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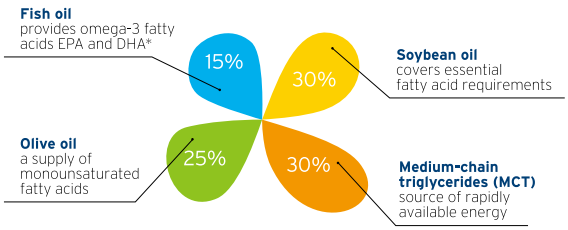

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The Cover Shot

This snapshot was taken from a fixed wing aircraft over Victoria Harbour during a navigation exercise.

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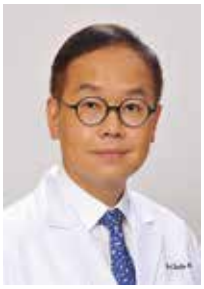

Prof Justin CY WU

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Editor

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In this month's issue of the Hong Kong Medical Diary, we have an updated review on the development of advanced diagnostics and how it facilitates the development of personalised medicine in the field of gastroenterology.

The introduction of artificial intelligence (AI) has further improved the diagnostic power of endoscopy in the early detection of advanced dysplasia and early gastric cancer. AI-enabled endoscopy also facilitates endoscopic management of early neoplasia. It allows more accurate prediction of early neoplasia that is amenable for endoscopic submucosal dissection. For hyperplastic polyps at the rectosigmoid region, AI may facilitate more accurate selection of polyps for "diagnose and leave" strategy. The clinical impact of AI will be further enhanced by the improvement in image resolution of endoscopy and image-enhancing technology.

The implementation of colorectal cancer (CRC) screening becomes more personalised with the understanding of the increased CRC risk in family members of CRC patients. The risk is further affected by the age of cancer diagnosis of the index patient, the age of the individual at-risk, being a first-degree relative, and the number of affected relatives. Current recommendations have suggested earlier and shorter interval of CRC screening. And colonoscopy is the preferred screening test for its better sensitivity.

The discovery of the role of intestinal microbiota in the pathogenesis and management of CRC creates the opportunity for the development of novel microbiota-based personalised prevention and management of CRC. Patients with advanced adenoma or CRC may be characterised by a distinct pattern of dysbiosis. Stool microbiota analysis may be an emerging tool that helps select individuals for more targeted screening with the use of more sensitive screening method such as colonoscopy. The microbiota can also be used to predict treatment responses and adverse reactions, and the modulation of the microbiota could potentially facilitate more personalised treatment and improve patient outcomes.

The widespread application of high-resolution manometry has revolutionised the diagnosis of oesophagal motility disorders. The Chicago Classification 4.0 further refines the protocol of high-resolution manometry with the addition of manoeuvres such as multiple rapid swallows and free drink challenges. This revision allows more accurate assessment of esophagogastric junction relaxation function and classification of an oesophageal motility disorder. The functional luminal imaging probe (FLIP) technology is a promising tool that measures the stiffness and distensibility of the oesophagal wall and esophagogastric junction. FLIP has emerged as an adjunct to high-resolution manometry with increasing clinical application such as pre-operative assessment.

Despite the decreasing incidence, gastric cancer remains a common cancer in Hong Kong. The potential association between long-term proton pump inhibitor (PPI) use and the risk of gastric cancer has created major concern among long-term PPI users. Mounting evidence suggests that the risk is significant only in a subset of individuals with pre-existing gastric precancerous lesions and *H. pylori* infection. A personalised approach should be taken in balancing the individual's risk-benefit profile for long-term PPI treatment.

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29 Sept 2021	Management of Pleural Diseases	Dr. CF Choy AC (MED)/ TKOH
6 Oct 2021	Indication, monitoring and troubleshooting for CPAP therapy	Ms. Maggie Lit KCC NC(Respiratory) / QEH NC(Respiratory)

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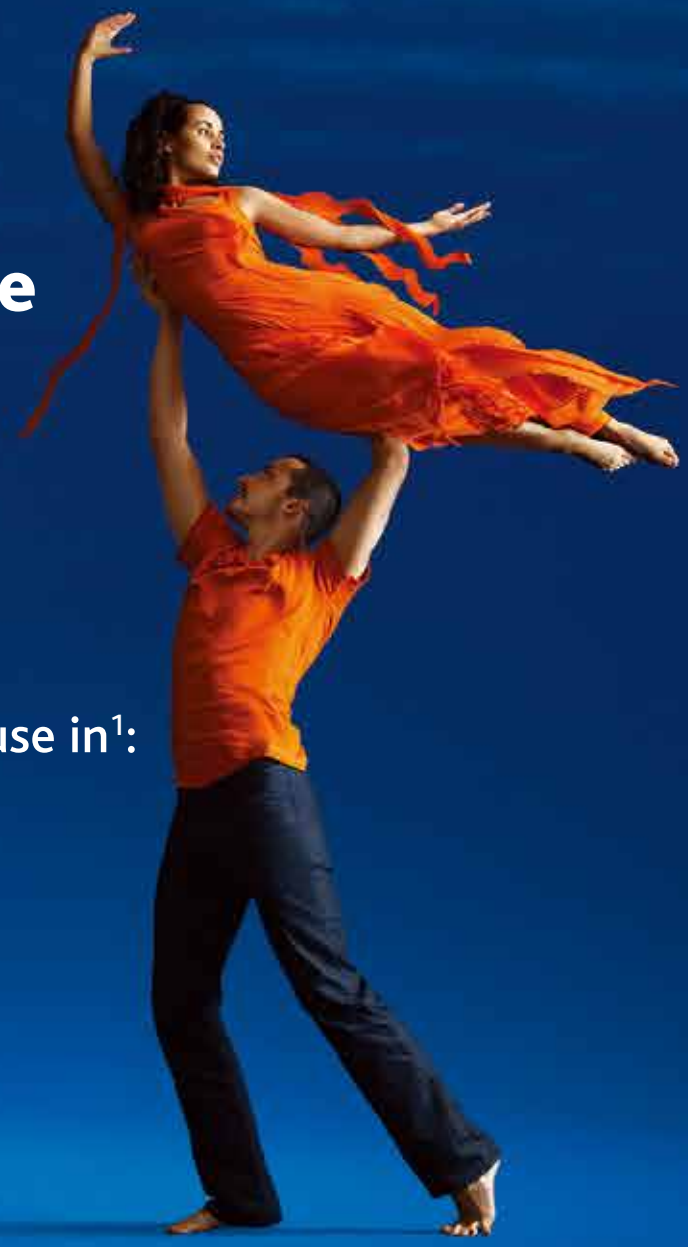

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Effects of Long-term Use of Proton Pump Inhibitors on Gastric Cancer Development

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INTRODUCTION

Gastric cancer (GC) is the fifth commonest cancer and the third leading cause of cancer-related mortality worldwide.[1] Helicobacter pylori (*H. pylori*) is the most important aetiological agent for GC development with a 2.8-fold higher risk.[2] *H. pylori* induces gastric carcinogenesis via the Correa's cascade, starting from chronic gastritis and progressing to precancerous lesions (atrophic gastritis, intestinal metaplasia [IM], dysplasia) and cancer.[3] However, eradication of *H. pylori* can only reduce GC risk by 46%, as shown in a recent meta-analysis of seven randomised controlled trials (RCTs),[4] due to the presence of pre-existing precancerous lesions. Eradication of *H. pylori* can reverse chronic gastritis and atrophic gastritis,[5] and even IM;[6] in fact, *H. pylori* eradication reduces GC risk even in patients with IM and dysplasia,[7] and those undergoing endoscopic resection for early GC.[4] However, the probability of IM reversal decrease with increasing Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) stages.[8]

Emerging data have shown that long-term use of proton-pump inhibitors (PPIs) are associated with a number of gastrointestinal and extraintestinal side effects, including enteric infections, acute kidney injury, fracture and pneumonia.[9] Among the gastrointestinal side effects, PPI-associated GC has come under the spotlight recently. In this review, we will discuss the possible underlying mechanisms and recent evidence from clinical studies. We will also provide recommendations on PPI prescription in clinical practice.

POSSIBLE MECHANISMS BY WHICH PROTON-PUMP INHIBITORS PROMOTE GASTRIC CARCINOGENESIS

While acid suppression by PPIs has been shown to cause gastric neoplasia in rodents, evidence from human studies remains controversial.[10] Proposed mechanisms include interaction with *H. pylori*, hypergastrinemia, and bacterial overgrowth (Fig. 1).

Interaction with *Helicobacter pylori*

H. pylori colonises gastric antrum leading to antrum-predominant gastritis with hypersecretion of gastric acid.[11] However, PPIs result in corpus-predominant gastritis in the presence of *H. pylori* infection, resulting in atrophic gastritis (a precancerous lesion) and hypochlorhydria.[12]

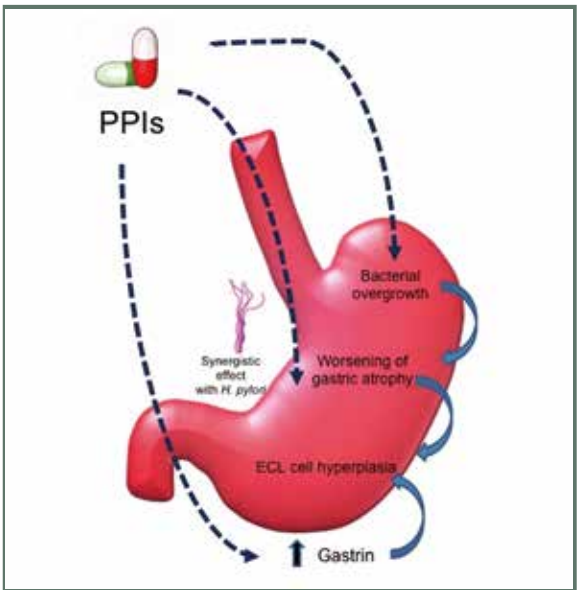

Fig. 1. Proposed mechanisms on how proton pump inhibitors lead to gastric cancer (Adapted from Cheung KS, Leung WK[10])

Abbreviations: PPIs, proton pump inhibitors; H. pylori, Helicobacter pylori; ECL, enterochromaffin-like cell

Hypergastrinemia

A systematic review showed that long-term (> 3 years) PPI use leads to an elevated level of serum gastrin in response to hypochlorhydria,[13] which poses a trophic effect on gastric mucosa, including hyperplasia of enterochromaffin-like (ECL) cells, particularly in *H. pylori*-infected patients. In addition, hypergastrinemia may stimulate the release of signal substances (e.g. histamine, regenerating gene [REG] protein) from the ECL cells, thereby fostering the growth of gastric carcinomas of "intestinal type".[14]

Bacterial Overgrowth

Acid suppression by PPIs can lead to non-*H. pylori* bacterial overgrowth in the stomach, which may in turn exacerbate chronic gastritis and hence atrophic gastritis.[10] *H. pylori* and non-*H. pylori* bacteria act synergistically to incite higher serum cytokines

(interleukin [IL]-1 beta and IL-8) and atrophic gastritis. In addition, there is a higher abundance of non-gastric micro-organisms (mostly oral flora), which can produce gastric carcinogens (N-nitroso compounds) from food nitrates via nitrate reductase.[15]

CLINICAL STUDIES ON THE ASSOCIATION BETWEEN PROTON-PUMP INHIBITORS AND GASTRIC CANCER

A prior meta-analysis of three observational studies showed that PPIs were associated with a higher GC risk (pooled odds ratio [OR]: 1.43, 95% CI: 1.23-1.66).[16] Interestingly, a significant association was only observed among those using PPIs < 1 year (pooled OR: 1.76, 95% CI: 1.24-2.52) but not those using PPIs ≥ 1 year. This observation was probably related to the fact that PPIs are part of the *H. pylori* eradication regimen. Nevertheless, the highest GC risk existed if patients used PPIs > 3 years (pooled OR: 2.45, 95% CI: 1.41 - 2.45), which may be due to the synergistic action of PPIs and *H. pylori* on increasing GC risk.

As GC is relatively uncommon and a sufficiently long observation period is needed to develop, randomised clinical trials (RCTs), studying the effects of PPIs requires a large sample size and are resource/labor-intensive. It is also unethical to conduct a trial to observe adverse events as the primary outcome of interest. Therefore, observational studies with good study design and addressing important biases and confounding variables are the best available evidence. However, the observational studies included in the above-mentioned meta-analysis did not have a large sample size, and failed to take into consideration of *H. pylori* infection status, indication bias reverse causality, and concomitant usage of other medications including aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NA-NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, statins and metformin.[10]

To address these limitations, we conducted a territory-wide retrospective cohort study on 63,397 *H. pylori*-eradicated patients with a median follow-up of 7.6 years.[17] PPI use (defined as at least weekly use) was associated with a 2.4-fold higher GC risk, while histamine two receptor antagonists (H2RAs), a negative control exposure, did not confer a higher risk. A frequency- and duration-response relationship existed (adjusted hazard ratio [aHR] 2.43 for weekly to < daily use, and aHR 4.55 for daily use; and aHR 5.04, 6.65 and 8.34 for ≥ 1-year, ≥ 2-year and ≥ 3-year use, respectively).

Subsequently, several other publications were echoing our study results. A recent meta-analysis of seven studies showed that PPIs were associated with a 2.5-fold higher GC risk.[18] In another meta-analysis, it was found that the risk was more prominent among Asians than Caucasians (OR: 2.44 [95% CI: 1.89-3.00] vs OR: 1.86 [95% CI: 0.54-3.18]), and for non-cardia than cardia subsite (OR: 2.45 [95% CI: 1.44-3.45] vs OR: 1.64 [95 % CI: 0.23-3.51).[19] Furthermore, the risk appears to be more prominent among *H. pylori*-infected (standardised incidence ratio [SIR]: 9.76, 95% CI: 8.87-10.71) than uninfected patients (SIR: 2.91, 95% CI: 2.78-3.05).[20] Notably, in a retrospective cohort study of 571 *H. pylori*-eradicated patients in Japan, which also considered the presence of gastric precancerous lesions (atrophic gastritis and IM),[21] PPI use was associated with a higher GC risk in patients with IM but not those without IM. In our territory-wide cohort study, we recruited a matched cohort of PPI users who had not received *H. pylori* therapy (n=142,460), showing that PPI users without prior HP therapy had the lowest incidence rate of GC (0.8 cases per 10,000 person-years vs other two groups [non-PPI users with prior *H. pylori* therapy: 2.9 per 10,000 person-years and PPI users with prior *H. pylori* therapy: 8.1 per 10,000 person-years].[17] Taken together, the evidence suggests that pre-existing precancerous lesions (e.g. induced by current or even prior *H. pylori* infection) plays a more important role in determining GC risk than PPIs, and PPIs likely increase GC risk significantly in the context of underlying precancerous lesions or *H. pylori* infection.

However, the causality between PPIs and GC development warrants further investigation as current evidence is still conflicting due to the presence of residual/unmeasured confounders inherent in all observational studies. For instance, important risk factors such as lifestyle factors, or family history of GC were not factored into analysis in some studies. In a nested case-control study with 1,233 GC cases, PPI use of ≥ 2-years was not associated with a higher risk of GC and consistent association was not found for increasing PPI dose.[22] In a 3 x 2 partial factorial double-blinded RCT, 17,598 subjects (taking aspirin and/or rivaroxaban for underlying cardiovascular or peripheral artery diseases) were randomly assigned to either pantoprazole 40mg daily or placebo.[23] Although no increased risk of all gastrointestinal cancers (n=169) was observed, the number of GC cases was not specified. An issue of underpower was likely present given the few cases of gastric atrophy (n = 45). Other limitations include a short follow-up time (median of 3 years) and concomitant use of aspirin in a large proportion of subjects. A meta-analyses reported that aspirin was associated with a 36% lower risk of GC via COX-2 and non-COX-2 pathways.[24] Post-hoc analysis of our territory-wide cohort study showed that PPI-associated GC risk was negated by concurrent aspirin use.[25]

RECOMMENDATIONS ON PRESCRIPTION OF PROTON-PUMP INHIBITORS IN CLINICAL PRACTICE

It could not be over-emphasised that PPIs should be prescribed in the presence of clinical indications (e.g. peptic ulcer disease, gastroesophageal reflux disease [GERD], prevention of NSAID-induced upper gastrointestinal bleeding [UGIB]) instead of being irrationally avoided or withdrawn. This is because the clinical benefit likely outweighs the possible side effects.

Nevertheless, the lowest effective dose of PPIs should be used with a finite period if possible, particularly for dyspepsia and non-erosive GERD. A step-down approach from high-dose PPIs to low-dose PPIs and even less potent acid suppressants (e.g. H2RAs) should be attempted. That being said, long-term PPI usage is

necessary for a certain group of patients, including those with a high risk of NSAID-induced UGIB[26] and Barrett's esophagus.[27] *H. pylori* should be tested and treated if present among all long-term PPI users so as to prevent corpus atrophy.[28]

CONCLUSION

Although there is increasing evidence from observational studies associating GC and long-term PPI use, causality remains undetermined due to residual and unmeasured confounders. Even if present, PPI-associated GC risk is likely to be of a concern only among those with pre-existing gastric precancerous lesions and current/prior *H. pylori* infection. Indications of PPIs should be reviewed with an individual's risk-benefit profile being taken into consideration.

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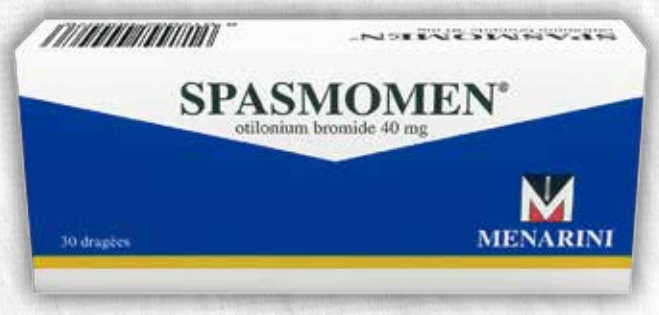
^SPASMOMEN® is the only antispasmodic to show consistent evidence of efficacy without the burden of anticholinergic side-effect.
Adapted from Wu JC *et al.* 2017.[2] The current treatment landscape of irritable bowel syndrome in adults in Hong Kong: consensus statements.



- Usual dose is one tablet 2-3 times daily[3]
- Does not cause atropine-like side effects[3]
- Does not alter the capacity to drive vehicles or use machinery[3]

IBS = Irritable Bowel Syndrome

References: 1. Clave P *et al. Aliment Pharmacol Ther.* 2011;34(4):432-442. **2.** Wu JC *et al. Hong Kong Med J.* 2017;23:641-647. **3.** SPASMOMEN® Dragées 40mg, Summary of Product Characteristics, Hong Kong, Mar 2017.

Abridged Prescribing Information

SPASMOMEN® Dragées 40mg

Active ingredient: Each dragée contains 40mg otilonium bromide. **Therapeutic Indications:** Irritable Bowel Syndrome (IBS) and painful spastic conditions of the distal enteric tract. **Posology:** Adults and elderly patients: The usual dosage is 1 dragée, 2-3 times a day, depending on the prescriber's judgement. Dragées should be swallowed whole with a glass of water, preferably 20 minutes before meals. Paediatric population: There are no available data referring to the use of SPASMOMEN in paediatric populations, and as such the use of this medicinal product is not recommended in children. **Duration of the treatment:** According to the prescriber's instructions. **Method of administration:** For oral use. **Contraindications:** Hypersensitivity to the active ingredient or any of the excipients. **Special warnings and precautions for use:** To be used with caution in subjects with glaucoma, prostatic hypertrophy, pyloric stenosis. This medicinal product contains lactose and is therefore not suitable for subjects with lactase deficiency, galactosemia, or glucose/galactose malabsorption syndrome. **Interactions with other medicaments and other forms of interaction:** No interaction studies have been conducted. **Fertility, pregnancy and lactation:** Although no embryo-toxic, teratogenic or mutagenic effects on animals have been reported, as with all medicinal products its use during pregnancy and lactation should be limited to cases of specific need and under direct medical supervision. **Effects on ability to drive vehicles and use machinery:** SPASMOMEN does not alter the capacity to drive vehicles or use machinery. **Undesired effects:** SPASMOMEN, in therapeutic doses, does not cause undesirable effects, namely atropine-like side effects. **Overdosing:** Otilonium bromide has shown to be virtually devoid of toxicity in animals and therefore no particular problems should arise in humans in relation to overdosing. **Date of revision of the text:** March 2017.

For further information, consult full prescribing information.

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HK/SPA/062021/166 (Aug 2021)

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Update in Oesophageal Motility Studies

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INTRODUCTION

High resolution manometry (HRM) stands as the centrepiece in managing oesophageal motility disorders. HRM is one of the few selected examples in which international guidelines are based on a single investigation. The first edition, known as the Chicago classification, was published in 2009[1] and has been in its 3.0 version (CCv3.0)[2] since 2015. The incorporation of Clouse plot and the introduction of the hierarchical approach to diagnosis have led to an easier understanding of the test and thus a plethora of interest and use. However, there are instances in which HRM delivers results of inconclusive significance, such as in Esophagogastric junction (EGJ) outflow obstruction (EGJOO). EGJOO accounts for up to 10% of all manometric diagnosis, but about one-third of them may be clinically irrelevant[3,4]. Nevertheless, this diagnostic term causes much anxiety and may lead to unnecessary interventions. Moreover, the way the test is done also varies across different centres, partly due to the availability of devices (water perfused system or solid-state catheter system). Against this background, an international HRM Working Group consisting of 52 oesophageal motility experts selected by six international motility societies representing 20 countries, was formed. Following two years of work examining the latest available studies and evidence and a series of meetings, the working group came up with the latest Chicago Classification version 4.0 (CCv4.0), which was recently published in the April issue of *Neurogastroenterology and Motility*[5]. This article aims to provide a brief summary highlighting the key changes in the CCv4.0, and summarising the updates on oesophageal motility studies.

CHICAGO 4.0 CLASSIFICATION

While the basic principles of the HRM test remain with the same set of equipment required, there are notable differences proposed by the CCv4.0. First of all, there is more clarity on how the test should be done. The test is preferably performed with a solid-state catheter with a proposed algorithm to start with ten wet swallows in the supine position followed by multiple rapid swallows (MRS). Then the patient would change to the erect position for five more wet swallows before concluding the test with a free drinking challenge (FDC). The revised guideline allows the clinician to start in either the erect or supine position as the primary position and proceed depending on the clinical resources, time and the test finding. This may be particularly relevant in conditions such as EGJOO, as some patients with high lower oesophageal sphincter (LES) relaxation pressure can be normalised when the test is performed in the supine position. Provocation tests are also formally included as part of the protocol, with the MRS and FDC being recommended to be performed routinely. Other supportive tests such as pharmacological provocation, solid test swallow and solid test meals are included as optional, with the protocol and expected response standardised. Provocative maneuvers are usually intended to elicit LES relaxation or to look for oesophageal peristaltic reserve[6]. They could be of value when HRM result is discordant with the symptom or other test results.

Concerning the diagnosis of motility disorders, there has been a major revamp of the approach to EGJ outflow obstruction. Manometrically, the median integrated relaxation pressure (IRP) must be elevated in both primary and secondary test positions. Crucially, it is recommended that patients should have relevant symptoms (dysphagia or atypical chest pain) in order to consider the IRP to be clinically significant. Moreover, complementary tests are suggested with timed barium tablet swallow and/or functional lumen imaging probe (FLIP). It is hoped that the more stringent criteria can help to select patients that would validate further investigations or intervention. Depending on the feature of peristaltic function, EGJOO can be subclassified into EGJOO with spastic features (presence of ≥ 20% premature swallows), EGJOO with hypercontractile features, EGJOO with ineffective motility, or EGJOO with no evidence of disordered peristalsis, although this subclassification is not mandatory. The requirement of relevant clinical symptoms is not only limited to EGJOO, but also included in the diagnosis of conditions including distal oesophageal spasm and hypercontractile oesophagus.

The CCv4.0 also incorporates changes in the manometric diagnosis of other oesophageal disorders. Jackhammer oesophagus in CCv3.0 has been put under the umbrella of the hypercontractile oesophagus, which includes other proposed subclasses, including single peak hypercontractile swallow and hypercontractile with LES after-contraction. On the other hand, fragmented peristalsis has been incorporated into ineffective oesophageal motility, with a requirement of > 70% ineffective (including weak, failed or fragmented) swallows or >= 50% failed swallows.

While the hierarchical approach of analysing HRM remains unchanged, oesophageal motility disorders are no longer classified into major motility disorders and minor motility disorders. Rather, in accordance to the

part of the oesophagus (the oesophageal body or the OGJ) being dysfunctional, the disorders are now termed as disorders of EGJ outflow and disorders of peristalsis (Table 1).

Table 1: Chicago 4.0 classification of oesophageal motility disorders. It is important to know that the hierarchical approach to diagnosis remains unchanged, and hence the diagnosis of disorders of EGJ outflow takes precedent over disorders of peristalsis.

Disorders of EGJ outflow	Disorders of peristalsis
Type I Achalasia	Absent contractility
Type II Achalasia	Distal oesophageal spasm
Type III Achalasia	Hypercontractile oesophagus
EGJOO	Ineffective oesophageal motility

FUNCTIONAL LUMINAL IMAGING PROBE (FLIP) TECHNOLOGY

The functional luminal imaging probe (FLIP) examination is a new addition to the Chicago classification. FLIP is a barostat catheter with multiple sensors that fills up in a controlled volumetric fashion. Aided by a technique called impedance planimetry, the cross-sectional area (CSA) can be converted based on the pressure and volume detected in each sensor. The distensibility (stiffness) is the product of CSA divided by the intra-balloon pressure[7,8].

The FLIP technology first presented itself commercially as the endolumenal functional lumen imaging probe (EndoFLIP®) in 2009. It was mainly used in highly specialised centres to measure the compliance of sphincters such as the LES and anal sphincter[9,10]. In 2017, there was an upgrade of the technology to EndoFLIP 2.0, where the data gathered through the FLIP probe could be displayed in the manner of a real time topography (Fig 1). EndoFLIP 2.0 allows detection of multiple new metrics such as the oesophageal secondary peristaltic response to the volumetric distension and thus significantly increases the value of the probe technology in motility testing. When used as an oesophageal motility test, the catheter is inserted intra-orally and the motility test is usually done in the same setting as when the patient undergoes OGD. In contrast to HRM, the patient is sedated and is not required to perform any active swallows. The FLIP catheter balloon, made of infinitely compliant plastic, carries no dilating potential, thus minimising the risk of trauma. The EndoFLIP received FDA approval in 2017 and has only been available outside America since late 2020. Due to the limited availability, most studies and data are from the EndoFLIP 1.0 system and confirmed the value of EndoFLIP in managing conditions including achalasia[11] and GERD[12,13]. From EndoFLIP 2.0 system, various metrics have been defined to show both the stiffness of the LES and the peristaltic function of the oesophagus through the secondary peristaltic response. Normative values are, however, based on a relatively small sample size and more data, especially from other ethnic groups, are in earnest need.

CONCLUSION

In summary, the Chicago 4.0 classification provides important changes that fill up the gaps noted in previous versions. There is more clarity on the protocol of both HRM and various supportive maneuvers while investigators are still allowed flexibility based on clinical need and circumstances. As there is no new equipment or software required for the HRM test, various centres can easily adopt the new classification. The demand for symptoms in making a diagnosis of some motility disorder does not weaken the importance of HRM, but rather empowers it to be more clinically relevant and the whole approach to oesophageal motility disorders coherent and sound. The FLIP technology emerges as a valuable supportive test in the arena of motility studies,

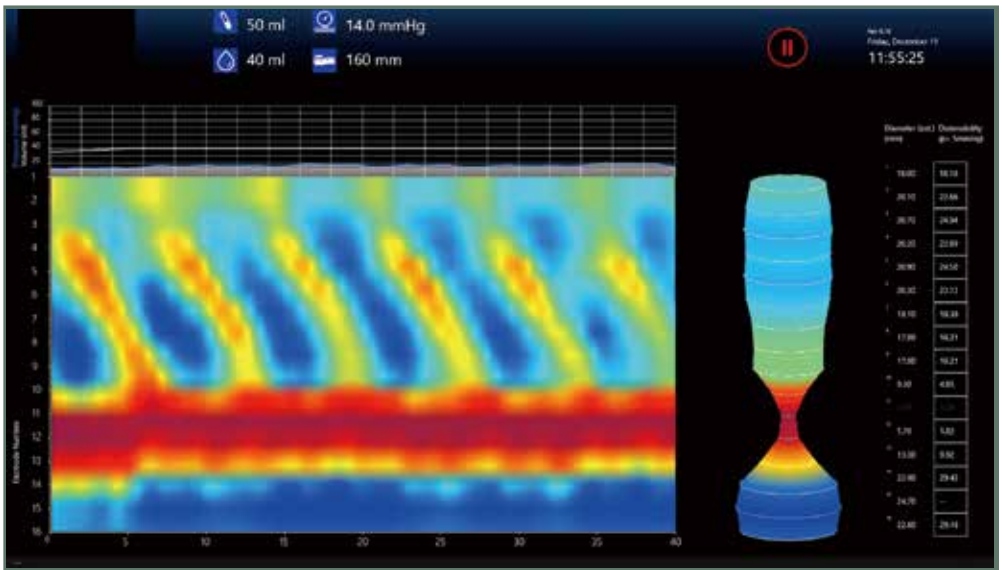

Fig. 1. FLIP planimetry of the oesophagus. The left panel shows real time planimetry of the oesophageal secondary peristalsis. The right panel shows the cross-sectional area and distensibility index (DI) of each segment. (Photo from personal collection)

and its role will be better defined with more data and studies. As the update of previous classifications has always been a dynamic process, the CCv4.0 will undoubtedly spur more interest into conditions such as the long-term significance and development of 'asymptomatic motility disorders', and indeed cases where tests such HRM and FLIP test are not **in agreement**.

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Radiology Quiz

Dr Carol PY CHIEN
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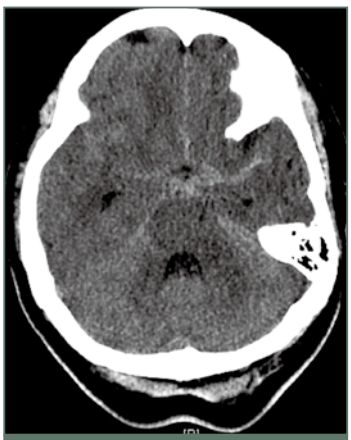

Case 1

Questions

1. What is the diagnosis?
2. What further investigations will you perform?
3. Question: What are the possible complications?

(See P.36 for answers)

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Abbreviated Prescribing Information of CORTIMENT 9mg

Active Ingredient: Budesonide. Indications: Induction of remission in adult patients w/ mild to moderate active ulcerative colitis where 5-ASA treatment is not sufficient. Dosage and Administration: One 9 mg tab in the morning, for up to 8 wk. Administration: Swallow w/ a glass of water, do not break/chew/crush. Avoid grapefruit or grapefruit juice. Contraindications: Hypersensitivity to budesonide, soya oil, peanut oil or any of the excipients. Special Precautions: Patients w/ infections, HTN, DM, osteoporosis, peptic ulcer, glaucoma or cataracts or w/ a family history of diabetes or glaucoma or cataracts or w/ any other condition where the use of glucocorticoids may have unwanted effects. Gradually reduce dose when treatment is to be discontinued. May result in lower systemic steroid levels than conventional oral glucocorticoid therapy. May reduce immune response to vaccines. Avoid concomitant administration w/ ketoconazole or other potent CYP3A4 inhibitors. Contains lecithin. Rare hereditary problems eg, galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. Adrenocortical suppression; increased susceptibility to infections; suppression of the HPA axis & reduced stress response; more serious course of chicken pox & measles; systemic effects of steroids. Patients w/ current or previous history of severe affective disorders in the patient or any 1st degree relatives. Replacement of high systemic effect corticosteroid treatment sometimes unmasks allergies eg, rhinitis & eczema. Occasional dizziness or tiredness may occur. Hepatic & renal impairment. Pregnancy & lactation. Childn 0-18 yr. Elderly. Undesirable Effects: Nausea, upper abdominal pain; headache; insomnia, mood altered; blood cortisol decrease; flu, upper resp tract viral infection. Side effects typical of systemic glucocorticosteroids may occur.

Abbreviated Prescribing Information of PENTASA Oral Formulations

Active Ingredient: Mesalazine. Indications: tab Ulcerative colitis. Crohn's disease. PR granules 1g/2g/4g Mild to moderate ulcerative colitis. PR granules 1 g/2g Crohn's disease. Dosage and Administration: (Adult) tab *Ulcerative colitis* Treatment of active disease: Up to 4 g daily in divided doses. Maintenance: 2 g once daily. *Crohn's disease* Treatment of active disease & maintenance: Up to 4 g daily in divided doses. PR granules 1g/2g/4g *Ulcerative colitis* Treatment of active disease: Up to 4 g once daily or in divided doses. Maintenance: 2 g once daily. PR granules 1g/2g *Crohn's disease* Treatment of active disease & maintenance: Up to 4 g daily in divided doses. (Childn ≥6 yr) Treatment of active disease: Initially 30-50 mg/kg/day in divided doses; max: 75 mg/kg/day in divided doses, not exceeding 4 g/day total dose. Maintenance: Initially 15-30 mg/kg/day in divided doses; not exceeding 2 g/day total dose. Administration: tab Swallow whole, do not chew/crush. If necessary, tab may be halved along scoreline or suspended in water/juice immediately before use. PR granules The contents of the sachet should be emptied onto the back of the tongue & washed down w/ water/juice. Do not chew. Contraindications: Hypersensitivity to mesalazine, salicylates or any of the excipients. Severe liver or renal impairment. Gastric or duodenal ulcer. Haemorrhagic diathesis. Special Precautions: Allergy to sulphasalazine (risk of allergy to salicylates). Discontinue in case of acute intolerance reactions. Assess liver function parameters like ALT or AST prior to & during treatment. Regularly monitor renal function (eg, serum creatinine) especially during the initial phase of treatment, especially when in concurrent use of nephrotoxic agents. Patient w/ pulmonary disease particularly asthma. Blood test for differential blood count is recommended prior to & during treatment. Increased risk of blood dyscrasia in concomitant w/ azathioprine, 6-mercaptopurine or thioguanine. Perform follow-up blood & urine tests 14 days after commencement of treatment, then a further 2-3 tests at 4-wk intervals. If the findings are normal, follow-up tests should be carried out every 3 mth. If additional symptoms occur, perform tests immediately. Pregnancy & lactation. Undesirable Effects: Commonly Headache, vertigo, diarrhoea, abdominal pain, nausea, vomiting, rash (incl. urticaria and erythematous rash), and fever.

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GA031/21/JUN/HK Jun/2021

Colorectal Cancer Screening for Individuals with Family History

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 August 2021.

INTRODUCTION

Colorectal cancer (CRC) is the commonest cancer in Hong Kong, with 5,634 newly diagnosed cases in 2018. It is also the second leading cause of cancer death in Hong Kong, accounting for 15.9% of cancer deaths in the same year.[1] Of all the CRC, around 10-20% are familial cancers, while 80-90% are sporadic cases.[2,3] Family members of CRC patients are at an increased risk of developing the disease, likely because of the shared genetic and environmental factors.[4]

FAMILY HISTORY OF COLORECTAL CANCER

Multiple meta-analyses and original studies have demonstrated that positive family history is associated with an increased risk of colorectal cancer.[3,5-10] The magnitude of increased risk is affected by specifics of family history, including the age of cancer diagnosis of the index patient, the age of the individual at-risk, the degree of familial relationship with the index patient and the number of affected relatives.[2,11-13]

Family members of CRC patients are at a higher risk of developing CRC if the affected relative was diagnosed with the disease at a younger age.[7,9,11,14] A large-scale study showed that the risk of first-degree relatives (FDR) of CRC patients developing the disease (compared to those without a family history) was in a continuum based on the age of CRC diagnosis of the index patient (Age < 40: hazard ratio (HR) 2.53; Age 40-49: HR 2.26; Age 50-59: HR 2.35; Age 60 - 69: HR 1.85; Age 70-79: HR 1.69; Age ≥ 80: HR 1.76).[7]

There is evidence that the effect of positive family history on the individual at-risk is higher when the person is younger and gradually declines as the person ages.[5,7,11,14] A meta-analysis involving 9.28 million subjects showed that family history of CRC in FDR conferred a higher risk of developing CRC for younger individuals (Relative risk (RR) 2.81, 95% CI, 1.94-4.07 for < 50 years versus RR 1.47, 95% CI, 1.28 - 1.69 for ≥ 50 years, p = 0.001).[5]

CRC risk is higher if the individual at-risk and the affected index patient has a closer familial relation. Studies showed that individuals with at least one affected FDR have around two times the risk of having colorectal cancer compared to those without family history.[8,12,15,16] A recent analysis showed that positive family history in 1 or more second-degree relatives (SDR) (with no affected FDR), however, was only associated with marginal increase risk of CRC (RR 1.18, 95% CI 1.00-1.38).[12]

For individuals who have FDR with CRC, the risk of developing CRC and colon adenoma was similar for different identities of the affected relatives (either parent versus siblings).[17]

The CRC risk of an individual was shown to increase with the number of relatives affected.[6,10,14,18] A meta-analysis showed that the RR for CRC in patients with one affected FDR was 1.37-1.92, while that for those with two or more affected FDRs was 2.4-2.81.[10]

In addition to the effect on CRC risk, the positive family history of CRC was also associated with a higher risk of developing conventional adenoma and serrated polyps.[19,20]

FAMILY HISTORY OF COLONIC POLYPS

Studies showed that a family history of colonic polyps is also associated with a higher risk of having colorectal neoplasia. A large-scale study showed a higher risk of CRC for those who had a family history of villous adenoma and sessile serrated lesions in FDR. (Odds ratios (OR) 1.4, 95% CI, 1.20-1.63 and OR 1.27, 95% CI 1.03-1.57 respectively).[21] Another study showed that family history of advanced adenoma (AA) (defined as adenoma ≥ 10 mm, high-grade dysplasia, villous or tubulovillous histology) in siblings was associated with a higher risk of advanced adenoma (OR 6.05, 95% CI, 2.74-13.36) and all colorectal neoplasia (OR 3.29, 95% CI, 2.16-5.03).[22]

SCREENING RECOMMENDATIONS

Guideline recommendations from professional organisations have suggested that individuals with a positive family history should start CRC screening earlier +/- receive more frequent testing because of their increased risk (Table 1).[2,11-13]

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the percentage of patients on 90mg q8w achieving clinical remission is:

76.3%[1]

& that on 90mg q12w is:

61.3%[1]

UNIFI LTE study^ at week 92 (2 years),

the percentage of patients on 90mg q8w achieving clinical remission is:

90.4%[2]

& that on 90mg q12w is:

89.5%[2]

Steroid-free remission:

IM-UNITI LTE study* at week 252 (5 years),

among the clinically remitted patients, the percentage of those who are steroid-free in the q8w group is:

93.3%[1]

& that in the q12w group is:

89.5%[1]

UNIFI LTE study^ at week 92 (2 years),

among the clinically remitted patients, the percentage of those who are steroid-free in the q8w group is:

97.5%[2]

& that in the q12w group is:

95.5%[2]

*The IM-UNITI LTE study evaluated the long-term efficacy, safety, and immunogenicity of subcutaneous Stelara® maintenance therapy (90mg q8w or q12w) in patients with Crohn's disease who had received intravenous Stelara® induction treatment. Patients completing safety and efficacy evaluations at week 44 of the IM-UNITI maintenance study were eligible to participate in the LTE and continue the treatment they were receiving. Of the randomized patients who entered the LTE, 82 of whom were in the q8w group, and 84 were in the q12w group. The data reported here are based on the final results of IM-UNITI LTE through 5 years. The clinical remission results are according to the modified observed case analysis, whereas the steroid-free remission results are according to the nonresponder imputation analysis.[1]

^The UNIFI LTE is an ongoing study that evaluates the efficacy and safety of subcutaneous Stelara® maintenance therapy (90mg q8w or q12w) in patients with ulcerative colitis who had responded to Stelara® induction treatment. Patients completing the 44-week UNIFI maintenance study were eligible to participate in the LTE. Of the 399 patients who were randomized in the LTE, 115 of whom received subcutaneous placebo, 141 received Stelara® 90mg q12w, and 143 received Stelara® 90mg q8w. The efficacy data reported here are up till week 92. The clinical remission results are according to the modified observed case analysis, whereas the steroid-free remission results are according to the nonresponder imputation analysis.[2]

Abbreviation:
LTE=long-term extension; **q8w**=every 8 weeks; **q12w**=every 12 weeks

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1. Sandborn WJ et al. *Clin Gastroenterol Hepatol.* 2021. In press. **2 .** Panaccione R et al. *Aliment Pharmacol Ther.* 2020;52(11-12):1658-75.

STELARA® 45 mg solution for injection in pre-filled syringe STELARA® 90 mg solution for injection in pre-filled syringe
ABBREVIATED PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): Ustekinumab. **INDICATION(S):** Plaque Psoriasis- Treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, MTX or PUVA. Psoriatic Arthritis- STELARA, alone or in combination with MTX, for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug therapy has been inadequate. Crohn's Disease- Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies. Ulcerative colitis - Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies. **DOSAGE & ADMINISTRATION:** Plaque Psoriasis & Psoriatic Arthritis- Initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg. Areas of the skin that show psoriasis should be avoided as injection sites. Crohn's Disease and Ulcerative Colitis - First dose is administered intravenously. See STELARA 130 mg concentrate for solution for infusion package insert for intravenous dosing posology. First 90 mg subcutaneous dose should take place at week 8 after intravenous dose, and then every 12 weeks thereafter. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. Clinically important, active infection (e.g. active tuberculosis). **SPECIAL WARNINGS & PRECAUTIONS:** Traceability: For better traceability of biological medicinal products, the tradename and the batch number of the administered product should be recorded. Infections: Serious bacterial, fungal, and viral infections have been observed in clinical studies. Caution should be exercised in patients with chronic infection or history of recurrent infection. Evaluate patients for tuberculosis infection before treatment. STELARA must not be given to patients with active tuberculosis. Closely monitor patients for signs and symptoms of active tuberculosis during and after STELARA treatment. Closely monitor patient in case of serious infection and discontinue STELARA until the infection resolves. Malignancies: Some patients developed cutaneous and non-cutaneous malignancies in clinical studies. Caution should be exercised in patients who have a history of malignancy or develop malignancy while receiving STELARA. Monitor patients for appearance of non-melanoma skin cancer. Systemic and respiratory hypersensitivity reactions: Serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) and cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia have been reported in postmarketing setting. Discontinue STELARA and institute appropriate therapy if hypersensitivity reaction occurs or if infection has been excluded and diagnosis is confirmed. Vaccinations: Live viral or live bacterial vaccines (e.g. BCG) should not be given concurrently with STELARA. Before live viral or live bacterial vaccination, STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Concomitant immunosuppressive therapy: Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics. Serious skin conditions: Exfoliative dermatitis has been reported in STELARA patients with psoriasis. Physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. Discontinue STELARA and institute appropriate therapy if such symptoms occur. Elderly: Because there is a higher incidence of infections in elderly in general, caution should be used in treating the elderly. **SIDE EFFECTS:** Nasopharyngitis, headache and serious hypersensitivity reactions including anaphylaxis. Refer to full prescribing information for other side effects. **PREGNANCY & LACTATION:** Use effective methods of contraception during STELARA treatment and for at least 15 weeks after treatment. It is preferable to avoid the use of STELARA in pregnancy. A decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman. **INTERACTIONS:** Live vaccines. **PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.** aPI version to be quoted on promotional material: Stelara aPI ver 6.0

STELARA® 130 mg concentrate for solution for infusion
ABBREVIATED PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): Ustekinumab **INDICATION(S):** Crohn's Disease- Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies. Ulcerative colitis - Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies. **DOSAGE & ADMINISTRATION:** Treatment initiated with a single intravenous dose based on body weight: ≤ 55 kg- 260 mg; > 55 kg to ≤ 85 kg- 390 mg; > 85 kg- 520 mg. Should be administered over at least one hour. The first subcutaneous dose should be given at week 8 following the intravenous dose. See STELARA solution for injection in pre-filled syringe package insert for subcutaneous dosing posology. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. Clinically important, active infection (e.g. active tuberculosis). **SPECIAL WARNINGS & PRECAUTIONS:** Traceability: Tradename and the batch number of the administered product should be recorded for traceability. Infections: Serious bacterial, fungal, and viral infections have been observed in clinical studies. Caution should be exercised in patients with chronic infection or history of recurrent infection. Evaluate patients for tuberculosis infection before treatment. STELARA must not be given to patients with active tuberculosis. Closely monitor patients for signs and symptoms of active tuberculosis during and after STELARA treatment. Closely monitor patient in case of serious infection and discontinue STELARA until the infection resolves. Malignancies: Some patients developed cutaneous and non-cutaneous malignancies in clinical studies. Caution should be exercised in patients who have a history of malignancy or develop malignancy while receiving STELARA. Monitor patients for appearance of non-melanoma skin cancer. Systemic and respiratory hypersensitivity reactions: Serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) and cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia have been reported in postmarketing setting. Discontinue STELARA and institute appropriate therapy if such reaction occurs. Vaccinations: Live viral or live bacterial vaccines (e.g. BCG) should not be given concurrently with STELARA. Before live viral or live bacterial vaccination, STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Concomitant immunosuppressive therapy: Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics. Serious skin conditions: Exfoliative dermatitis has been reported in STELARA patients with psoriasis. Physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. Discontinue STELARA and institute appropriate therapy if such symptoms occur. Elderly: Because there is a higher incidence of infections in elderly in general, caution should be used in treating the elderly. Sodium content: The product shall dilute in sodium chloride solution for infusion and this should be taken into consideration for patients on a controlled sodium diet. **SIDE EFFECTS:** Nasopharyngitis, headache and serious hypersensitivity reactions including anaphylaxis. Refer to the full prescribing information for other side effects. **PREGNANCY & LACTATION:** Use effective methods of contraception during STELARA treatment and for at least 15 weeks after treatment. It is preferable to avoid the use of STELARA in pregnancy. A decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman. **INTERACTIONS:** Live vaccines. **PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.** API version to be quoted on promotional material: Stelara IV aPI ver 2.0

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Table 1 Guideline recommendations for individuals with family history of non-hereditary CRC

Organisation	Family history	Recommendation
CHP Cancer Expert Working Group 2017[2]	1 FDR with CRC at ≤ 60y or ≥ 2 FDR with CRC at any age	Start CLN at 40y or 10y before the earliest CRC (but not earlier than 12y), repeat every 5y
American College Gastroenterology 2021[11]	1 FDR with CRC (or AP) at < 60y or ≥ 2 FDR with CRC (or AP) at any age 1 FDR with CRC (or AP) at ≥ 60y 1 SDR with CRC (or AP)	Start CLN at 40y or 10y before the earliest CRC (whichever is earlier), repeat every 5y Start screening at 40y or 10y before the earliest CRC, repeat as average risk Screen as average risk
National Comprehensive Cancer Network 2021[13]	≥ 1 FDR with CRC at any age SDR or TDR with CRC at any age FDR with AP	Start CLN at 40y or 10y before the earliest CRC, repeat every 5y Screen as average risk Start CLN at 40y or age of onset of adenoma in relative (whichever is earlier), repeat every 5 - 10y
Canadian Association of Gastroenterology Banff Consensus 2018[12]	≥ 2 FDR with CRC 1 FDR with CRC ≥ 1 FDR with AA ≥ 1 SDR with CRC	Start CLN at 40y or 10y before the earliest CRC (whichever is earlier), repeat every 5y CLN is the preferred test, FIT as second-line option Start screening 40-50y or 10y before diagnosis of CRC in FDR (whichever is earlier), repeat CLN 5-10y Start screening (with either CLN or FIT) at 40-50y or 10y before the earliest AA (whichever is earlier), repeat CLN 5-10y or repeat FIT 1-2y Screen as average risk

AA: advanced adenoma; AP: advanced polyp; CHP, Centre for Health Protection; CLN: colonoscopy; CRC: colorectal cancer; FDR: first-degree relatives; FIT: faecal immunochemical test; SDR: second-degree relatives; TDR: third-degree relatives
Advanced polyp (AP) includes advanced adenoma (≥ 1cm, high grade dysplasia, villous or tubulovillous histology) and advanced serrated polyp (≥1cm, any dysplasia, traditional serrated adenoma)

It is recommended that persons with a family history of CRC in FDR start screening at age 40 or 10 years prior to the earliest CRC diagnosed in the family. The reason to start screening earlier for individuals with a family history is that they tend to have early-onset disease. Fuchs CS et al. showed that the age-specific cumulative incidence of CRC for persons with family history in FDR at around 35-40 years of age was similar to that for average-risk people at 50 years of age.[14]

Multiple professional organisations suggested that for individuals with a family history of CRC in FDR, the screening interval should be five years. Studies showed that positive family history in FDR is associated with metachronous colorectal adenoma after polypectomy.[23,24] A large-scale study with a long follow-up period showed that the protective effect of colonoscopy for individuals without family history lasts beyond five years (multivariate HR for CRC 0.43, 95% CI, 0.32-0.58) but the protective effect was no longer observed beyond five years after colonoscopy for individuals with family history (multivariate HR for CRC 0.91, 95% CI, 0.55-1.52).[25] Another study showed that for patients with a family history of CRC and a history of normal colonoscopy five years earlier, 8% and 33% of patients were found to have advanced adenomas and adenomas, respectively, on surveillance colonoscopy.[26] These findings support that persons with a family history of CRC in FDR should receive more frequent screening than average-risk persons.

Colonoscopy is the preferred screening test for patients with a family history of CRC in FDR because it offers the highest sensitivity for CRC and colonic polyps.[2,11,13] Faecal immunochemical test (FIT) is considered the alternative option if the patient refuses colonoscopy. A meta-analysis evaluating the use of FIT in patients at increased risk of CRC (include patients with a family history or personal history of CRC) showed that FIT had overall high diagnostic accuracy for CRC (sensitivity 93%, specificity 91%) and moderate diagnostic accuracy for advanced adenoma (sensitivity 48%, specificity 93%).[27]

Enhanced screening is also recommended for individuals with a family history of AA or advanced serrated lesions (sessile serrated lesion ≥ 1cm, sessile serrated lesion with dysplasia and traditional serrated adenoma) in FDR, given the increased risk of colorectal neoplasia associated with such family history.[21,22] In practice, however, family history of advanced polyps (which include both AA and advanced serrated polyps) may be difficult to ascertain since patients may not know the details of their relative's colonic polyp. Therefore, the recommendation of enhanced screening only applies to those with a family history of "documented advanced polyp". If the details of FDR's colonic polyps are not known, they should be considered "non-advanced polyp".

The risk of CRC amongst individuals with a family history in only SDR is only marginally increased.[12] Current guidelines do not recommend enhanced screening for family members who have CRC in only SDR.

ASSESSING CRC RISK DUE TO FAMILY HISTORY

We should assess each component of the patient's family history, including the number of relatives with CRC (and/or advanced polyps), familial relationship with the affected relatives and relative's age of CRC diagnosis. With this information, we can assess the degree of increased risk of CRC due to family history for the patient and provide appropriate CRC screening recommendations.

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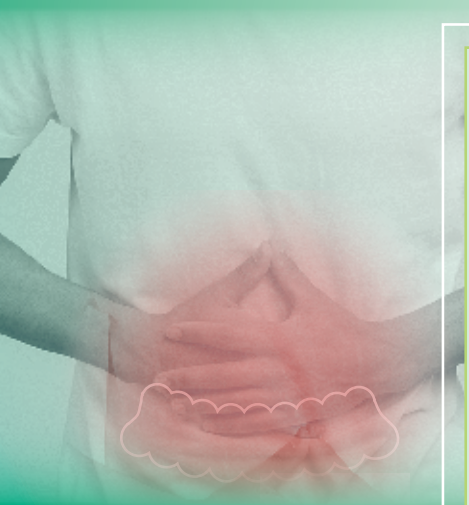

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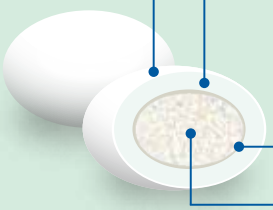

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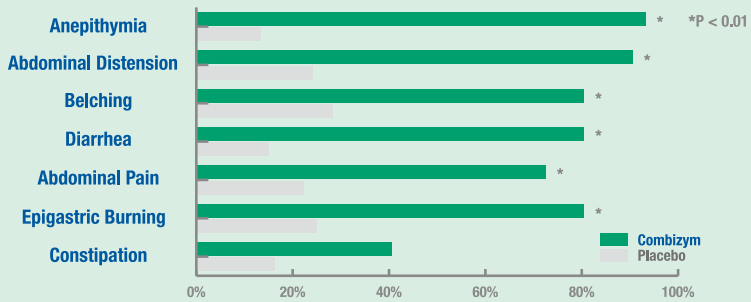

^FIP: International Pharmaceutical Federation (1974)

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and the occurrence of CRC and multiple other cancers in a single individual, hereditary CRC syndrome (e.g. Lynch syndrome, familial adenomatous polyposis) should be suspected. These families should be referred for genetic counselling and testing. If the diagnosis of hereditary colorectal cancer syndrome is confirmed, affected individuals should receive enhanced screening based on their underlying diagnosis.[2,11,16]

CONCLUSION

Individuals with a family history of CRC are at increased risk of developing the disease. In order to reduce the incidence and mortality of CRC, enhanced screening is recommended for them, and the screening schedule can be tailored based on the specifics of their family history.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Colorectal Cancer Screening for Individuals with Family History" by Dr Frank Yuk-fai LAM and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 August 2021. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. Of all the colorectal cancer (CRC), around 40% are familial cancers.
2. Family members of colorectal cancer patients are at a higher risk of developing cancer if the affected relative was diagnosed with the disease at a younger age.
3. Colorectal cancer risk is higher if the individual at-risk and the affected index patient have a closer familial relation.
4. The colorectal cancer risk of an individual increases with the number of relatives affected.
5. People with a family history of colorectal cancer (CRC) in first degree relatives should start screening five years prior to the earliest CRC diagnosed in the family.
6. For individuals with a family history of colorectal cancer in first degree relatives, the screening interval should be ten years.
7. Colonoscopy is the preferred screening test for patients with a family history of colorectal cancer in first degree relatives.
8. Enhanced screening isrecommended for individuals with a family history of advanced adenoma even though there is no colorectal cancer.
9. Enhanced screening is recommended for family members who have colorectal cancer in only second-degree relatives.
10. For families with multiple members diagnosed with colorectal cancer (CRC), early-onset CRC, and the occurrence of CRC and multiple other cancers in a single individual, they should be referred for genetic counselling and testing.

ANSWER SHEET FOR AUGUST 2021

Please return the completed answer sheet to the Federation Secretariat on or before 31 August 2021 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Colorectal Cancer Screening for Individuals with Family History

Dr Frank Yuk-fai LAM

MBBS (HK), MRCP (UK), FHKCP, FHKAM (Medicine)

Specialist in Gastroenterology and Hepatology
Clinical Assistant Professor, Department of Medicine and the HKU Endoscopy Centre, The University of Hong Kong

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

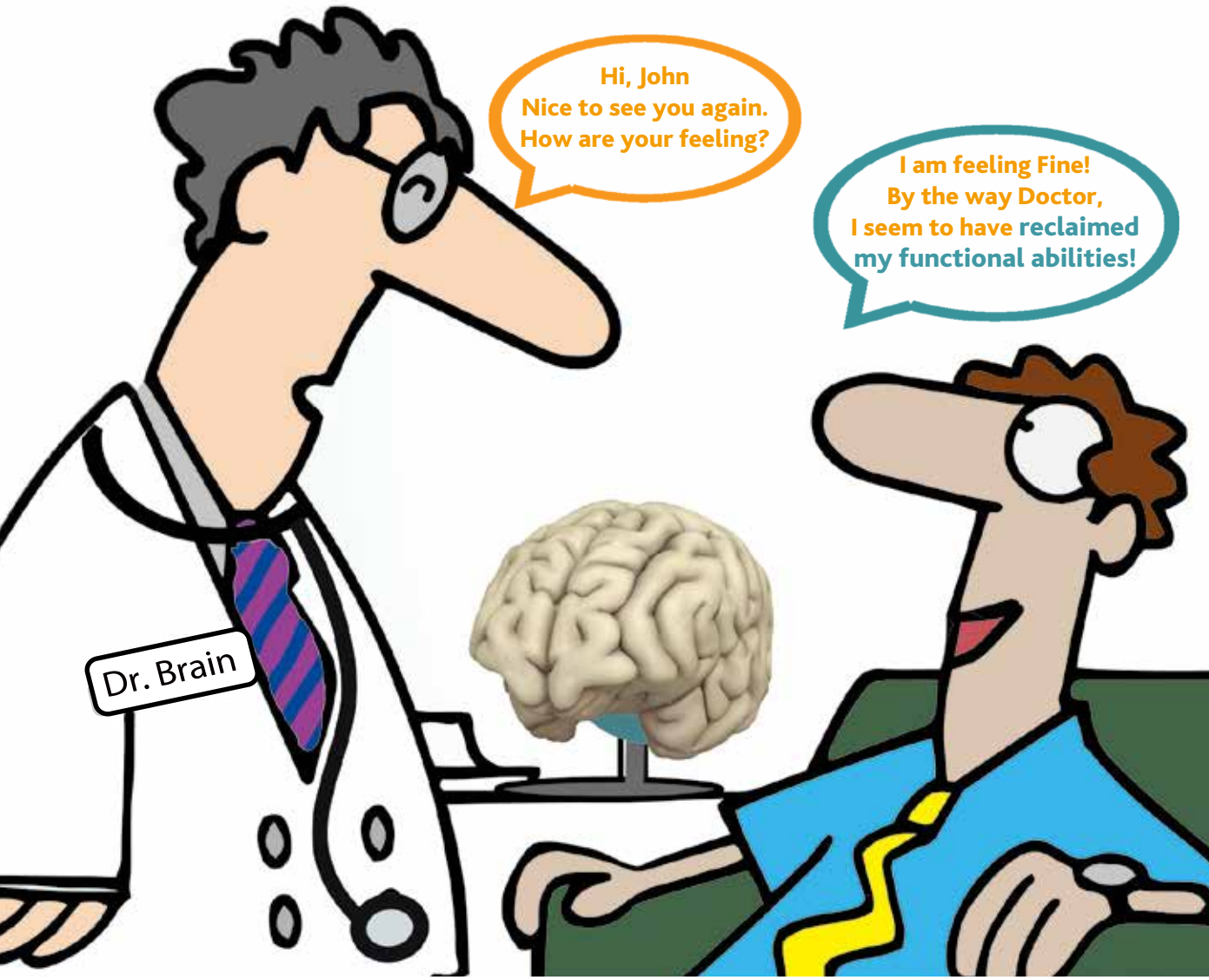
Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to July 2021 Issue

Why is My Wrist Painful after Sports?

1. F **2.** F **3.** F **4.** T **5.** T **6.** F **7.** F **8.** T **9.** T **10.** T

Restore Patients' Functioning from Depression



BRINTELLIX® (VORTIOXETINE) - ABBREVIATED PRESCRIBING INFORMATION
Brintellix®: Active Substance: Vortioxetine Hydrobromide. **Presentation:** Film-coated tablets 5mg, 10mg and 20mg. **Indication:** Treatment of major depressive episodes in adults. **Dosage:** Adults: starting and recommended dose is 10mg, once-daily, taken with or without food. Elderly ≥65 years: Starting dose 5mg. Children and adolescents (<18 years): should not be used. Discontinuation: Patients can abruptly stop taking the medicinal product without the need for a gradual reduction in dose. **Contraindications:** Hypersensitivity to vortioxetine or to any of the excipients. Combination with MAO-inhibitors. Should not be used during pregnancy or lactation unless clearly needed and after careful consideration of the risk/benefit. **Special warnings and precautions:** Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide. It is a general clinical experience that the risk of suicide may increase in the early stages of recovery. Close supervision of high-risk patients should accompany drug therapy. Patients (and caregivers) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present. Should be introduced cautiously in patients who have a history of seizure or in patients with unstable epilepsy. Patients should be monitored for the emergence of signs and symptoms of Serotonin Syndrome or Neuroleptic Malignant Syndrome. Should be used with caution in patients with a history of mania/hypomania and should be discontinued in any patient entering a manic phase. There have been reports of cutaneous bleeding abnormalities with the use of SSRIs/SNRIs. Hyponatraemia has been reported rarely with the use of SSRIs/SNRIs. Caution should be exercised for patients with renal or hepatic impairment. **Interactions:** Caution is advised when taken in combination with MAO-inhibitors, serotonergic medicinal products, products lowering the seizure threshold, lithium, tryptophan, St. John's Wort, oral anticoagulants or antiplatelet agents, and products predominantly metabolised by the enzymes CYP2D6, CYP3A4, CYP2C9, and Cytochrome P450. **Undesirable effects:** Adverse reactions are most frequent during the first or second week of treatment and usually decrease in intensity and frequency with continued treatment. Very common: Nausea. Common: abnormal dreams, dizziness, diarrhoea, constipation, vomiting, pruritus, including pruritus generalised. Uncommon: flushing, night sweats. Not known: Hyponatraemia, Serotonin Syndrome, Angioedema, Urticaria. **Overdose:** Symptomatic treatment. The most frequently reported symptoms were nausea and vomiting for overdoses of up to 80 mg and seizure and serotonin syndrome for overdoses above 80 mg. **Marketing Authorisation Holder:** Lundbeck HK Limited. Revision Date: Feb 2020 based on HK SmPC dated Aug 2019. **Further information is available upon request.**

HK-LU-2021.04-AD01

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Microbiota and Colorectal Cancer

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INTRODUCTION

Colorectal cancer (CRC) is a prevalent cancer, accounting for about 10% of all new cases worldwide. Due to its proximity to the colorectal epithelium, the intestinal microbiota plays an increasingly important role in CRC. Recent studies have identified the role of several bacteria in the development of CRC. These findings provide new opportunities for using these microorganisms for clinical applications, such as detecting them as diagnostic or prognostic biomarkers. With new evidence suggesting that the gut microbiome plays a role in cancer treatment, its modulation has the potential to shrink tumours, enhance treatment, reduce treatment side effects and prevent cancer recurrence. The purpose of this article is to review the recent advances in the occurrence of microbial CRC and the translational potential of these findings.

GUT MICROBIOTA IN CRC

CRC is one of the most common cancers and presents a major burden on global health. Like many common diseases, cancer formation in the large intestine is multifactorial and is caused by various genetic and environmental factors. However, twin and family studies estimate that the heritability of CRC is only 12-35%[1], reflecting the importance of the environment as a major determinant of disease.

Among environmental factors, the role of intestinal microbiota in the development of CRC has received the most attention. There is early evidence from animal studies supporting the pathogenic role of microorganisms in CRC. In one experiment in which both germ-free and conventional mice were treated with carcinogens, 93% of the conventional mice and only 21% of the germ-free mice developed colon tumours[2]. In addition, human studies using comparative metagenomic methods have shown that the CRC microbiota differs from that of healthy controls. In general, the CRC microbiota exhibits a different microbial structure, often referred to as ecological dysregulation, reflecting the different ecological environments of patients with CRC. While specific strains of *Bacteroides fragilis, Escherichia coli*, and *Streptococcus gallolyticus* have been linked to CRC, recent studies have found new associations with other bacteria. These bacteria include *Fusobacterium nucleatum*[3], a species not previously associated with cancer, as well as *Parvimonas, Peptostreptococcus, Porphyromonas* and *Prevotella*. They were found to be more abundant in patients with CRC. Some of these bacteria are closely associated with inflammation, immune regulation and biofilm formation - pathologic processes that are closely associated with cancer formation[4]. Understanding these mechanisms may provide insights into their modulation for therapeutic purposes.

GUT MICROBIOTA AS BIOMARKERS FOR SCREENING CRC

An emerging application of the gut microbiota discovery is on biomarkers. A biomarker is an indicator of the presence or severity of a disease. Given the global health burden of CRC, there is an urgent need for an accurate, affordable and non-invasive CRC test, especially for early neoplasia, which can be treated with excellent clinical outcomes. For example, the 5-year survival rate for Stage I CRC is as high as 90%, compared with approximately 10% for Stage IV metastatic disease. Current stool-based occult blood tests have limited sensitivity in the detection of CRC and advanced adenoma[5]. Although the multi-target faecal DNA test may detect more cancers than the faecal immunochemical test (FIT), the sensitivity of the latter to detect advanced adenomas is still not ideal.

In this regard, some studies have made use of the abundance of bacterial species to distinguish patients with CRC from healthy individuals. Two case-control studies used > 20 microbial biomarkers, giving an area under the receiver operating characteristic (AUROC) curve of 0.84[6,7]. In a metagenomic study comparing patients with CRC with healthy individuals in Hong Kong, a panel of 20 microbial genes were identified to be associated with disease status[8]. This set of microbial markers can be trimmed into two information-rich biomarkers, quantifiable by polymerase chain reaction (PCR), to achieve an AUC of 0.84[8]. Among different candidate bacteria, *F nucleatum* appeared as a key marker either when tested alone or with other bacteria[9]. The faecal abundance of *F nucleatum* can enhance the detection of CRC by FIT[9,10], with superior sensitivity and specificity. For example, the addition of faecal *F nucleatum* has been shown to increase the AUC of FIT from 0.85 to 0.95[9]. This finding illustrates the advantage of multi-target testing, in which individual components can complement each other to enhance test performance. The best test may come from a panel balancing the number of markers, the diagnostic performance, the logical feasibility and simplicity of analysis.

An even more useful screening test would be the detection of colorectal adenoma. CRC develops

QINLOCK™
(ripretinib) 50 mg tablets

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Reliable Protection

Qinlock: the FIRST switch-control kinase inhibitor
indicated for 4th-line treatment of advanced GIST*[1]

Now Recommended
by the National Comprehensive Cancer Network® (NCCN®)[2]
Category 1

GIST=gastrointestinal stromal tumor
*Advanced GIST can be locally advanced or metastatic[3]

Reference: 1. QINLOCK Abbreviated Prescribing information. Jun 2020 **2.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastrointestinal Stromal Tumors (GISTs) V.1.2021. ©National Comprehensive Cancer Network, Inc. 2020. Accessed October 30, 2020. **3.** Understanding Advanced and Metastatic Cancer. American Cancer Society. https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html. Accessed on May 5, 2021.

Abbreviated Prescribing Information

INDICATIONS
Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib.

DOSAGE AND ADMINISTRATION
150mg (three 50mg tablets) taken orally once daily. Dosage reduction for adverse reaction is 100mg orally once daily. Permanently discontinue QINLOCK in patients who are unable to tolerate 100 mg orally once daily. Please refer to the full prescribing information for recommended dosage modifications for adverse reactions and missed dose.
Qinlock is not indicated in pediatrics (<18 years old). No dose adjustment is required for geriatrics (≥65 years old).
Renal impairment - No dose adjustment is recommended for patients with mild and moderate renal impairment [creatinine clearance (CrCl) 30 to 89 mL/min estimated by Cockcroft-Gault]. The pharmacokinetics and safety of Qinlock in patients with end-stage renal disease (CrCl <15mL/min estimated by Cockcroft-Gault or requiring dialysis) or severe renal impairment (CrCl 15 to 29 mL/min) have not been studied.
Hepatic impairment - No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin 1.0 to 1.5 x ULN). The pharmacokinetics and safety of Qinlock in patients with moderate or severe hepatic impairment have not been studied.

CONTRAINDICATIONS
Hypersensitivity to ripretinib or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.

WARNINGS AND PRECAUTIONS
The following are clinically significant adverse events: 1) Cardiac dysfunction. Cardiac failure and Grade 3 decreased ejection fraction has occurred in clinical study. Cardiac dysfunction has led to dose discontinuation. An assessment of the ejection fraction by echocardiogram or MUGA scan is recommended prior to initiation and during treatment, as clinically indicated. Permanently discontinue Qinlock for Grade 3 or 4 left ventricular systolic dysfunction; 2) Hypertension. Higher incidence of hypertension in patients treated with Qinlock than in placebo-treated patients in clinical study. Do not initiate Qinlock in patients with uncontrolled hypertension. Adequately control blood pressure prior to initiating Qinlock; 3) New primary cutaneous malignancies. Squamous cell carcinoma (SCC) of the skin and melanoma, actinic keratosis, keratoacanthoma and melanoma were reported in patients who received Qinlock in clinical study. Dermatological assessment should be performed when initiating Qinlock and patients should receive dermatological examinations routinely.
Other warnings and precautions include cardiac ischaemic events, hypersensitivity, wound healing, reproduction, fertility, palmar-plantar erythrodysesthesia syndrome [PPES] and photosensitivity.

PREGNANCY AND BREAST-FEEDING
Pregnancy - Qinlock should not be administered to pregnant women. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception to commence 2 weeks prior to treatment, during treatment and for at least one complete uterine cycle after the final dose of Qinlock.
Breast-feeding - Advise women not to breastfeed during treatment and for at least 2 weeks after the final dose.

ADVERSE REACTIONS
The most common adverse events (≥20%) observed in clinical study were alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia syndrome, and vomiting. Serious adverse events occurred in 31% of patients who received Qinlock. Serious adverse reactions that occurred in >2% of patients were abdominal pain (4.7%), anemia (3.5%), nausea (2.4%), vomiting (2.4%).
Dosage interruptions due to an adverse event occurred in 23.5% of patients who received Qinlock. Adverse events requiring dosage interruption in >2% of patients included nausea (3.5%), increased blood bilirubin (2.4%), and PPES (2.4%).
Dose reductions due to an adverse event occurred in 7.1% of patients who received Qinlock. Adverse events resulting in a dose reduction in ≥1.2% of patients were abdominal pain, agitation, alopecia, arthritis, dermatosis, gastrointestinal disorder, hyperesthesia, myalgia, PPES, and decreased weight.
Permanent discontinuation due to an adverse event occurred in 8.2% of patients who received Qinlock. Adverse events resulting in permanent discontinuation in ≥1% of patients included general physical health deterioration (2.4%), anemia (1.2%), cardiac failure (1.2%), PPES (1.2%), and vomiting (1.2%).

DRUG INTERACTIONS
In vitro data suggested that CYP3A4/5 is the major metabolizer of ripretinib. Potential interactions may occur with drugs/foods/herbs that are inhibitors or inducers of this enzyme system. Monitor patients more frequently for adverse reactions if Qinlock is given concurrently with a strong CYP3A inhibitor. Avoid concomitant use of Qinlock with strong CYP3A inducers. Monitor patients who ingest grapefruit juiced while taking Qinlock. Avoid concomitant use with St. John's wort.
Please refer to the full prescribing information before prescribing.
Ref. HKPI Nov 2020 (Canadian PM 19 Jun 2020)

HK-QIN-202104-03

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through progressive evolution from normal mucosa to a precursor lesion and finally a malignant tumour. An adenoma is the primary precursor lesion of CRC, and once identified, it can be removed by colonoscopic resection. Therefore, there is a need to detect adenomatous polyps, especially advanced neoplasms, in the screening tests apart from detecting early CRC. In this regard, people have studied the use of microbial markers to detect colorectal adenoma. Combining five bacterial abundance data and clinical parameters, faecal microbial markers have been shown to distinguish adenomas from the control group with an AUC of 0.90[7,11]. A subsequent study has also identified a *Lachnoclostridium* marker for diagnosing colorectal adenoma[12]. Although the difference from healthy control was less distinctive, this finding showed that a non-invasive biomarker for this cancer precursor is possible.

GUT MICROBIOTA FOR CRC THERAPEUTIC MODULATION

In addition to its pathogenic role in tumour formation, there is evidence that the intestinal microbiota can affect the efficacy and side effects of oncological therapies[11]. The microbiota can be used to predict treatment responses and adverse reactions, and its modulation could potentially facilitate cancer treatment and improve patient outcomes. Some of these studies provide insights into managing patients in novel and personalised ways.

Data from studies suggest that the efficacy of some chemotherapeutic agents, including cyclophosphamide[13] and oxaliplatin[14], can be affected by the gut microbiota. The chemotherapeutic drug 5-fluorouracil has been shown to induce its cytotoxic effects through bacterial ribonucleotide metabolism[15]. Apart from chemotherapy, there is considerable interest in manipulating the microbiota to improve immunotherapy. Immunotherapy is an effective treatment for many cancers. The gut microbiota is required for mounting an effective immune response following administration of checkpoint inhibitors, including those targeting the programmed cell death protein 1 (PD-1) axis[16]. Specific bacteria were positively correlated with immunotherapy response, including *Akkermansia muciniphilia*[17], *Bifidobacterium*[16] and *Faecalibacterium*[18]. In addition, the intestinal microbiota may modulate the side effects of immunotherapy as certain bacteria have been found to be associated with susceptibility to immunotherapy-induced colitis[19]. Faecal microbiota transplantation (FMT) has been used to treat patients with refractory immunotherapy-associated colitis[20].

CONCLUSION

Over the past decade, extensive research has identified the microbiota as important in cancer formation, particularly in CRC, where the cancer growths are closely located to the microbiota. The important role of microbiota in the development of CRC presents unprecedented opportunities, though not without challenges, for new applications of CRC diagnosis and management. Some challenges include the validation of biomarkers in different populations to determine the best marker combination, as well as developing effective microbial products as part of cancer treatment. Regardless, valuable microbiota studies have expanded our understanding of cancer formation and provided new opportunities for developing novel diagnosis and treatment applications. With exciting developments in this rapidly growing field, the microbiota will become an important part of cancer prevention and treatment in the future.

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☑ % Patients with CSBM 24 hr after 1st dose[3]

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6.4%	17.0%	10.6%
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☑ Median time to 1st SBM after 1st dose[3]

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		$p < 0.0001$

No Worsening of Symptoms Compared with Baseline Following Withdrawal[4]

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Recommended dosing for IBS-C in adults:

- 290 mcg one-capsule once-daily[5]
- Take on empty stomach ≥ 30 min before first meal[5]

International Guideline Recommendations:

World Gastroenterology Organisation
2015 Global Guidelines[6]
- ☑ Linaclotide is safe and effective for IBS-C treatment

American Gastroenterological Association
2014 Institute Guideline[7]
- ☑ Strong recommendation
- ☑ High-quality evidence

Canadian Association of Gastroenterology
2019 Practice Guidelines[8]
- ☑ Strong recommendation
- ☑ High-quality evidence

Abbreviations: CSBM = complete spontaneous bowel movement. GC-C = guanylate cyclase-C. IBS-C = irritable bowel syndrome with constipation. SBM = spontaneous bowel movement.

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Abbreviated Prescribing Information (version API.HK.LIN.0118):
Presentation: 290 micrograms linaclotide capsule. **Indications:** Symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults. **Dosage:** 290 micrograms once daily. Taken at least 30 minutes before a meal. **Contraindications:** Hypersensitivity to linaclotide or excipients. Known or suspected mechanical gastrointestinal obstruction. **Precautions:** Discontinue in prolonged (e.g. more than 1 week) or severe diarrhoea until resolved. Control electrolyte if prone to disturbance of water or electrolyte balance (e.g. >65 years old, CV diseases, diabetes, hypertension). Not recommended in <18 years old, and during pregnancy or breast-feeding. **Interactions:** Neither a substrate nor an inhibitor/inducer of the cytochrome P450 enzyme. Proton pump inhibitors, laxatives or NSAIDs may increase risk of diarrhoea. Efficacy of oral contraceptives and medicinal products absorbed in the intestinal tract with a narrow therapeutic index (e.g. levothyroxine) may be reduced. **Undesirable effects:** The most frequently reported adverse reaction (<20%) was diarrhoea. Other common adverse reactions (<10%) were abdominal pain, abdominal distension, flatulence, viral gastroenteritis and dizziness. Uncommon adverse reactions (<1%) included lower gastrointestinal bleeding, hypokalaemia, dehydration, decreased appetite and orthostatic hypotension. **Full local prescribing information is available upon request.**

Please contact (852) 2420-7388 or HKPatientSafety@astrazeneca.com for adverse drug reactions (ADR) reporting to AZHK.

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Helping Patients Since 2001[1]

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20 Years AND STILL GROWING

High 8-Week Healing Rate

89.1% – 95.5%[3–9]

(And **82.4%** in a study[10] that recruited only Los Angeles grade C or D patients).

4% Absolute Increase in Healing Rate

vs. lansoprazole 30 mg, omeprazole 20 mg, and pantoprazole 40 mg.[11]

Effective Symptom Relief

In **patients with persistent GERD symptoms** after PPI treatment,*
8 weeks of Nexium™ 40 mg delivered:[12]

- ⬇ **Heartburn Frequency: –3.4 days / wk**
- ⬇ **Acid Regurgitation: –2.6 days / wk**
- ⬇ **Epigastric Pain: –3.6 days / wk**

} $p < 0.0001$

*Omeprazole 20 mg (71%), lansoprazole 30 mg (27%), or rabeprazole 40 mg (2%).

Sustained Acid Control

⬆ 3.1 – 6.3 Hrs of Intragastric pH > 4

Nexium™ 40 mg vs. lansoprazole 30 mg, omeprazole 20 mg, rabeprazole 20 mg (all $p < 0.0001$), and pantoprazole 40 mg ($p < 0.001$) at steady state.[2]

MUPS Technology

(Multiple-Unit Pellet System)[15]

for Flexible Administration

Tablet can be dispensed in non-carbonated water and administered through a gastric tube.[9]

Effective *H. Pylori* Eradication

Demonstrated high eradication rates in two **Hong Kong studies** of standard triple therapy:

84.6% – 92.7%[13,14]

Dosing[9]

For GERD

- Treatment of Erosive Reflux Esophagitis: 40 mg once daily for 4 weeks.*
- Long-term Management of Patients with Healed Esophagitis to Prevent Relapse: 20 mg once daily.
- Symptomatic Treatment of GERD: 20 mg once daily in patients without esophagitis.†,‡,§

* An additional 4 weeks treatment is recommended for patients with unhealed esophagitis or persistent symptoms.
† Patient should be further investigated if symptom control not achieved after 4 weeks.
‡ Once symptoms resolved, symptom control may be achieved using 20 mg once daily.
§ In adults, on-demand 20 mg once daily can be used when needed (not recommended in NSAID-treated patients at risk of developing gastric and duodenal ulcers).

For *H. Pylori* Eradication

- 7-Day BID Triple Therapy: 20 mg Nexium™ + 1 g Amoxicillin + 500 mg Clarithromycin

Abbreviations: BID = twice daily. GERD = gastroesophageal reflux disease. *H. pylori* = *Helicobacter pylori*. PPI = proton pump inhibitor.

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Abbreviated Prescribing Information (version API.HK.NEX.0416):
Presentation: Esomeprazole film-coated tablet. **Indications & Dosage:** Treatment of erosive reflux esophagitis: 40 mg once daily for 4 weeks and an additional 4 weeks for patients in whom esophagitis has not healed or have persistent symptoms. Long-term management of patients with healed esophagitis to prevent relapse: 20 mg once daily. Symptomatic treatment of GERD: 20 mg once daily (consult doctors if symptoms have not disappeared after 4 weeks). Healing or prevention of relapse of peptic ulcers associated with H. pylori: 20mg esomeprazole with 1g amoxicillin & 500 mg clarithromycin, all bd for 7 days. Healing of gastric and duodenal ulcers in patient requiring continued NSAID therapy: 20 mg once daily for 4 - 8 weeks. Prevention of gastric and duodenal ulcers in patient requiring continued NSAID therapy: 20 mg once daily. Prolonged treatment after IV induced prevention of rebleeding of peptic ulcers: 40mg once daily for 4 weeks after i.v. induced prevention of rebleeding of peptic ulcers. Treatment of Zollinger Ellison Syndrome: 40 mg twice daily initially, 80-160mg for maintenance, with doses >80mg, shouldbe divided into twice daily. Prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers: 80mg IV bolus infusion over 30 minutes followed by Nexium IV infusion of 8mg/h over 3 days, followed by oral acid suppression therapy. **Contraindications:** Hypersensitivity to esomeprazole, substituted benzimidazoles or any of the other constituents of the formulation, or other proton pump inhibitors (e.g. pantoprazole, lanzoprazole, rabeprazole, omeprazole). Co-administration with nelfinavir. **Precautions:** Severe renal and hepatic impairment; Pregnancy & lactation; Exclude gastric malignancy before treatment; Increased risk of gastrointestinal infections; Co-administration with atazanavir; Discouraged use of esomeprazole and clopidogrel. Concomitant use with methotrexate may elevate and prolong serum levels of methotrexate. Severe hypomagnesemia has been reported. High dose or >1 year use may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. May reduce absorption of vitamin B12. Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus. **Interactions:** Ketoconazole; Itraconazole; Atazanavir; Nelfinavir; Digoxin, Drugs metabolized by CYP2C19 (e.g. diazepam, citalopram, imipramine, clomipramine, phenytoin); Warfarin; Cisapride; Clarithromycin; Clopidogrel. **Undesirable effects:** Headache, abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation, skin reactions, sensation of burning/prickling/numbness, difficulty sleeping, feeling sleepy, dizziness, vertigo, dry mouth, peripheral swelling. **Full local prescribing information is available upon request.**

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HK-5433 6/17/2021

Artificial Intelligence-assisted Gastrointestinal Endoscopy

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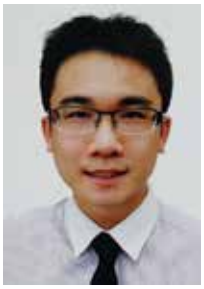

Dr Thomas KL LUI

INTRODUCTION

Artificial intelligence (AI) has been increasingly applied in clinical medicine over the past decade. For instance, AI-assisted predictive models can be used in the diagnosis of disease, treatment guidance as well as prognosis estimation. The advances in computation power and deep learning algorithms enabled highly accurate image classification, which have led to applications in areas such as facial recognition, autopilot, augmented reality, customer behaviour prediction, and medical imaging. Since gastrointestinal endoscopy is highly dependent on real-time interpretation of images, it has become a perfect target for this rapidly advancing technology.

AI-ASSISTED OGD

One of the main purposes of oesophagogastroduodenoscopy (OGD) is the detection of neoplastic lesions, including pre-cancerous dysplastic lesions, in the upper aerodigestive tract. However, unlike advanced cancer, dysplasia or early mucosal cancer is usually subtle and sometimes requires an expert endoscopist further aided by image-enhanced endoscopy (IEE) for detection.[1] As deep learning model has sharpened the accuracy of image analysis, AI holds the great potential to fill in this gap, serving as an assistant of a non-expert endoscopist. Several preclinical studies have shown that a well-trained AI can differentiate the dysplastic area from normal mucosa in the stomach with > 90% accuracy.[2] Luo et al. reported a prospective evaluation of an AI system on upper endoscopic images from 1,794 patients. The diagnostic accuracy in terms of the area under the receiver operating characteristics curve (AUC) for the diagnosis of gastric dysplastic lesions was 92.7%.[3] A meta-analysis involving 23 studies of 969,318 endoscopic images on the application of AI in upper endoscopy demonstrated that the accuracy of AI in the detection of dysplastic lesions approached 90% not only in the stomach, but also in Barrett's oesophagus and squamous oesophagus.[2] In addition to the detection of these dysplastic lesions, the use of AI has also been shown to hasten the learning curve of junior endoscopists for endoscopic diagnosis of dysplastic lesions. The performance of junior endoscopists in the diagnosis of dysplastic lesions clearly demonstrated a significant improvement following their having received feedback from AI.[4] Despite promising results from these early studies, most of these studies were retrospective in nature and in lack of proper control. The only randomised controlled trial (RCT) in AI-assisted OGD by Wu et al. demonstrated AI could improve the blind spots of the endoscopist at the expense of longer inspection time. They reported that all mucosal cancer and high-grade dysplasia were identified by their AI system.[5]

AI-ASSISTED COLONOSCOPY

Similarly, detection and removal of polyps in the colon via colonoscopy have been the cornerstone for prevention of colorectal cancer. A number of retrospective studies demonstrated that AI had very high accuracy (> 90%) in the detection of polyps.[6] A recent meta-analysis summarised the accuracy of AI in the detection of polyps to be > 95%.[6] In fact, there were several RCTs showing that AI-assisted colonoscopy can improve the detection of adenomatous polyps.[7] Wang et al. reported the first randomised trial of AI-assisted colonoscopy in 2019. Among a total of 1,130 patients randomised, the adenoma detection rate of the AI group was significantly higher than that of the conventional colonoscopy group (0.29 vs 0.20, $p < 0.001$); similar difference was observed between the two groups in the mean number of polyps per patient (0.95 vs 0.50, $p < 0.001$) and in the mean number of adenomas per patient (0.53 vs 0.31, $P < 0.001$).[8] Repici et al. reported another RCT involving three centres in Italy. The AI system was found to provide a higher chance of adenoma detection than conventional colonoscopy, with an odds ratio (OR) of 1.30 (95% CI: 1.14 - 1.45). Furthermore, the AI performance was not affected by the size, shape nor location of the polyps. The pooled analysis of RCTs showed that the adenoma detection rate of the AI system approached double that of conventional colonoscopy, with pooled odds ratio of 1.91 (95% CI: 1.51-2.41).[9] Another prospective trial also showed AI could significantly reduce missed adenomatous polyps in the colon by 26.9%.[10] Most of the extra lesions detected by AI were small (< 5 mm), although some studies suggested some vague sessile lesions or advanced lesion missed by the endoscopists could also be picked up by AI.[10]

Thanks to the advances in endoscopic techniques in the recent decade, many large dysplastic or mucosal cancerous lesions in the colon which used to be removed by surgical means can now be removed by endoscopic therapy. However, since only colonic lesions without submucosal deep invasion are suitable for endoscopic removal, the selection of suitable lesion(s) to be removed by an advanced endoscopic technique such as endoscopic submucosal dissection usually requires ample experience in image-enhanced endoscopy so as to interpret the endoscopic image of these large

colonic lesions. Since the deep learning model provides excellent image classification, there is great potential for AI to assist the endoscopist in selecting suitable lesions for endoscopic removal. Accuracies of up to 85-90% were demonstrated by previous studies on AI analysis of the endoscopic image to identify the suitability of these lesions for endoscopic therapy.[11,12]

Another important area of AI use in colonoscopy is the application of "remove and discard" strategy for colonic polyp and "diagnose and leave" strategy for diminutive polyp at rectosigmoid region.[13] Traditionally, all colonic polyps removed were sent for histology assessment in order to determine the surveillance colonoscopy interval. Along with the improvement in endoscopic image quality, a trained endoscopist can possibly and accurately undertake endoscopic assessment of the pathology of a colonic polyp. The "remove and discard" or "diagnose and leave" approach is to replace histologic assessment with endoscopic assessment. The endoscopist would assess the pathology of a colonic polyp by endoscopic images and either remove the polyp without histology assessment or leave the hyperplastic polyp untouched at the rectosigmoid area. This approach is cost-effective since it can save the cost of pathology and provide immediate advice on surveillance duration based on the endoscopic assessment.[14] The American Society for Gastrointestinal Endoscopy (ASGE) also accepts this approach provided that the polyp is less than or equal to 5 mm in size (diminutive polyp), and the endoscopist could prove that his/her histology assessment of polyps via endoscopy can achieve > 90% agreement with the histopathology results in terms of surveillance interval or with > 90% negative predictive value for the rectosigmoid diminutive polyp.[13] Nevertheless, endoscopists might require further training in IEE in order to achieve these cut-off values.[15] Again, AI can potentially fill in this gap. Chen et al. reported an accuracy of 90.1% for a deep learning model in distinguishing adenomatous from hyperplastic diminutive polyps.[16] Byrne et al. also showed another deep learning model with an accuracy of 94.0% for a similar function on diminutive polyps.[17] A meta-analysis inclusive of nine studies showed that the pooled accuracy of AI was greater than 95% for histology prediction for diminutive polyps.[6] However, most of these trials were retrospective in nature. Mori et al. reported a prospective real-time trial involving 325 patients and showed that a special computer-aided endocytoscopy can achieve a 96.4% negative predictive value for histology prediction of rectosigmoid diminutive polyps; such excellent prediction readily meets the requirement for "diagnose and leave" approach.[18]

CURRENT REAL-LIFE APPLICATION OF AI-ASSISTED GASTROINTESTINAL ENDOSCOPY

Most of the current graphical user interface (GUI) of the AI system used in endoscopy uses a real-time on-screen indicator. The most established GUI would be the AI colonic polyp detection model. A localisation box would appear on the screen to indicate the presence of polyp (Fig. 1). The AI actually serves as an assistant to remind the endoscopist of the potential suspicious area on the screen. Since the current application of AI in gastrointestinal endoscopy is not a fully automatic procedure, the interpretation still relies on endoscopists. Despite the accuracy of the most of the well-designed AI models, false signals would still occur occasionally. False positive signals sometimes occur during the procedure such as suction artefact and wrinkled mucosa. However, these signals are usually transient and would disappear after further examination. Most of the current AI also suffers a limitation in that they analyse the "on-screen" images. However, about 20% of missed lesions are probably not shown "on-screen", i.e. lesions may be hidden behind the colonic mucosal fold or underneath the debris. It has been shown in an earlier study that the quality of bowel preparation was found not to be associated with detection of missed adenomas by AI, suggesting that the current AI-assisted colonoscopy probably may not be able to reduce adenoma miss rate in patients with poor bowel preparation.[10] The endoscopist should bear in mind this limitation of the current AI system.

Another important issue would be the procedure time. Although the AI system can improve the detection rate, the current system still requires the interpretation by the endoscopist. Extra procedure time is also required, as already reflected by some of the RCTs[8,19], to remove the additional lesions, and to allow ongoing interaction between the AI and the endoscopist, such as the need to verify the presence of genuine polyp detected by the AI localisation system.

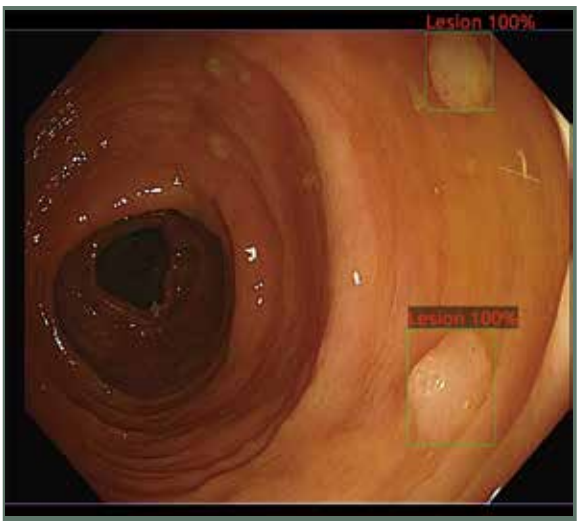

Fig. 1. Localisation boxes indicate the presence of colonic polyps (Photo belongs to personal collection)

FUTURE PROSPECTS AND CONCLUSION

Although early data suggest that the application of AI could improve our endoscopy practice, the "black-box" nature of the AI models may be an important hurdle for the regulatory approval and wide implementation in clinical practice. Clinicians should follow this area closely and be aware of its potential impact on our practice.

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1	2 * Certificate Course on Cytogenomics 2021 (Video Lectures)	3 * Live Lecture HKMA - HKS&H CME Programme 2021 Topic: Glaucoma - Beyond intraocular pressure, the Updates we should know * Certificate Course on Childhood Arthritis and Rheumatic Disease II (Video Lectures)	4	5 * Live Lecture The Role of Blood and Urine Biomarkers in Prostate Cancer Diagnosis	6 * Live Lecture Post-ACS Treatment	7
8	9 * Certificate Course on Cytogenomics 2021 (Video Lectures)	10 * Live Lecture Post Stroke Dementia * Certificate Course on Childhood Arthritis and Rheumatic Disease II (Video Lectures)	11 * Live Lecture Keys for Effective AR Management: Individualised Treatment & Improved Patient Adherence	12 * Live Lecture The New Diabetes Paradigm - Insight from Clinical to Real Life	13 * Live Lecture Nutrition Intervention for Polymorbid Older Adults	14
15	16 * Certificate Course on Cytogenomics 2021 (Video Lectures)	17 * Live Lecture HKMA-GHK CME Programme Topic: Treatment on Breast Cancer * Certificate Course on Complaint Management 2021 (Video Lectures)	18	19 * FMSHK Executive Committee Meeting * FMSHK Council Meeting	20	21
22	23 * Live Lecture Protection against gastroenteritis- Rotavirus vaccines	24 * Certificate Course on Complaint Management 2021 (Video Lectures)	25	26 * Live Lecture Current Management of Lung Cancer	27 * Live Lecture The New Era for SGLT2i: A Tool for Heart Failure Treatment and Cardiorenal Protection	28
29	30	31 * Live Lecture Reducing CV Risk in T2DM Patient: How Can Go Further				

Certificate Course on

Renal Medicine 2021

(Video Lectures)

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society of Nephrology

Objectives:

To update the participants on new advances in renal medicine and clinical practice of common renal problems, and to help the participants to interpret results of common renal investigations.

Date	Topics	Speakers
2 Sept 2021	Common Investigation Tests for Renal Disease Including Approach to Proteinuria and Haematuria	Dr. Sze-kit YUEN Associate Consultant Department of Medicine & Geriatrics Caritas Medical Centre
	Update and Management of Acute Kidney Injury	Dr. Chun-hay TAM Clinical Associate Professor (Honorary) Department of Medicine & Therapeutics The Chinese University of Hong Kong Honorary Clinical Assistant Professor Department of Medicine, University of Hong Kong
9 Sept 2021	ABC of Hemodialysis Therapy	Dr. Gensy Mei-wa TONG Director Renal Care Hong Kong Baptist Hospital Nephrologist-in-charge Kai Tak Haemodialysis Center
	Update and Management of Glomerular Disease	Dr. Elaine Tsz-ling HO Associate Consultant Department of Medicine Tseung Kwan O Hospital
16 Sept 2021	Nutritional Management in Kidney Diseases	Ms. Cherry Pui-yee LAW Dietitian Pamela Youde Nethersole Eastern Hospital
	Kidney Involvement in Multi-System Disorders	Dr. Desmond Yat-hin YAP Clinical Associate Professor Department of Medicine University of Hong Kong
23 Sept 2021	Drug Prescribing in Renal Failure	Dr. Anthony Kai-ching HAU Associate Consultant Department of Medicine & Geriatrics Tuen Mun Hospital
	ABC of Peritoneal Dialysis Therapy	Dr Joseph Ho-sing WONG Associate Consultant Department of Medicine Queen Elizabeth Hospital
30 Sept 2021	Update on Diabetic Nephropathy	Dr. Maggie Kam-man MA Associate Consultant Department of Medicine Queen Mary Hospital
	Update and Management of Chronic Kidney Disease	Dr. Wing-fai PANG Associate Consultant Department of Medicine & Therapeutics Prince of Wales Hospital
7 Oct 2021	Update and Management of Hypertension	Dr. Wai-yan LAU Associate Consultant Department of Medicine Alice Ho Miu Ling Nethersole Hospital
	ABC of Renal Transplantation	Dr. Ka-fai YIM Associate Consultant Department of Medicine & Geriatrics Princess Margaret Hospital

Date : 2, 9, 16, 23, 30 September & 7 October, 2021 (Every Thursday)
Duration of session: 1.5 hours (6 sessions)
Time : 7:00 pm – 8:30 pm
Course Feature: Video lectures (with Q&A platform for participants to post the questions)
Quiz for doctors: To tie in with the CME requirements for video lectures, DOCTORS are required to complete a quiz after the completion of each lecture
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$1,000
Certificate : Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Deadline : 25 August 2021
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel : 2527 8898 Fax : 2865 0345 Email : vienna.lam@fmshk.org

CME / CNE Accreditation in application
Online Application from website: http://www.fmshk.org

Calendar of Events

Date / Time	Function	Enquiry / Remarks
2 MON 7:00 PM	**Certificate Course on Cytogenomics 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Anita Sik-yan KAN	Ms Vienna LAM Tel: 2527 8898
3 TUE 2:00 PM	**Live Lecture** **HKMA - HKS&H CME Programme 2021** **Topic: Glaucoma - Beyond intraocular pressure, the Updates we should know** Organiser: Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Speaker: Dr BAIG Nafees Begum	HKMA CME Dept. Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Childhood Arthritis and Rheumatic Disease II (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr KN CHEONG	Ms Vienna LAM Tel: 2527 8898
5 THU 2:00 PM	**Live Lecture** **The Role of Blood and Urine Biomarkers in Prostate Cancer Diagnosis** Organiser: Hong Kong Medical Association Speaker: Dr Peter Ka-fung CHIU	HKMA CME Dept. Tel: 3108 2507 1 CME Point
6 FRI 2:00 PM	**Live Lecture** **Post-ACS Treatment** Organiser: HKMA-YTM Community Network Speaker: Dr Andrew Kei-yan NG	Ms Candice TONG Tel: 3108 2513 1 CME Point
9 MON 7:00 PM	**Certificate Course on Cytogenomics 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr WONG Wai-shan	Ms Vienna LAM Tel: 2527 8898
10 TUE 2:00 PM	**Live Lecture** **Post Stroke Dementia** Organiser: HKMA-Shatin Community Network Speaker: Dr Ray Chun-chung CHAN	Ms Candice TONG Tel: 3108 2513 1 CME Point
7:00 PM	**Certificate Course on Childhood Arthritis and Rheumatic Disease II (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Lettie LEUNG	Ms Vienna LAM Tel: 2527 8898
11 WED 2:00 PM	**Live Lecture** **Keys for Effective AR Management: Individualised Treatment & Improved Patient Adherence** Organiser: HKMA-Central, Western & Southern Community Network Speaker: Dr TANG Chi-ho	Ms Antonia LEE Tel: 3108 2514 1 CME Point
12 THU 2:00 PM	**Live Lecture** **The New Diabetes Paradigm - Insight from Clinical to Real Life** Organiser: HKMA-KLN East Community Network Speaker: Dr Enoch WU	Ms Antonia LEE Tel: 3108 2514 1 CME Point
13 FRI 2:00 PM	**Live Lecture** **Nutrition Intervention for Polymorbid Older Adults** Organiser: HKMA-KLN City Community Network Speaker: Dr YIP Wai-man	Ms Candice TONG Tel: 3108 2513 1 CME Point
16 MON 7:00 PM	**Certificate Course on Cytogenomics 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Edmond Shiu-kwan MA	Ms Vienna LAM Tel: 2527 8898
17 TUE 2:00 PM	**Live Lecture** **HKMA-GHK CME Programme** **Topic: Treatment on Breast Cancer** Organiser: Hong Kong Medical Association & Gleneagles Hong Kong Hospital Speaker: Dr Roger Kai-cheong NGAN & Dr Lorraine Chi-yan CHOW	HKMA CME Dept. Tel: 2527 8452 1 CME Point
7:00 PM	**Certificate Course on Complaint Management 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Ludwig TSOI	Ms Vienna LAM Tel: 2527 8898
19 THU 7:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Council Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
23 MON 2:00 PM	**Live Lecture** **Protection against gastroenteritis- Rotavirus vaccines** Organiser: Hong Kong Medical Association Speaker: Dr Robert LAW	HKMA CME Dept. Tel: 3108 2507 1 CME Point
24 TUE 7:00 PM	**Certificate Course on Complaint Management 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Ludwig TSOI	Ms Vienna LAM Tel: 2527 8898
26 THU 2:00 PM	**Live Lecture** **Current Management of Lung Cancer** Organiser: HKMA Hong Kong East Community Network Speaker: Dr Alan Wai-sing SUEN	Ms Candice TONG Tel: 3108 2513 1 CME Point
27 FRI 2:00 PM	**Live Lecture** **The New Era for SGLT2i: A Tool for Heart Failure Treatment and Cardiorenal Protection** Organiser: Hong Kong Medical Association Speaker: Dr. NG Kei Yan, Andrew	HKMA CME Dept. Tel: 3108 2507 1 CME Point
31 TUE 2:00 PM	**Live Lecture** **Reducing CV Risk in T2DM Patient: How Can Go Further** Organiser: HKMA-KLN West Community Network Speaker: Dr. CHAN Yu Ho	Ms Antonia LEE Tel: 3108 2514 1 CME Point

Upcoming Event

5 September 2021 (Sun) 08:20 - 12:30	**LI SHU PUI SYMPOSIUM 2021 (WEBINAR) - COVID-19 and Beyond** Organiser: Hong Kong Sanatorium & Hospital LSP Lecture Speaker: Prof YUEN Kwok-yung; Keynote Speakers: Prof Ivan HUNG, Dr Joseph CHAN, Dr Raymond YUNG; Speakers: Dr LAM Bing, Dr LEE Tak-hong, Dr YUEN Shiu-man, Dr Chris CHAN, Dr Edmond MA, Dr Jonpaul ZEE	Enquiry: Hong Kong Sanatorium & Hospital Website: www.hksh.com/lsp2021

Answers to Radiology Quiz

Answers:

1. Acute subarachnoid haemorrhage (SAH). SAH may occur as a result of head injury, or spontaneously from rupture of a cerebral aneurysm, an arteriovenous malformation, or a tumour. Risk factors include high blood pressure, smoking, family history, and cocaine use. Adult polycystic kidney disease is also associated with intracerebral aneurysm. Spontaneous SAH occurs in about 1/10,000 people per year. Females are more commonly affected.

2. CT cerebral angiogram, cerebral digital subtraction angiography to look for aneurysm or arteriovenous malformation.

3. Hydrocephalus, vasospasm.

Dr Carol PY CHIEN
MBBS, FRCR

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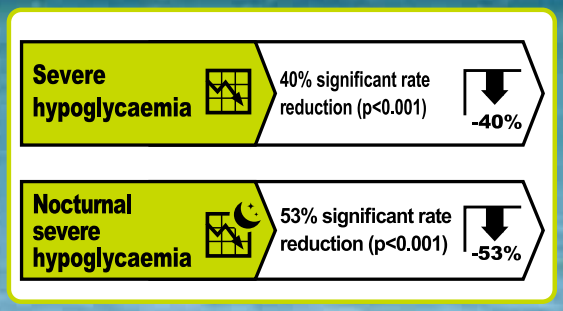
  ...delivered in a once-daily dose.[1]
- **Significantly lower day-to-day variability in glucose-lowering effect vs glargine U100 and U300** [8,9]
- **Approved for a broad range of patients**[1#]

DEVOTE Trial[5]

In **7,637** patients with type 2 diabetes at high risk of cardiovascular events[5]

At baseline: mean age was 65 years, diabetes duration was 16.4 years, HbA_{1c} was 8.4%, and 83.9% were on insulin therapy[5]



* Once daily (OD) plus additional antidiabetic treatments in accordance with standard of care.
\# Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year, elderly patients, renal and hepatic impairment patients.

Abbreviated prescribing information

Tresiba® (insulin degludec) 100U (100 units/mL insulin solution for injection) in a prefilled pen (FlexTouch.) Consult Summary of Product Characteristics before prescribing.

Presentation: Tresiba® FlexTouch®, All presentations contain insulin degludec, Tresiba® 100 units/mL — 1 mL of solution contains 100 units insulin degludec (equivalent to 3,66 mg), One pre-filled device or one cartridge contains 300 units of insulin degludec in 3 mL solution, Indications: Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year. Posology and administration: Tresiba® is a basal insulin for once-daily subcutaneous administration any time of the day, preferably at the same time of day. On occasions when administration at the same time of the day is not possible, Tresiba® allows for flexibility in the timing of insulin administration. A minimum of 8 hours between injections should be ensured. In patients with type 2 diabetes mellitus, Tresiba® can be administered alone, or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin. In type 1 diabetes mellitus, Tresiba® must be used with short-/rapid-acting insulin. Administration by subcutaneous injection only. Tresiba® is available in 100 units/mL. For Tresiba® 100 units/mL a dose of 1–80 units per injection, in steps of 1 unit, can be administered. The dose counter shows the number of units regardless of strength, No dose conversion should be done when transferring a patient to a new strength. When initiating patients with type 2 diabetes mellitus the recommended daily starting dose is 10 units followed by individual dosage adjustments. Transferring from other insulins; in type 2 diabetes changing the basal insulin to Tresiba® can be done unit-to-unit, based on the previous basal insulin component, and when transferring from a twice daily regimen or from insulin glargine (300 units/ml) a dose reduction of 20% should be considered; in type 1 diabetes a dose reduction of 20% based on the previous insulin dose or basal component of a continuous subcutaneous insulin infusion should be considered with subsequent individual dosage adjustments. Doses and timing of concomitant treatment may require adjustment. Using Tresiba® in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus; when adding Tresiba® to GLP-1 receptor agonists, the recommended daily starting dose is 10 units; when adding GLP-1 receptor agonists to Tresiba®, it is recommended to reduce the dose of Tresiba® by 20% to minimize the risk of hypoglycaemia. In all cases doses should be adjusted based on individual patients' needs; fasting plasma glucose is recommended to be used for optimising basal insulin doses. In elderly patients and patients with renal/hepatic impairment glucose monitoring should be intensified and the dose adjusted on an individual basis. In paediatric population, when changing basal insulin to Tresiba®, dose reduction of basal and bolus insulin needs to be considered on an individual basis in order to minimise the risk of hypoglycaemia. Tresiba® comes in a pre-filled pen, FlexTouch®, designed to be used with NovoFine® needles. Contraindications: Hypersensitivity to the active substance or any of the excipients. Special warnings and precautions: Too high insulin dose, omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. In children care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimize the risk of hypoglycaemia. Reduction of warning symptoms of hypoglycaemia may be seen upon tightening control and also in patients with long-standing diabetes. Administration of rapid acting insulin is recommended in situations with severe hyperglycaemia. Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement. Transferring to a new type, brand or manufacturer of insulin should be done under medical supervision and may result in a change in dosage. When using insulin in combination with pioglitazone, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between the two strengths of Tresiba® and other insulins. Hypoglycaemia may constitute a risk when driving or operating machinery. Pregnancy and lactation: There is no clinical experience with use of Tresiba® in pregnant women and during breastfeeding. Animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity. Undesirable effects: Refer to SmPC for complete information on side effects. Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1.000 to < 1/100); rare (≥ 1/10.000 to < 1/1.000); very rare (< 1/10.000); not known (cannot be estimated from the available data). Very common: Hypoglycaemia. Common: Injection site reactions. Uncommon: Lipodystrophy and peripheral oedema. Rare: Hypersensitivity and urticaria. With insulin preparations, allergic reaction may occur; immediate-type allergic reactions may potentially be life threatening. Injection site reactions are usually mild, transitory and normally disappear during continued treatment. FlexTouch®, NovoFine®, Penfill®, and Tresiba® are registered trademarks of Novo Nordisk A/S.

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