing cancer.

Some chronic infections are also regarded as high-risk factors for cancers as well; this is particularly crucial in some low- and middle-income countries. It has been found that approximately 13% of cancers diagnosed in 2018 globally were attributed to carcinogenic infections, such as Helicobacter pylori, human papillomavirus (HPV), hepatitis B virus, hepatitis C virus, and Epstein-Barr virus.[15] Hepatitis B and C viruses and some types of HPV increases the risk for liver and cervical cancer, respectively. More recently, it has been found that infection with HIV substantially increases the risk of cervical cancers.[15]

PREVENTING CANCER BY EARLY DETECTION

The historical background of cure mongering, and the deep divisions within the medical profession, have made the evaluation of cancer treatment difficult. Traditionally, surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, hormone therapy and even stem cell transplant are some typically adopted methods for treatment of cancers.[18] These methods all have their place and value in the treatment of cancer disease. Surgery for small tumors can be lifesaving in many situations. Radiation therapy and chemotherapy can also extend life, improve quality of life, and even cure in other situations. In recent years, some other innovative treatment methods have been introduced and adopted for some particular cases[19] and frequently, they are used in conjunction. However, cancer treatments

in general are not always safe. And ultimately, they are not effective for about 40 to 50 percent of the patients. Hence, prevention and early detection rather applying treatment at a later stage is better.

Prevention via reducing cancer burden

Recent studies on strategy to minimize cancer burden have reached to a conclusion that between 30 – 50% of cancers can be prevented by avoiding risk factors and by implementing some existing evidence-based prevention strategies. A list of good lifestyles has been drawn by medical professional to remind people that some life habits can effectively reduce cancer burden **(Table 2)**.

Table 2. Good lifestyles that can reduce the incidence of cancer
◆ Not using tobacco
◆ Maintaining a healthy body weight
◆ Eating healthy diet, such as fruit and vegetables
◆ Doing physical exercises on regular basis
◆ Avoiding harmful use of alcohol
◆ Get vaccinated against some pathogens, such as hepatitis B, HPV *etc*
◆ Avoiding ultraviolet radiation, which primarily results from exposure to the sun
◆ Reducing exposure to ionizing radiation through occupational or medical diagnostic imaging
◆ Reducing exposure to outdoor and indoor air pollution containing radon, decay of radioactive substances.

Although cancer burden could be reduced through living a good lifestyle, there is no 100% guarantee of evulsion of cancer as aging and family background also play a role. As mentioned above, they are part of a life process and inherited defects, respectively. The only way to circumvent cancer development is to adopt an early detection of cancer cells supplemented with appropriate treatment wherever necessary.

COMPARISON OF VARIOUS CANCER SCREENING METHODS

Early detection is important because when abnormal tissue or cancer is found early, it may be easier to treat. By the time symptoms appear, cancer may have begun to spread and be harder to treat. Several screening tests have been shown to detect cancer early and to reduce the chance of dying from that cancer.

Cancer screening are tests that look for the presence of cancer in people who have no symptoms of a cancer. They are designed to help doctors find and treat cancers at an early stage. Early detection is important because when abnormal tissue or cancer is found early, it may be easier to treat. By the time symptoms appear, cancer may have begun to spread and be harder to treat.

There are several types of cancer screening methods available. Some of them have been shown both to find cancer early and to lower the chance of dying from the disease. Others have been shown to find cancer early but have not been shown to reduce the risk of dying from cancer, however, they may still be offered to people, especially those who are known to be at increased risk of cancer.

Screening tests can have false-positive results—that is, the test indicates that cancer may be present even though it is not. False-positive test results can cause anxiety and are usually followed by additional tests and procedures that also have potential harms. Screening tests can have false-negative results—that is, the test indicates that cancer is not present even though it is. False-negative test results may provide false reassurance, leading to delays in diagnosis and possibly causing an individual to put off seeking medical care even if symptoms develop. Screening can lead to overdiagnosis—that is, the screening test correctly shows that a person has cancer, but the cancer is slow growing and would not have harmed that person in his or her lifetime. Treatment of such cancers is called overtreatment.

Table 3 shows various screening tests available today for cancer detection. It reveals that each method has its advantages and disadvantages in terms of specificity and sensitivity relevant to accuracy, and time consuming and cost regard to handling. Overall speaking, nucleotide sequencing is probably the best in all aspects among various methodologies. In this aspect, the latest nucleotide sequencing technique is what people call next-generation sequencing.

Table 3. Comparison of various screening methods for cancer detection

Screening Principle	Screening Methods	Accuracy		Time-efficiency	Cost-effective
		Specificity	Sensitivity		
Physical	**Endoscopy** (Colonoscopy laparoscopy, gastroscopy) **CT, MRI, PET, Mammography** **Ultrasound, Biopsy & physical check etc.**	+ / ++	+ / ++	++	++++
Biochemical	**Enzymology Cell morphology etc.**	++	++	+++	+
Immunological	**Antigens/Monoclonal antibodies**	+++	+++	+++	++
Molecular	**Nucleotide Sequencing**	++++	+++	++++	++ / ++++

Remark: + = low; ++ = medium; +++ = good; ++++ = excellent

WHAT IS NEXT GENERATION SEQUENCING (NGS)?

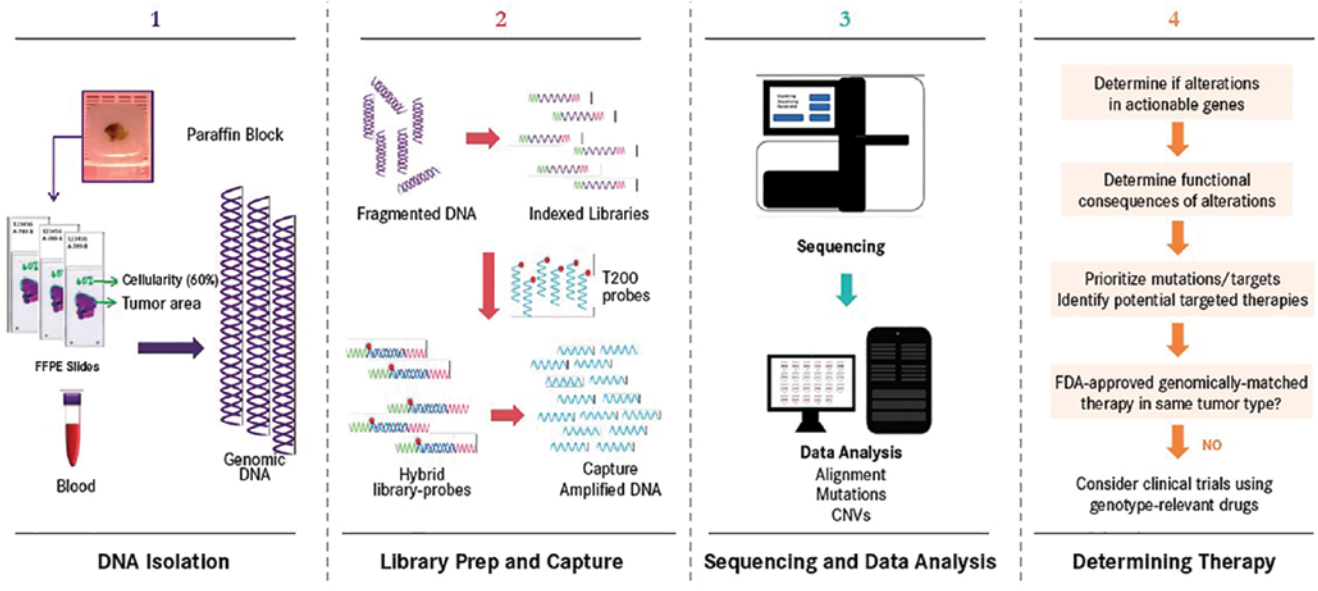
Next Generation Sequencing (NGS) is a DNA sequencing method that works on massive parallel sequencing employing micro- and nano-technologies to perform nucleotide sequence analysis.[20,21] It is a fast and quick screening method that take less time and is cost effective. Although this technique can only read a short stretch of nucleotides (30-400 bp) than the conventional Sanger Sequencing method, their drawback of sequence reading is overcome by machine automation that allows assembling all the short sequences into longer sequence of a complete genome. It has the potential to revolutionize oncology through the classification of tumors and identification of biomarkers that can predict response to individualized therapy.[3]

PRINCIPLE OF NGS TECHNOLOGY FOR DETECTION OF GENETIC PROBLEMS AND CANCER

As scientists have a deeper understanding of life, the latest achievements of human genomics allow healthcare professional to offer a better diagnosis and treatment of a disease with what people clone as the practice of precision medicine, which is a new medical concept that adjusts medical treatment plans according to the exact characteristics of each patient. In order to design a precision medicine for individual, genetic code information derived from nucleotide sequencing plays a particularly important medium.

NGS technology can be applied to identify gene mutations for risk assessment of cancer. The required conditions for cancer screening is outlined in **Figure 2.**[22] The diagram illustrates the outline steps involved in order to apply NGS technology for identification of potential mutations in biological samples. In brief, its covers DNA isolation in stage 1; library preparation and capture in stage 2; conducting sequencing and data analysis in stage 3; and designing therapy strategy after determining any functional alterations in DNA. Details of the workflow for conducting a NGS work are attached in the legend of the figure.

Currently, there are several NGS platforms commercially available in market: they are, namely, the Illumina Hiseq and Miseq, the Roche 454 GS and Junior version, the personal genome machine Ion torrent, and the Life Technologies SOLiD **(Table 4)**. Some NGS platforms, such as Miseq and Ion torrent, are more favorable for clinical use because of their flexible throughput and shorter turnaround time. Because in this review, we focus on the application of NGS to cancer prevention, diagnosis, and treatment. Other brands are therefore not included. Nevertheless, with introduction of these platforms, analysis of a genome could be done within couple of days, making the whole sequencing process more rapid and cost reduced.



(1) Slides are cut from tumor samples embedded in paraffin blocks. For each tumor sample, hematoxylin and eosin stains are performed and cellularity is assessed. Matching peripheral blood is also collected for each patient. Genomic DNA is isolated from both the formalin-fixed, paraffin-embedded tissue and blood. Alternately, frozen fresh tissue samples as well as other normal DNA sources such as saliva, buccal swab, or normal tissue can be used. (2) DNA is fragmented and libraries are made by ligating indexed adaptors (Indexed Libraries) that allow for sample pooling. Hybridization with probes is performed; the captured DNA is washed and amplified and proceeded to DNA sequencing. (3) Captured DNA is sequenced; after sequencing, samples are demultiplexed, or separated, and the raw data is submitted to data analysis for mutations and copy number variations identification. (4) The genomic alterations are reviewed and alterations in actionable genes are identified. Functional impact of alterations in actionable genes is assessed and therapeutic implications of known and predicted functional alterations are determined.

Modified from Chen et al. Clin Chem.2015.[33]

Figure 2. *Workflow of a potential next-generation DNA sequencing for screening genetic problems.*

Table 4. List of next generation sequencing platforms available in market				
Platform	**Technology**	**Run Time (hr or day)**	**Nucleotide Read Length (bp)**	**Applications**
Complete Genomics	DNA nanoball PCR, ligation sequencing	12 day	70	Whole-genome sequencing
Helicos	Single molecule dye terminator	8 day	35	Whole-genome sequencing
Illumina HiSeq 1000/2000	Bridging amplification, reversible terminator dye and imaging system	8.5-11 day	100	Whole genome sequencing, de novo sequencing, amplicon sequencing SNP discovery
Illumina HiSeq 1500/2500	Bridging amplification, reversible terminator dye and imaging system	High output: 11 day Rapid run: 27 hr	100	Whole genome sequencing, de novo sequencing, amplicon sequencing SNP discovery
Illumina MiSeq	Same as HiSeq	4-39 hr	36-250	Amplicon sequencing, clone, checking, ChIP-Seq, and small-genome sequencing
Life Technologies SOLiD	Emulsion PCR, ligation sequencing	2-7 day	35-75	Whole genome /exome sequencing, SNP detection
Life Technologies Ion Torrent	Hydrogen release detection, semiconductor sequencing	2 hr	35-200	Targeted sequencing, amplicon sequencing, small-genome sequencing
Pacific Biosicence PacBioRS	Single molecule sequencing using fluorescent dNTP	<1 day	3,000-10,000	Genomic DNA, PCR products, infectious agent sequencing
Roche 454 GS FLX	Emulsion PCR pyrosequencing	10 hr	400	Targeted region sequencing, SNO discovery
Rosche 454 GS Junior	Emulsion PCR pyrosequencing	10 hr	400	Targeted region sequencing, SNO discovery

NGS APPLICATION FOR EARLY SCREENING OF CANCER IN LIQUID BIOPSY

Traditionally, tissue biopsy is the most widely-use material for cancer detection, staging, and prognosis, but sometimes tumor tissue can be difficult to obtain, especially in metastatic diseases like late-stage lung cancer. Moreover, it is unrealistic to use tissue biopsy for cancer screening and early diagnosis when the tumors have not formed to visible size. Although mammogram, pap test and colorectal cancer screening and low-dose computed tomography have been found good methodology to detect breast cancer, cervical cancer, colorectal cancer and lung cancer, respectively.[23] Unfortunately, all these methods have problem of sensitivity and specificity; they are only applicable to a unique cancer.

Liquid biopsy is a powerful technique that can be used to different stages of cancer screening and treatment. In the blood or our body fluid, there are many types of biological materials like circulating cells, platelets, extracellular vesicles, mRNA, miRNA, protein, and cell-free DNA (cfDNA). By applying the NGS technology to analysis nucleotides in the body fluid, it can provide a molecular profile of changes in genetic materials and allow professional to determine status of cancer. Hence, liquid biopsy is a better alternative as it is not only non-invasive approach but also allows largescale screening to be performed simultaneously. It is a more general and cost-effective methodology. Consequently, analysis of cell-free DNA (cfDNA) in blood or saliva has become a common practice.[24]

From the blood of a cancer patient, a portion of the cfDNA is released by tumor cells through apoptosis, necrosis, or active release,[25] and this DNA is called circulating tumor DNA (ctDNA). As concentrations of ctDNA in plasma has been shown to correlate with tumor size and stages,[26,27] The tumor-specific mutations in ctDNA sequence can act as a new type of cancer biomarker and assist to identify cancer. Compared to traditional cancer diagnosis using tissue biopsy, liquid biopsy is more feasible and less invasive and is more comprehensive than tissue biopsy to evaluate tumor heterogeneity because all tumor sites release ctDNA into the blood.[28]

Today NGS has been used in routine non-invasive prenatal testing (NIPT),[29] screening of single-gene mutation diseases,[30] individualized cancer treatment,[31] and pharmacogenomics testing in many advance countries. It is not only an important research method and tool for genomics analysis, but also one of the technical factors driving the realization of the vision of precision medicine. It has a wide range of application and plays an active role in many non-invasive screening, such as tumor clinical diagnosis, and genetic disease detection.

Up to now, there are quite a few liquid biopsy-based assays available for disease detection, diagnosis, profiling and treatment selection. Table 5 shows a few commercial companies that offer screening services for diagnosis and detection of cancer based on the use of liquid biopsy. All these new developments reflect that NGS sequencing of nucleotides in body fluid has already been accepted and approved by official with the aims to achieve a higher sensitivity and lower cost than that derived from tissue biopsy for different clinical purposes.[32]

Table 5. List of some liquid biopsy products or services offered by companies			
Company	**Product/Services**	**Usage/Application**	**Ref.**
Biocept	Target Selector™ ctDNA EGFR Kit	EGFR mutation detection	33
Biodesix	GeneStrat® test	Providing blood-based mutation results of EGFR, ALK, ROS1, RET, BRAF, and KRAS for cancer diagnosis	34
CellMaxLife	FirstSightCRC™	Using circulating tumor cells for colorectal cancer, adenomas, and colorectal cancer screening and profiling	35
Cynverio	The LiquidBiopsy® Platform	NGS-based techniques to detect mutations in as few as 1 target cell per mL/blood	36
Exosomedx	Exosome-based biomarker tests*	Diagnosing non-small cell lung cancer and prostate cancer	37
Freenome	Screening test	Using AI-based algorithm for early detection of colorectal cancer and pre-cancerous lesions known as advanced adenomas	38
Grail	The Summit Study	Evaluating a blood test designed to detect multiple types of cancer, including lung cancer	39
Guardant 360	Lunar-2	Early cancer detection among higher-risk asymptomatic individuals	40
Inivata	InVisionSeq™ and InVisionFirst™-Lung	Around 40 mutation biomarkers (including mutations, CNV, SNV, fusions, indels) panel for advanced cancers molecular profiling, monitoring and diagnosis	41
Personal Genome Diagnostics	PlasmaSELECT™-R64	Cancer diagnosis using NGS with 64 genes panel	42

* Exosomes are extracellular vesicles (EVs) produced by cells. They contain RNA, proteins, lipids and metabolites that are reflective of their origins[43]

APPLICATION OF NGS TECHNOLOGY FOR DRUG DISCOVERY

It has been believed about a decade ago that the vast information in human genome posses some drug targets for us to discover. On top of this, it is also a good site to validate therapeutic hypotheses and predict the potential safety of some inhibitory compound aimed at molecular targets.[44] Consequently, genetic target-identification efforts based on mammalian cells have been increasingly focused. For example, examination of compound-resistant clones of cells, using transcriptome sequencing (RNA-seq), identified intracellular targets of normally cytotoxic compounds96. Advantages of this approach include the ability to perform cell type–specific analyses and not having to chemically modify the compound to perform the analysis. Clones of HCT116 colon cancer cells resistant to the polo-like kinase 1 (PLK1) inhibitor BI 2356 were sequenced and compared to the parental line. Although PLK1 was not mutated in every clone, it was the only gene mutated in more than one group; moreover, mutations were present in the known binding site of BI 2356. This proof-of-principle study paves the way for more rapid target identification in other mammalian cells, although this approach is currently limited to cell viability as a phenotype.[44]

Similar to the oncology sector, NGS technology has been adopted for characterizing changes in nucleotide components in most cases of interaction between a compound and the human genome, it ushers a new era of genetics-informed drug development.[45] With the help of the NGS technology, three pharmaceutical products or device, namely, Kymriah™, Luxturna™, Keytruda® and MSK-Impact™ were stiffly invented and approved in year 2017 by FDA for gene therapy of cancer, treatment of inherited diseases, targeting a genetic signature in genome and for companion diagnostic purposes, respectively. All these new inventions require the use of NGS technologies to unveil changes in cellular DNA.

It is now believed that population-scale NGS with paired bioinformatic data will become a routine measure in the drug development process for the identification of novel drug targets, and that genetically stratified clinical trials will be widely adopted to improve power in precision-medicine-guided drug development.[45] NGS is gaining momentum as a means of choice for drug target identification. It has already overtaken the proxy markers in genome-wide association studies (GWAS) for unknown causal variants or genes and expected to advance and make drug discovery process more rapid, efficient and fruitful. As a result of this alternative approach in recent year, precise personalized medicines have become realistic, and proper medication has been tailored designed for treatment of individual cancer patient **(Figure 3)**.

TREND OF NGS IN DIAGNOSTIC MARKET

From its wide applications, the NGS technology used in molecular diagnosis (MDx) allows the nucleotide sequencing to help identification of the genetic variants of human genomic diseases and to apply it in microbiology study as well.

It is anticipated that the NGS based molecular diagnostic market during the period of 2020-2025 will be propelled quickly in biomedical field. The NGS-based diagnostic market is estimated to reach $2255.79 M by 2025, growing at a compounding annual growth rate (CAGR) of 6.4% during this forecast period. CAGR is a measurement used by investors to calculate the rate at which a quantity grew over time. The word “compound” denotes the fact that CAGR considers the effects of compounding, or reinvestment over time. For example, suppose a company whose revenue grows from $3 million to 30 million over a span of 10 years. In that scenario, the CAGR would be approximately 25.89%.

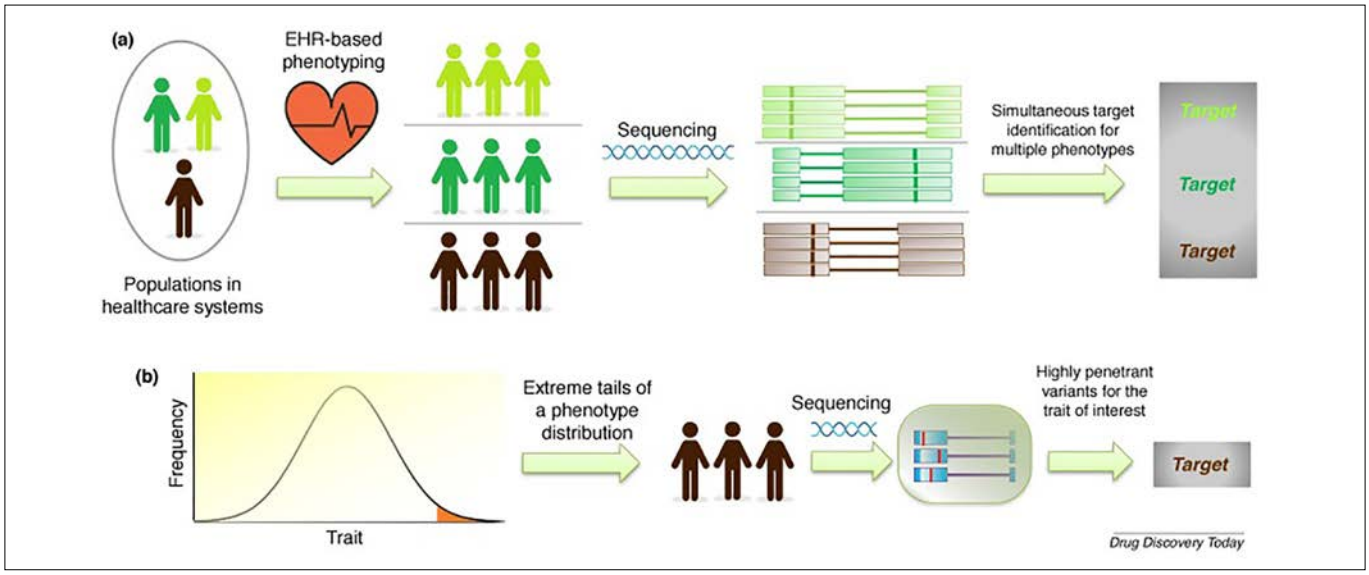


Figure 3. *Simplified illustrations on how next-generation sequencing (NGS) helps identification for drug development. (a) NGS on well-phenotyped populations from healthcare systems can potentially reveal phenotype-specific drug targets for multiple diseases or traits simultaneously; (b) NGS can be leveraged on extreme tails of a phenotype distribution to identify genetic targets of a specific phenotype of interest. [adopted from Torshizi & Wang[45]]*

Hence, the CAGR figures in **Table 6** summarizes a steady annual growth rate of diagnostic market based on NGS technologies. It reveals a rate of not less than 7.8% annual growth from 2015-2017 and a substantial growth by year 2022 probably due to the maturity of this technology. This significant steady growth rate is attributed to the advancement in genomics and proteomics and increasing application of NGS based molecular diagnostic for human diseases; all these achievements nurture the NGS market growth.

Table 6. Global market of NGS applications for disease screening ($ Millions)

Disease Category	2015	2016	2017	2022	CAGR* (2017-2022)
Non-cancer	1,576.6	1,979.8	2,352.8	5,441.0	22.3
Cancer	669.5	778.1	838.8	4,093.2	37.3
Total	2,246.1	2,757.9	3,191.6	10,534.2	27.0

*** CAGR:** a measurement used to calculate the rate at which a quantity grew over time.

CONCLUSION

The world has now entered a new era of genomics because of the continued advancements in the high throughput NGS technologies. With the development and improvement of more new platforms, NGS has been applied increasingly in many areas of biomedical fields over the last 15 years. These high throughput sequencing technologies include sequencing by synthesis-fluorescent in situ sequencing (FISSEQ), pyrosequencing, sequencing by ligation using polony amplification, supported oligonucleotide detection (SOLiD), sequencing by hybridization along with sequencing by ligation, and nanopore technology. Great impacts of these methods can be seen for solving not only the human genome but genomes related health problems in human beings. All NGS methods ultimately overcome the Sanger sequencing method that requires many years' effort because they work on massive parallel sequencing that thousands of nucleotide sequences are analyzed simultaneously. Consequently enormous amount of data is generated.

Nowadays NGS has been commonly adopted in clinical oncology to advance personalized treatment of cancer. NGS has been used to identify novel and rare cancer mutations, detect familial cancer mutation carriers at early stage, and provide molecular rationale for appropriate targeted therapy. The 2 most important components of cancer prevention are early diagnosis (or downstaging) and screening at pre-cancerous stage. Early diagnosis focuses on detecting symptomatic patients, while screening consists of testing healthy individuals to identify those having cancers before any symptoms appear. The former approaches aim at reducing the proportion of patients who are diagnosed at a late stage and the later aims to prevalence of the disease. As early and precise detection of cancer greatly increases the chances for successful treatment, early screening of changes in DNA is the best choice to monitor and to prevent the proliferation and metastasis of cancer cells. Both approaches require application of NGS to reveal the in-situ nucleotide components in genetic materials. NGS technologies provide a quick and precise screening of any changes in DNA molecules, which is the root of all evolving cancer.

Although this report hasn't provided a detail description of the development of recombinant vaccine against the COVID-19 viral disease, swift unveil of the COVID-19 viral sequences through this high-throughput sequencing technology, is the driving force accelerating prompt design of various types vaccines for combating this pandemic infectious disease.[46] Hence, NGS has offered ample clinical applications to the detection of genetics diseases and cancer as well as the development of new therapeutic no matter whether it is tailor made or not for individual treatment. Hence, its' future use in biomedical areas is tremendous.

Author's background

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Prepared by Ivy Chan

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Nintedanib

Presentations:
OFEV soft capsules are available in two different strengths of 100 and 150 mg of nintedanib (as a free base) corresponding to 120.40 mg and 180.60 mg of nintedanib ethanesulfonate (esilate), respectively.

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Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases including: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3 and colony stimulating factor 1 receptor (CSF1R). In addition, nintedanib inhibits non-receptor tyrosine kinases including: Lck, Lyn and Src kinases. Nintedanib binds competitively to the ATP binding pocket of these kinases and blocks the intracellular signalling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling in interstitial lung diseases. In *in vivo* studies, nintedanib was shown to have potent anti-fibrotic and anti-inflammatory activity.

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Idiopathic Pulmonary Fibrosis
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Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype
OFEV (nintedanib) is indicated for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (also known as progressive fibrosing ILD)

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No dose adjustment is necessary in patients 65 years and older.

Pediatrics (< *18* years of age):
The safety and efficacy of OFEV in pediatric patients have not been studied in clinical trials and therefore, OFEV should not be used in patients under 18 years of age.

Forensic Classification:
P1S1S3