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Genomic Medicine

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significant improvement vs placebo in both time to 1st and 2nd subsequent therapy

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no statistically significant differences vs placebo

* Lynparza™ is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy[5].

† Required threshold for statistical significance was p<0.0095[4].

Study design[3]
This study was a retrospective, preplanned analysis of data by BRCA mutation status from a randomized, double-blind, phase 2 study in a total of 265 patients with platinum-sensitive recurrent serous ovarian cancer who had received two or more platinum-based regimens and who had a partial or complete response to their most recent platinum-based regimen. In this phase 2 study, maintenance treatment with Lynparza™ 400 mg twice daily (capsules)(n=136) versus placebo (n=128; one patient randomly assigned to the placebo group was voluntarily withdrew consent without receiving treatment) was assessed. The primary endpoint was PFS, analyzed for the overall population and by BRCA status.

AE = adverse event. BRCAm = BRCA mutated/mutation. PARP=poly (ADP ribose) polymerase. PFS = progression-free survival. QoL = quality of life.

Presentation: Lynparza hard capsules contain Olaparib 50mg. **Indications:** Monotherapy for maintenance treatment of platinum-sensitive relapsed BRCA-mutated high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy. **Dosage:** 400mg bd; start Lynparza within 8 weeks after last dose of the platinum-containing regimen; take Lynparza at least one hour after food and no food for two hours after administration. **Contraindications:** Breast-feeding, during treatment and one month after last dose; Hypersensitivity to any of its ingredients. **Precautions:** Haematological toxicity, patients should not receive Lynparza until they recover from haematological toxicity caused by previous anticancer therapy; Myelodysplastic syndrome/acute myeloid leukaemia; Pneumonitis; Embryotoetal toxicity; Pregnancy, women should not become pregnant during treatment and one month after last dose; Caution should be observed when driving or using machines; Co-administration with statins, vaccines and immunosuppressant agents. **Interactions:** Other anticancer medications; CYP3A4 substrates, inducers and inhibitors; P-gp substrate, inhibitors and inducers; substrates of BRCP, OATP1B1, OCT1 and OCT2. **Undesirable effects:** Very Common Decreased appetite, headache, dizziness, dysgeusia, nausea, vomiting, diarrhea, dyspepsia, fatigue (including asthenia), anaemia, neutropaenia, lymphopaenia, increase in blood creatinine, mean corpuscular volume elevation; Common upper abdominal pain, stomatitis, thrombocytopaenia. **Full local prescribing information is available upon request. API.HK.LYN.1415**

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

Reference: 1. Frampton J. BioDrugs 2015;29:143-150. 2. Moding E, et al. Nat Rev Drug Discov 2013;12:526-542. 3. Ledermann J, et al. Lancet Oncol. 2014;15:852-861. 4. Ledermann J, et al. Lancet Oncol. Epub 2016 Sep 8. Doi:10.1016/S1470-2045(16)30376-X. 5. Lynparza™ Hong Kong prescribing information. Doc ID-002890163. April 2015.

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Disclaimer

The Cover Shot

This picture was taken in 2016 at the Grand Prismatic Spring in Yellowstone National Park, USA. This is the largest and most colourful hot spring there. The temperature of the water is about 700C and hence the constant steaming. I chose this as the cover photo because it is relevant to the development of genetics and genomics. A thermophilic bacterium that can thrive under such a high temperature is called Thermus aquaticus and was first discovered in Yellowstone back in 1969. The Taq polymerase that is essential for polymerase chain reaction is derived from this species of bacteria.

Dr Ivan FM LO

MBChB, MRCPCH, FHKCPaed, FHKAM(Paed)

Consultant Clinical Geneticist, Clinical Genetic Service, Department of Health
President, Hong Kong Society of Medical Genetics

Message from the President

Dr Mario Wai-kwong CHAK

President
The Federation of Medical Societies of Hong Kong

Dr Mario Wai-kwong CHAK

To begin the New Year, I would like to share with you all a famous ancient Chinese couplet「一元復始，萬象更新」In the beginning of every year, everyone hopes for a new start. As a New Year begins, everything looks fresh and gay. Let us also start anew. All things take on a new aspect.

It is my great honour and privilege to be elected and to serve the Federation for my second term in the coming two years. The Federation of Medical Societies of Hong Kong, as an umbrella society of at present 141 medical, dental, nursing and allied health societies, will continue our mission to take up the role of promoting the advancement of knowledge and high quality medical and health care, as well as by providing various continuing educational activities.

For example, the certificate courses held jointly with member societies have proved popular, covering diverse topics and areas. Our publication, the Hong Kong Medical Diary, is of professional interests with different monthly topic reviews and update knowledge. Annual scientific meetings with the theme of "Innovations in Medical Care" have addressed important areas of medicine with talks delivered by various local experts.

To foster the development of palliative and end-of-life services for advanced diseases in Hong Kong, a "Care for the Advanced Diseases Consortium" (Chinese name of the consortium: 晚期病患醫療及各界關顧聯盟)was formed with founder members and advisors from leading doctors and nurses, Non-Governmental Organisations and Patients' Associations with the aim to raise public awareness and to unite different stakeholders and gather broader views from health care professionals, patients and carers and to provide suggestions to Government. In order to kick off in engaging medical professionals, three joint CME seminars have been organised by the Consortium with the HKMA on Care for Advanced Diseases.

Apart from offering continuing education, the Federation also provides lots of other support to our member societies. For example, our Federation premises are popular venues and open for rental by our member societies for meetings, seminars and conferences. Furthermore, we offer administrative support to assist different member societies to organise local and international conferences. Our secretariat has different packages of services to suit societies' needs include handling minutes, accounts, regular meetings, as well as annual scientific meetings etc.

On the charity side, the Federation's Foundation continues to organise Public talks on different important health issues, as well as conduct projects for children in need, such as, our Music & Academic Scholarships and Expressive Art Therapy Classes for bereaved children and those with emotional and stress problems. On the fraternity side, we have successfully organised the President Cup Soccer Five & Basketball Tournament in October this year.

Finally, I have to thank all for the effort and support from our past Exco members, Foundation directors, council members and staff of the secretarial board in 2017. We cannot succeed without your collaboration. With continuous support and contribution, we are confident in further excelling in 2018. We look forward to working alongside with newly elected Exco members and Foundation directors in the near future.

Once again, on behalf of the Federation, I wish you and your family all the best, and may you all have a happy, healthy, wealthy and prosperous year ahead.

Editorial

Dr Ivan FM LO

MBChB, MRCPCH, FHKCPaed, FHKAM(Paed)

Consultant Clinical Geneticist, Clinical Genetic Service, Department of Health
President, Hong Kong Society of Medical Genetics

Editor

Dr Ivan FM LO

It is timely to have "Genomic Medicine (基因組醫學)" as a theme in this issue of the Hong Kong Medical Diary, as this subject has just been mentioned in the Chief Executive's policy address a couple of months ago. To the great majority of the general public that was probably the very first time they heard about this term. But I believe even among medical professionals, a lot also have such a question in their head: what is "genomic medicine"? And maybe a more relevant question is: will it affect my practice?

When people can barely articulate what "gene (基因)" is, the word "genome (基因組)" sounds even a bit sci-fi. "Genome" means the entire genetic makeup of an organism; and in humans it comprises all the genetic information carried in the chromosomes (chromosomes 1-22, X and Y) and the mitochondrial genome. "Genomics (基因組學)" means the study of the genome, in contrast to "genetics (遺傳學)" which means the study of individual gene. This term was believed to be first coined in 1986, so it actually predated the Human Genome Project (HGP,人類基因組計劃), a monumental multinational collaborative project that was launched in 1990 and was completed in 2003, with the goals of sequencing the entire human genome and finding all the human genes. As a result of HGP we now have a reference sequence of mankind, our blueprint, though gene discovery is still ongoing as of today. Having our own blueprint allows comparisons with those of other species, which in turn adds to the understanding of evolution. So people realised that our genome differs from that of chimpanzees by just 1.2%, while the difference between two different persons is only about 0.1%. It is this apparently trivial difference that contributes to the uniqueness of every individual person, from all the physical to physiological traits including health and disease. It is also this apparently trivial difference that genomic medicine is about. For instance, knowing an individual's genomic variants may tell whether he or she is more susceptible than others to hypertension, diabetes mellitus, cancer, psychiatric diseases, etc., and if so what the best choice of drug should be. In essence, "genomic medicine" means the practice of medicine in the light of the genomic information of patients. Every person has a unique genetic makeup. As a result, the underlying genetic susceptibility of every diabetic patient is different; and hence response to the same drug varies. "Genomic medicine" is also known as "precision medicine" and "personalised medicine", meaning that medical care can be tailored to individual patient's or individual tumuor's genomic profile, with consequent increased assurance of treatment success and avoidance of untoward side effects in every patient.

In this issue I have invited local pioneers to write on some current applications of genomics in medicine, from rare diseases to common conditions and from diagnosis to prevention. Genomic medicine is not science fiction anymore; it is reality.

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Incorporate Precision Medicine Into Your Practice Today

Precision Medicine in Lung Adenocarcinoma

Dr Jacky Yu-chung LI

MBBS (H.K.), FRCR (U.K.), FHKCR, FHKAM (Radiology)

Specialist in Clinical Oncology

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 January 2018.

Introduction

With the rapid development in the fields of genetics, biotechnology and genomics, molecular genetic profiling will soon become an indispensable tool for clinicians to guide individualised management of many medical conditions. Precision medicine, also known as personalised medicine, refers to the application of individual patient- and disease- specific profiles, in the light of genetic and genomic data as well as clinical and environmental factors, to assess individual risks and benefits from medical therapies. We take lung adenocarcinoma as an example to illustrate the practice of precision medicine along with anti-cancer therapy.

Lung adenocarcinoma in the past era

The understanding and detection of genomic changes in lung adenocarcinoma evolved dramatically in the past two decades and opened great therapeutic potential for non-small cell lung cancer (NSCLC) patients. Back in the early 1990s, little could be done to distinguish individual subtypes of lung cancers, and most clinical trials focused on finding the best platinum-based combination therapies[1], irrespective of histological subtypes[2,3]. The importance of such differentiation was recognised only later after a large randomised clinical trial had demonstrated in subgroup analysis a survival difference between patients with squamous and non-squamous histology treated with different chemotherapeutic agents[4].

Lung adenocarcinoma in the current era

The development of tyrosine kinase inhibitors (TKI) against epidermal growth factor receptor (*EGFR*) mutated NSCLC opened an era of precision medicine in lung cancer and prompted a paradigm shift towards development of molecularly targeted agents against other putative driver aberrations in NSCLC[5]. Tumours harbouring these distinct and mutually exclusive "driver" mutations can be treated with anticancer therapies largely in the form of TKI that targets respective aberrant gene products. *EGFR* mutations and *ALK* or *ROS1* fusions confer sensitivity to selective kinase inhibitors, which in turn dictate the choice of therapy[5-11]. Additional alterations such as *BRAF*^{V600E}, RET fusions, MET exon 14 skipping, MET and ERBB2 amplifications are found in smaller subsets of patients, but when present may also predict response to some available targeted inhibitors which are FDA-approved therapies for other tumour types[12-16]. In other patients, defined oncogenic drivers such as NTRK and PIK3CA mutations are detected, for which preclinical studies have nominated targeted approaches, but the clinical utility of such therapies has yet to be established[17,18]. In a prospective comprehensive molecular testing of lung adenocarcinoma trial, up to 86.9% (747/860) of patients carry potentially actionable somatic alterations (Fig.1)[19]. The prevalence of these somatic alterations in Asian ethnicity is expected to be higher due to a much higher prevalence of *EGFR* mutations in both never and ever smokers, when compared to studies with patients in majority Caucasian ethnicity[20].

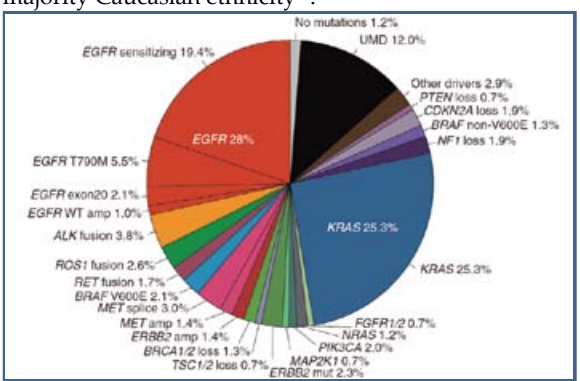

Fig. 1. Potentially actionable oncogenic drivers identified by MSK-IMPACT# testing.
**Figure adopted from reference[19].*
 # MSK-IMPACT: Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets, a hybridization capture-based, next-generation sequencing platform or matched tumor: normal sequencing to comprehensively profile somatic alterations in all known cancer genes in solid tumors.

Somatic mutations detection methods

The aforementioned driver gene alterations can be grouped into three categories – mutations, gene rearrangement, and amplifications – and appropriate molecular testing should be used for detection[21]. A variety of methods can be used for detecting mutations including direct sequencing, real-time polymerase chain reactions, and commercial kits (Table 1)[21]. Fluorescence in situ hybridisation (FISH), immunohistochemistry (IHC), reverse-transcriptase polymerase chain reaction (RT-PCR) and next-generation sequencing (NGS) are options for gene rearrangements, while FISH using a

locus-specific intensifier (LSI) gene and a chromosome-specific centromere (CEP) probe is a standard method for the detection of gene amplifications (Table 1)[21]. Each testing method has to be validated by well conducted clinical trials for corresponding targeted therapies and is often developed as a companion diagnostic under the FDA approved diagnostic framework. However, as targetable genetic alterations are increasingly discovered, individual genotyping may become relatively inefficient, especially when there is inadequate tissue for successive testing, and is drastically costly. NGS technology using DNA or RNA is reported to be useful for multiplexed and deep genomic sequencing[22,23], as well as simultaneously detection of gene rearrangements and genes with copy number gain. Its application allows comprehensive molecular characterisation of lung adenocarcinoma before labelling it as "wild" type, for which no available target therapies can be employed. Nowadays, targeted deep sequencing of selected gene sets (so-called cancer panels) has been integrated into daily clinical practice. Some local diagnostic laboratories have developed platforms for clinicians to order.

Table 1. Representative methods categorized by mechanisms of oncogene activation and by targeted molecules. PCR, polymerase chain reaction; NGS, next-generation sequencing; FISH, fluorescence in situ hybridization; qPCR, quantitative polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction; IHC, immunohistochemistry.
**Table adopted from reference[21]*

Category	Mutation	Gene rearrangement	Amplification
DNA	Direct sequencing PCR-based methods NGS	FISH NGS	FISH qPCR NGS
RNA		RT-PCR (fusion transcript) NGS	
Protein	IHC (mutation-specific antibody)	IHC (protein expression)	IHC (protein overexpression)

Tackling acquired resistance

Despite an initial benefit from molecularly targeted agents in *EGFR*-mutant and *ALK*-rearranged NSCLC, tumours invariably develop acquired resistance and progressive disease. Tumour- or liquid- based re-biopsy at the time of disease progression is valuable for clinicians to understand and tackle the mechanism of acquired resistance accordingly. *EGFR* exon 20 T790M, for example, is the commonest mechanism of resistance after *EGFR-TKI* and can be effectively treated by a third generation T790M mutant specific inhibitor osimertinib[24]. The landmark AURA3 study drives osimertinib therapy a full approval by FDA since Mar 2017 and is currently the only FDA approved therapy after *EGFR-TKI* failure[25]. Non-T790M mediated resistance mechanisms include activation of alternative bypass pathways (e.g. *MET* or *ERBB2* gene amplifications, *IGF-1R* activation, *RET* rearrangement[26]), activation of downstream signalling of the *EGFR* (e.g. *PTEN* downregulation, *CRKL* gene amplification, *BRAF* mutations, or *ERK1/2* reactivation), and phenotypic changes such as SCLC transformation or epithelial to mesenchymal transition (EMT)[27]. Apart from SCLC transformation which should better be treated with etoposide-platinum chemotherapy[28], the vast majority of these resistance mechanisms tell no additional information on the choice of therapy. Empirical cytotoxic chemotherapies usually in the form of pemetrexed-platinum, with or without concurrent antiangiogenic agent, is the only hope to control metastatic lesions in current clinical practice. Nonetheless, the information could be valuable for patients who have exhausted therapeutic options to rationalise the choice of molecular targeted therapies used for other indications in NSCLC or other cancers. For example, monotherapy use of a *MET* inhibitor in *EGFR*-mutant with *MET* amplification as the acquired resistance mechanism has been advocated[29]. The pan-HER dual inhibition trial using afatinib and cetuximab in patients with acquired resistance has shown an objective response rate of 25% among T790M-negative patients[30]. Such dual pan-HER inhibition, which occasionally initiates to *EGFR*-mutant patients who have exhausted all therapeutic options, is only reasonable in acquired mechanisms other than non-HER alternative bypass pathways and EMT phenotypic change, and to a lesser extent, other than downstream signalling activation.

Similarly, the rebiopsy of *ALK*-rearranged NSCLC has provided information on the acquired resistance mechanism of crizotinib and other older generation *ALK* inhibitors (*ALKi*). *ALK* kinase domain "gatekeeper" mutations, including L1196M, C1156Y and G1202R among others, have been observed in around a third of patients after crizotinib resistance[31] and were highly variable after new generation *ALKi* resistance[32]. While L1196M and C1156Y can be effectively treated by ceritinib and alectinib, G1202R confers resistance to most new generation *ALKi* except lorlatinib[32-34]. Lorlatinib remains an investigational agent but could possibly be obtained under a local investigational early access programme with strict patient selection criteria. Alice Shaw et al once demonstrated the beauty of precision medicine through a patient of *ALK*-rearranged lung cancer who had received multiple *ALKi* during the treatment course, including first-, second-, and third-generation inhibitors. The eventually acquired L1198F mutation on tissue rebiopsy conferred resistance to lorlatinib but unexpectedly restored sensitivity to crizotinib[35]. With a rapidly expanding number of new *ALKi*, which include but not exclusively, brigatinib, ensatinib, entrectinib, it is likely that resistance mechanism detected in rebiopies influences the treatment choice in the future era.

Precision immunotherapy in lung cancer

Similar to the advances in targeted therapy, significant progress in tumour immunotherapy has resulted in several new strategies for cancer therapy, including T-cell immune checkpoint inhibitors (ICPI), oncolytic viruses, chimeric antigen receptor T cells, among others[36,37]. Immunotherapy is associated with several unique features, most notably the potential for inducing durable clinical responses, lack of typical drug resistance, and induction of autoimmune-like toxicities. Currently, the immunotherapy in clinical use among lung cancer patients includes pembrolizumab (a PD-1 Ab) monotherapy in highly selected patients with PDL-1

expression over 50% or in combination with pemetrexed-cisplatin regardless of PDL-1 expression in first line situation[38,39], while pembrolizumab, nivolumab (a PD-1 Ab) and atezolizumab (a PDL-1 Ab) monotherapy are utilised as second line treatment after platinum-doublet chemotherapy[40-44]. Of note, most of the landmark trials establishing the role of immunotherapy carry only a small subset or none with *EGFR* or *ALK* mutations and the presence of which were suggested to be associated with lower objective response rate to PD-1 inhibitors. *MET* exon 14 altered lung cancer also carries lower response rate of 6.7% to a PD-1 inhibitor, as reported by Sabari et al at ASCO 2017[45]. Most of these gene alterations are typically associated with a lack of tobacco exposure, an expected lower load of mutation burden, and a lower rate of PDL-1 expression that contributes to the lack of clinical benefit from ICPI. On the contrary, *BRAF* gene aberration and *MET* short variants (SV) mutations are found to be associated with prolonged time on immune checkpoints inhibitor, with *MET SV* linked with increased immune infiltration and an immune activation phenotype[46]. Along with some established roles of microsatellite instability and total mutation burden, comprehensive molecular comprehensive genomic profiling may help further to gauge the degree of benefit from an ICPI in the future era.

Conclusion

The management of advanced lung adenocarcinoma continues to evolve rapidly due to recent advances made in precision medicine diagnostics. The utilisation of comprehensive molecular genotyping allows identification of molecular subgroups of patients with driver mutations who may benefit from molecularly targeted therapies, allows identification of acquired resistance mechanism which may confer sensitivities to newer or alternative molecularly targeted therapies and allows potentially better selection of patients subjecting to immunotherapy. Application of precision medicine diagnostics in the form of NGS, for its methodological complexity, needs extensive trial validation and quality control before implementation into routine clinical use. It would be a tedious and difficult task, but an ultimate goal and a necessary step for all to conquer lung cancer in the future.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Precision Medicine in Lung Adenocarcinoma" by Dr Jacky Yu-chung LI 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 January 2018 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. *MET* exon 14 skipping is one of the potentially actionable somatic alterations.
2. Only up to 30% of lung adenocarcinoma patients carry potentially actionable somatic alterations.
3. The prevalence of *EGFR* mutation among lung cancer patients is higher in Asians than Caucasians.
4. The application of next-generation sequencing allows comprehensive molecular characterisation of lung adenocarcinoma for potentially actionable somatic alterations.
5. Small cell lung cancer transformation is one of the non-T790M mediated resistance mechanisms for *EGFR* mutated adenocarcinoma of lung patients who progress on 1st line *EGFR-TKI*.
6. The spectrum of additional *ALK* domain mutations after *ALK* inhibitors is similar among all newer generation *ALK* inhibitors.
7. The *ALK* G1202R mutation confers resistance to most new generation *ALK* inhibitors except lorlatinib.
8. *MET* exon 14 altered lung cancers have expected excellent treatment outcome to an immune checkpoint inhibitor.
9. Comprehensive molecular comprehensive genomic profiling may help to predict who is likely to respond to immune checkpoint inhibitors.
10. The application of precision medicine diagnostics in the form of NGS is in extensive regional usage, and quality control is not necessary for clinical use.

ANSWER SHEET FOR JANUARY 2018

Please return the completed answer sheet to the Federation Secretariat on or before 31 January 2018 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Precision Medicine in Lung Adenocarcinoma

Dr Jacky Yu-chung LI

MBBS (H.K.), FRCR (U.K.), FHKCR, FHKAM (Radiology)

Specialist in Clinical Oncology

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

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

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Contact Tel No.:_____ MCHK No.: _____ (for reference only)

Answers to December 2017 Issue

How to Use HIV Pre-exposure Prophylaxis

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

Expanded Carrier Screening

Dr Richard CHOY
PhD
Associate Professor, Department of Obstetrics & Gynaecology, The Chinese University of Hong Kong

Dr Sarah WYNN
PhD, DIC, MRSB
Genetic Specialist, Central Health Medical Practice, Hong Kong

Dr Angeline LIAUW
MBBS, FRCOG, FHKCOG, FHKAM(O&G)
Specialist in obstetrics and gynaecology, Prestige Medical Centre



Dr Richard CHOY Dr Sarah WYNN Dr Angeline LIAUW

Background

Screening for carrier status is a popular topic in the field of genetics, maternal foetal medicine and reproductive medicine. Monogenic diseases are inherited in Mendelian fashion. The nature of disease depends on the functions performed by the modified gene. Monogenic diseases are responsible for a heavy loss of life. Monogenic diseases can be inherited as autosomal dominant, autosomal recessive or X-linked. The global prevalence of all single gene diseases at birth is approximately 10/1,000, which is not rare. In Canada, it has been estimated that taken together, monogenic diseases may account for up to 40% of the work of hospital based paediatric practice.[1,2]

For years, clinicians have offered gene-by-gene carrier screening to patients and couples considering future pregnancy or those with an ongoing pregnancy early in gestation. Examples include ethnic specific screening such as thalassaemia offered to our local patients and pan-ethnic screening for cystic fibrosis. Next generation sequencing (NGS) methods now available permit screening for many more disorders with high fidelity, short turnaround time, and lower costs. High throughput NGS methods have become available allowing rapid expanded carrier screening (ECS) for a substantial number of conditions. This paves the era of ECS for monogenic diseases. However, the basis for the selection of disorders on ECS panels should be disclosed. For monogenic diseases inherited in autosomal recessive fashion, the offspring of a carrier couple will have 25% chance being affected by the disease (Fig. 1). While for X-linked recessive diseases, the male offspring of a carrier woman will have 50% chance being affected and the female offspring will have 50% chance being carriers themselves. Therefore, determining the genetic background and understanding the mode of inheritance are of vital importance to performing ECS.

Based on a retrospective modelling analysis of results from ECS including 346,790 reproductive age individuals without known indication for specific genetic testing (primarily from the US), the carrier rate of the study population for at least one autosomal recessive disease is expected to be 25%. It is also no surprise that some cases are a carrier of more than one monogenic disease[3]. Haque, Lazarin et al[4] showed that the probability of a hypothetical foetus, conceived from random pairing of individuals undergoing ECS, to suffer from a severe or profound disease ranged from 94.5 per 100,000 for Hispanic couples to 392.2 per 100,000 for Ashkenazi Jewish couples.

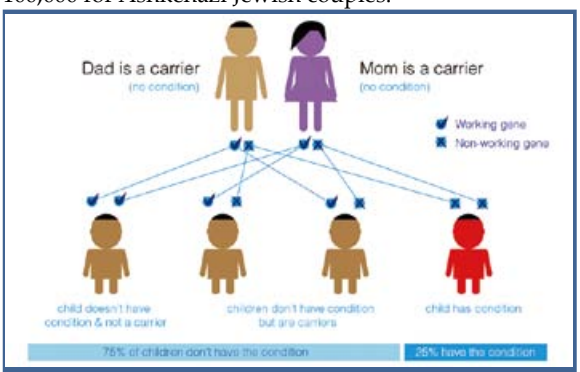

Fig. 1. Illustrating the mode of inheritance of an autosomal recessive (AR) condition.

Who to screen

The goal of carrier testing is to identify couples that are carriers of mutations in the same gene, and thus, their offspring are at risk of the respective disease. The American College of Obstetricians and Gynecologists (ACOG) published guidelines on ethnic-based carrier screening programme, e.g. haemoglobinopathies screening for individuals of Southeast Asian, African and Mediterranean descent; screening for cystic fibrosis, Tay-Sachs disease, familial dysautonomia and Canavan disease for individuals of Ashkenazi Jewish descent[2,3] However, ancestry-based screening could also lead to unequal distribution of genetic testing and may miss diagnosis of diseases in populations without screening. Thus, both ACOG and American College of Medical Genetics and Genomics (ACMG) recommended carrier screening of cystic fibrosis for all couples in 2001.[5,6] ACMG also recommended carrier screening for spinal muscular atrophy for all couples in 2008 (Table 1).[7] Current data show that ancestry-based carrier screening has significant drawbacks and may result in inequitable distribution of genetic testing and services. The low cost of multigene panels and the argument to maximise detection rates by NGS method support the practice of ECS. However, the panels usually also include mild conditions such as familial Mediterranean fever and pseudocholinesterase deficiency, which might not provide real benefit for pregnancy planning but increases the workload for post-test counselling. Clinicians should cautiously review the gene panel designed by different providers or order the most appropriate test for their patients.

Table 1: Genetic conditions recommended for screening by American College of Medical Genetics & Genomics (ACMG) and American College of Obstetricians & Gynecologists (ACOG).

Condition	Gene	ACMG	ACOG
Alpha-Thalassemia	*HBA1/HBA2*		Y
Beta Thalassemia	*HBB*		Y
Bloom Syndrome	*BLM*	Y	
Canavan Disease	*ASPA*	Y	Y
Cystic Fibrosis	*CFTR*	Y	Y
Familial Dysautonomia	*IKBKAP*	Y	Y
Fanconi Anemia, Group C	*FANCC*	Y	
Gaucher Disease	*GBA*	Y	
Mucolipidosis, Type IV	*MCOLN1*	Y	
Niemann-Pick Disease, Types A/B	*SMPD1*	Y	
Sickle Cell Disease	*HBB*		Y
Spinal Muscular Atrophy	*SMN1*	Y	
Tay-Sachs Disease	*HEXA*	Y	Y

Clinical utility and concern in reproductive health

According to the ACOG Committee Opinion in 2017, carrier screening, whether targeted or expanded, allows individuals to consider their range of reproductive options. Ultimately, the goal of genetic screening is to provide individuals with meaningful information that they can use to guide pregnancy planning based on their personal values.[5] The carrier screening can be done sequentially or concurrently. Having the knowledge of the genetic disease carrier status of themselves and/or their partners allow couples to decide on the reproductive options. They can continue with natural conception and choose prenatal diagnostic method to test for the genetic condition of their foetuses. On the other hand, the use of assisted reproductive technology, *in-vitro* fertilisation (IVF) and pre-implantation genetic diagnosis (PGD) can further allow couples to have embryos without the disease in question transplanted, thus avoiding the need of termination of pregnancy upon the knowledge of an affected foetus.

Another important issue of ECS is its use in gamete donors. The use of donated gametes is an accepted treatment for women with advanced age, ovarian dysfunction or repeated IVF failures, and for men with azoospermia. Every effort should be made to help the recipient families to have healthy babies. In this context, pre-conception counselling to the recipient couples and genetic risk assessment of the gamete donor and the recipient using ECS is crucial. The use of gamete donors having positive genetic carrier status same as that of the recipient can be avoided after ECS, and hence, the possibility of having birth of children with diseases of severe or profound disability can be minimised.

The importance of pre-test and post-test counselling

Professional organisations have begun to recommend that multi-gene panels only be ordered in consultation with a genetics professional due to their intrinsic complexity. As costs decrease, ECS is becoming more commonplace, in particular in the US. Studies have shown that although uptake has been slower in Europe and other countries, there is interest in ECS and it is therefore also likely to increase worldwide in the near future. One of the challenges of offering ECS at a population level is the provision of quality genetic counselling. Several studies investigating geneticists' (and other health care professionals) views on ECS, in addition to the recommendations made by professional organisations (ACMG and ACOG), emphasised that pre- and post-test genetic counselling is essential.[11–16]

Pre-test counselling involves ensuring that the individual (or couple) understands the benefits and limitations of ECS. Counselling should be non-directive and after counselling a patient may decline ECS. It should be made clear that ECS does not include all genetic conditions but only those included on the ECS panel. The aim of pre-test counselling is to achieve informed consent from the individual. Due to the nature of ECS panels including a large number of conditions (often more than 100), it is not feasible to achieve disease-specific consent. Instead, generic consent, covering the nature of the test rather than focusing on individual conditions, is recommended by the ACMG and other professional bodies[17]. The questions of how and by whom this pre-test counselling is performed have been raised. While ideally it should be a face-to-face appointment with a genetic counsellor or geneticist, it has been recognised that when implementing ECS population-wide, this will not be possible. Therefore, pre-test counselling can be conducted by other health care professionals and includes informational brochures, videos and/or computer-based interactive tools, with genetic counselling available to those who desire it.[11,13,15]

Regarding post-test counselling, face-to-face counselling should be given to all couples or individuals who are identified as carriers.[1,5] If an individual has been found to be a carrier for a specific condition, his/her partner should be offered ECS. The post-test counselling session should include information regarding clinical features of the condition, options for prenatal testing and the reproductive options available. The information provided should be comprehensive and up to date.[5] It is critical that all genetic counsellors are equipped to provide information and support for all the conditions included on the ECS panel.

Summary

In summary, it looks as though ECS is here to stay and its uptake will undoubtedly increase over the coming years. In fact, one recent study found strong support for ECS from genetic counsellors, including those working in the reproductive health sector. Additionally, the study found that 92% of the genetic counsellors surveyed expected that ECS will become part of routine practice[13]. The most recent ACOG committee opinion on

carrier screening suggested that ethnic-specific and pan-ethnic ECS are acceptable strategies for pre-pregnancy and prenatal carrier screening. Our previous Fragile-X screening study also demonstrated that maternal carrier frequency of Fragile-X syndrome in a Chinese population is not as low as previously reported[13]. ECS should be provided to identify carrier status of couples and provide an opportunity for informed pregnancy planning.

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Hereditary Cancer Syndromes

Dr Ho-ming LUK

MBBS, FHKCPaed, FHKAM

SM&HO, Clinical Genetic Service, Department of Health

Dr Ho-ming LUK

Cancer is common. It is estimated that 1/3 of the population will develop cancer in their lifetime. This constitutes a substantial burden to the health care system and the economy of Hong Kong. There are solid evidence and epidemiological data showing that 5-10% of all cancer cases have a strong genetic component[1]. This is known as "hereditary cancer syndrome". These cancer syndromes are caused by abnormal genetic variants (germline mutations) in some cancer predisposition genes, like BRCA1 and BRCA2 genes in the case of breast cancer and mismatch repair genes in the case of colorectal cancer. Carriers of these mutant genes not only have a much higher risk of cancer compared to the general population, but also with a younger age of onset, and higher chance of multiple and recurrent cancers that lead to a poor clinical outcome. And most of these hereditary cancer syndromes are transmitted from one generation to the next in autosomal dominant fashion, i.e. an offspring of a mutation carrier has 50% chance inheriting the mutation. Therefore, multiple family members in different generations are at risk. This familial nature is particularly important in colorectal cancer and breast cancer, which were the 1st and the 3rd most common cancers with 5,036 and 3,920 new cases, respectively, in Hong Kong in 2015[2]. Therefore, it is estimated that 400-500 new cases of colorectal cancer and 350-400 new cases of breast cancer each year in Hong Kong fall into this hereditary cancer syndrome category.

Availability of genomic technology and diagnostic yield

Cancer genetics testing has been hindered by genetic heterogeneity, i.e. more than one gene is implicated for one disease. In the case of hereditary breast cancer, not only *BRCA1* and *BRCA2*, but also *PTEN, BRIP1* and others are implicated. Among these at least 4-5 are high penetrance genes and 5-6 are of moderate penetrance. For hereditary colorectal cancer, there are at least 4 mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) responsible for Lynch syndrome and the APC gene for Familial Adenomatous Polyposis. With conventional sequencing technology, it used to be a labour-intensive and time-consuming task to detect the causative mutation, because multiple genes had to be examined one by one and exon by exon. This technical difficulty has been overcome due to the advent of the Next Generation Sequencing (NGS) technology, which allows simultaneous analysis of many genes in one go. The application of NGS technology not only significantly improved the diagnostic yield up to 30% in selected high risk population[3], but also reduced the turnaround time.

Clinical utility of cancer genetic testing

The clinical utility, validity and usefulness of mainstreaming cancer genetics testing in the management of hereditary colorectal cancer[6], and breast and ovarian cancer[7,8], were evident in practice guidelines published by different authorities and professional bodies including NICE, Royal College of Obstetrics and Gynaecologists and American College of Medical Genetics and Genomics.

Through testing of the cancer predisposition genes, health care providers can learn about the genetic basis of cancer in the patients, which in turn can guide decisions regarding the best treatment option and the most suitable drug to use. Of equal importance, through genetic counselling and testing we can accurately determine which family members are gene carriers and which are not. The gene carriers, who are at high risk of cancer, can then be referred for early surveillance regardless of age and benefit from preventive and risk reduction strategies; whereas the family members who are not gene carriers can be reassured and do not need to undergo unnecessary surveillance and intervention.

Variant of uncertain clinical significance

One important caveat in genetic testing for hereditary cancer syndrome is the identification of "variant of uncertain clinical significance" (VUS). This is defined as a genetic variant with unknown or uncertain effect on its protein function and its clinical implication. Such uninformative findings should not be used for clinical decision of invasive procedure and treatment like prenatal diagnosis and/or risk reducing surgery. In the current genomic era when multiple cancer predisposing genes are analysed simultaneously by the NGS technology, it is inevitable to have VUS detected. The larger the gene panel used, the higher the chance of detecting VUS. There is approximately 5-10% chance to have VUS detected by current panel testing according to the literature.

Pre-test and Post-test counselling

It is essential to have thorough pre-test and post-test counselling for all patients who undertake cancer genetic testing, so as to avoid miscommunication, erroneous diagnosis and management. Genetic counselling should be conducted in a "nondirective"

manner. During the pre-test counselling session, a detailed family history should be obtained, with a focus on but not limited to malignancy. Basic concepts of cancer genetics should be explained and cancer risks assessed. The benefits, risks and limitations of testing like potential finding of VUS and the residual cancer risks should be addressed. Social implications of testing like insurance, discrimination, and impact to family dynamics should also be discussed.

During the post-test counselling session, test results should be disclosed with proper explanation of the implications. For those with positive results, the potential cancer risks, advice on life style modification, cancer surveillance, reproductive options (like prenatal diagnosis or preimplantation genetic diagnosis), and risk-reduction strategies (like surgery or chemoprevention) should be discussed. Family cascade screening will also be offered to other at-risk family members. For those with VUS results, regular follow-up in cancer genetic clinics is recommended for future re-classification to positive or negative results in the light of new medical knowledge. For those with negative results, residual risk should be addressed. Psychological support is essential for the whole cancer genetic counselling process.

Referral indications and guidelines

For the indications and referral guidelines, it is generally agreed that those cancer cases with "early onset", "rare type cancer" and/or with "strong family history" should be referred for cancer genetics testing[1]. Different countries and institutes have their own recommendations and guidelines that take into consideration resources and availability of expertise. The common referral indications are summarised in Table 1.

Table 1. Commonly used referral /testing guidelines for hereditary breast/ovarian cancer and hereditary colorectal cancer (modified from References 6,7,8)

Hereditary breast/ovarian cancer	Hereditary Colorectal Cancer
• Breast cancer under 40 • Grade 3 triple negative breast cancer under 50 • Two cases of breast cancer (including bilateral breast cancer), average under 50 • Three cases of breast cancer, average under 60 • Four or more cases of breast cancer • Male breast cancer at any age plus breast cancer (male or female) under 60 • Breast cancer and ovarian cancer in a single individual • High grade serous papillary ovarian cancer under 60 • Ovarian cancer at any age plus breast cancer under 60 • Two or more cases of ovarian cancer • Families in whom a BRCA1 or BRCA2 mutation has been identified	• Colorectal cancer under 50 • Two cases of colorectal cancer, average under 60 • Colorectal cancer plus one gastrointestinal, endometrial, ovarian, renal or urinary tract cancer, average under 60 • Three or more cases of gastrointestinal, endometrial, ovarian, renal or urinary tract cancers • Multiple gastrointestinal polyps • Families in whom a Lynch syndrome (HNPCC) or Familial Adenomatous Polyposis (FAP) mutation has been identified

Cancer genetics testing is the standard of care for high risk cases

Recent technological, therapeutic and societal developments in the understanding of cancer biology have already revolutionised the field of medical genetics and oncology. Genetic and genomic testing has become the mainstream investigation for cancer patients. A designated cancer genetic clinic has been proposed for many developed countries. The recommended workflow of cancer genetic clinics for high risk families with hereditary cancer syndrome is depicted in Fig.1.

The cost-effectiveness of this service model for these high risk individuals with hereditary breast and colorectal cancer syndrome has also been studied[4,5] and proven to be cost saving for the society because of the reduction in cancer-related morbidity and mortality. To make this model effective, different specialists should collaborate as a team for different tasks like clinical evaluation, risk assessment, genetic/genomic testing, bioinformatics analysis, pre- and post-test counselling, tracing of at-risk family members, referral to specialists for surveillance/intervention, and regular monitoring of surveillance compliance. Only with this multidisciplinary dimensional approach that the highest standard of care to families with hereditary cancer syndrome can be provided.

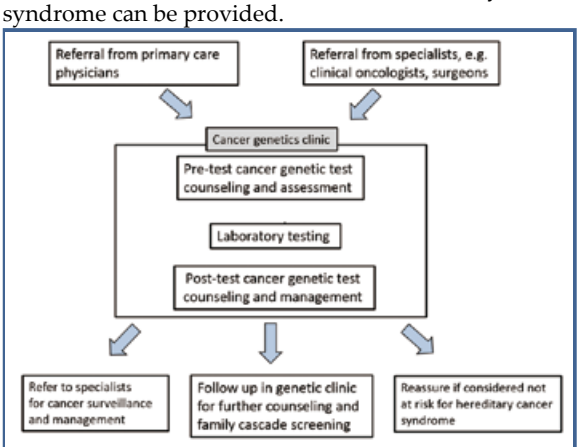

Fig. 1. The proposed workflow of cancer genetic clinic

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11 Jan	Integrated Skills Teaching: Simulated Mediation 1	Mr Vod Chan & tutors
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25 Jan	Integrated Skills Teaching: Simulated Mediation 3	Mr Vod Chan & tutors
1 Feb	Integrated Skills Teaching: Simulated Mediation 4	Mr Vod Chan & tutors
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Genetic and Genomic Testing in Hereditary Cardiomyopathy and Channelopathies

Dr Chloe MAK

MD, PhD, FHKAM (Pathology)

Chemical Pathology & Genetic Pathology Laboratories
Department of Pathology
Princess Margaret Hospital, Hong Kong

Dr Chloe MAK

Introduction

Cardiovascular disease encompasses a wide range of conditions from coronary heart disease, rheumatic heart disease, peripheral arterial disease to congenital/hereditary heart diseases. In recent decades, there are significant and rapid developments in the understanding and clinical applications of genetics in many cardiac diseases especially hereditary cardiomyopathies and channelopathies. Genetic causes are found in various potentially lethal channelopathies and cardiomyopathies including long and short QT syndromes (LQTS and SQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), Barth syndrome and left ventricular non-compaction.[1] Such developments enlighten new understanding of the disease pathogenesis, natural history and bring new possibilities for the diagnosis of these genetic disorders through genetic testing. It is not uncommon nowadays that clinicians have to face new expectations and demands from patients and their family members for genetic testing in cardiac diseases. Clinicians are required to integrate the genetic information into their clinical practice in order to aid the diagnosis, predict prognosis, perform cascade screening and sometimes guide treatment plans. While there is a growing tendency in applying genetic data into the conventional clinical management, the importance of careful interpretation of genetic results together with the provision of adequate genetic counselling cannot be overemphasised to ensure proper utilisation of genetic information.

There are elaborate international guidelines available regarding the application of genetic testing in cardiac diseases such as the current Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) expert consensus recommendations for genetic testing for the channelopathies and cardiomyopathies[2] and the HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes[3]. In addition, the United Kingdom Genetic Testing Network (UKGTN) provides a comprehensive list of gene dossiers and testing criteria for individual conditions (https://ukgtn.nhs.uk/find-a-test/gene-dossiers/). In the local public health care systems, the genetic test menu and the information of providing laboratories can be found in the HA Genetic Test Formulary (http://gtf.home/) and also by the Clinical Genetic Service, Department of Health (http://www.dh.gov.hk/english/main/main_cgs/files/Laboratory%20Investigation.pdf).

Long QT syndrome (LQTS)

LQTS is a cardiac electrophysiologic disorder characterised by QT prolongation and T-wave abnormalities on the ECG and torsade de pointes. Syncope typically occurs during exercise and high emotions, less frequently at rest or during sleep, and usually without warning. In some instances the torsade de pointes degenerates to ventricular fibrillation and causes aborted cardiac arrest or sudden death. However, some patients may not present with QT prolongation on resting 12-lead ECG. The prevalence is estimated up to 1 in 2,500 individuals. The cardiac events may occur from infancy through middle age, yet they are most common from the pre-teen years through the 20s. The condition is mainly inherited in an autosomal dominant manner. The mutation can either be inherited or de novo. Penetrance is incomplete. This means that patients carrying the mutation do not necessarily develop the phenotype. Long QT syndrome is genetically heterogeneous and associated with mutations in at least 15 genes at the time of reporting, including LQT1 (*KCNQ1*), LQT2 (*KCNH2*), LQT3 (*SCN5A*), LQT4 (*ANK2*), LQT5 (*KCNE1*), LQT6 (*KCNE2*), LQT7 (*KCNJ2*), LQT8 (*CACNA1C*), LQT9 (*CAV3*), LQT10 (*SCN4B*), LQT11 (*AKAP9*), LQT12 (*SNTA1*), LQT13 (*KCNJ5*), LQT14 (*CALM1*) and LQT15 (*CALM2*). The diagnostic yield of genetic tests in patients with long QT syndrome is about 75 – 80%.[2] In addition, about 20% of autopsy-negative sudden unexplained deaths in the young and 10% of sudden infant deaths may be related to LQTS.[4,5] The recessive form of LQTS is known as Jervell and Lange-Nielson syndrome and is associated with sensorineural deafness. One local case has been reported.[6]

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

CPVT could present with syncope and sudden death during physical exertion or emotion, due to catecholamine-induced bidirectional ventricular tachycardia, polymorphic ventricular tachycardia or ventricular fibrillation. The reported mean age of onset was about 8 years of age, with normal resting electrocardiogram. Exercise stress tests or adrenaline provocation tests might induce the ventricular arrhythmia for clinical diagnosis. About half of these cases are related to dominantly inherited *RYR2* gene mutation, with a small number (1 – 2%) related to recessively inherited *CASQ2* gene mutation. CPVT may account for 15% of autopsy-negative sudden unexplained deaths in the young.[4]

Brugada syndrome

Brugada syndrome is characterised by cardiac

conduction abnormalities (ST-segment abnormalities in leads V1-V3 on ECG and a high risk for ventricular arrhythmias) that can result in sudden death. Brugada syndrome presents primarily during adulthood although age at diagnosis may range from infancy to late adulthood. Clinical presentations may also include sudden infant death syndrome and the sudden unexpected nocturnal death syndrome. Other conduction defects can include first-degree atrio-ventricular block, intraventricular conduction delay, right bundle branch block, and sick sinus syndrome. The Shanghai Score System is recently published for the diagnosis of Brugada syndrome.[7,8] The prevalence of Brugada syndrome is reported higher among Asians from 0.14% to 1.22%.[9,10] The condition is inherited in an autosomal dominant manner in most cases. Recent literatures indicate that the genetic inheritance is likely more complex and models of an oligogenic disorder or susceptibility risk/genetic predisposition are suggested.[11] Expressivity is variable. Penetrance is incomplete and low. The genetically heterogeneous condition has been associated with pathogenic variants in at least 23 genes (*ABCC9, CACNA1C, CACNA2D1, CACNB2, FGF12, GPD1L, HCN4, KCND2, KCND3, KCNE5, KCNE3, KCNH2, KCNJ8, PKP2, RANGRF, SCN1B, SCN2B, SCN3B, SCN5A, SCN10A, SEMA3A, SLMAP,* and *TRPM4*). The diagnostic yield of genetic testing in Brugada syndrome is about 20 - 30%.[2] It is important to bear in mind that the majority of Brugada syndrome remain genetically elusive and a negative genetic result does not necessarily rule out the diagnosis in the patient.

Arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVD/C)

ARVD/C is a heritable cardiomyopathy with clinical hallmarks of right ventricular enlargement and dysfunction, fibrofatty replacement of right ventricular myocytes and characteristic ECG abnormalities. Patients can present in adulthood with palpitations, syncope, chest pain, dyspnoea, and sudden cardiac death. However, up to 40% of patients can remain asymptomatic. The frequency of ventricular arrhythmias varies with the severity of ARVD/C. The most common arrhythmia is monomorphic ventricular tachycardia (sustained or nonsustained) with a left bundle branch block pattern. Sudden cardiac death occurs in patients with ARVD/C and can be the first presentation of the disease before structural heart abnormalities are seen. ECG abnormalities observed in ARVD/C include QRS prolongation, incomplete or complete right bundle branch block, prolonged S wave upstroke, epsilon wave and T-wave inversion. The echocardiographic characteristics of ARVD/C include increased right ventricular dimensions, reduced right ventricular fractional area change and other right ventricular morphologic abnormalities. Diagnosis of ARVC is a combination of clinical, radiological, histological and genetic findings, according to the Task Force Criteria 2010.[12] The prevalence is reported to be 1 in 2,000 to 5,000. It can be inherited as autosomal dominant or recessive modes. Incomplete penetrance and variable expressivity have been reported. Compound heterozygosity and digenic heterozygosity have been reported up to 10%. ARVD/C is genetically heterogeneous with at least nine genes implicated (ARVC1 (*TGFB3*), ARVC2 (*RYR2*), ARVC5 (*TMEM43*), ARVC8 (*DSP*), ARVC9 (*PKP2*), ARVC10 (*DSG2*), ARVC11 (*DSC2*), ARVC12 (*JUP*) and ARVC13 (*CTNNA3*)). The diagnostic yield of genetic test in ARVD/C patients is about 60 %.[2]

Hypertrophic cardiomyopathy (HCM)

HCM is typically defined by the presence of left ventricular hypertrophy in the absence of other cardiac or systemic diseases that is capable of causing secondary changes in the left ventricular wall thickness. Patients with HCM may be completely asymptomatic, or may present with arrhythmia, chest pain and heart failure symptoms; they may also develop syncope and sudden cardiac death. HCM is estimated to affect approximately 1 in 500 persons and is the most common inherited cardiovascular disease and cause of sudden cardiac death in young patients. HCM is a group of genetically heterogeneous disorder, typically inherited in an autosomal dominant manner with incomplete penetrance, although de novo mutation is also possible. According to the HRS/EHRA expert consensus statement, genetic testing for HCM is recommended for patients with established diagnosis of HCM by cardiologists[2]. Identification of HCM-causative mutation in an index case should be followed by mutation-specific genetic testing for their relatives.

There are more than 30 causative genes and 1,500 individual pathogenic variants identified to date, and most of the genes implicated are those encoding the different components of the sarcomere. Among all identified genes associated with the disease, pathogenic variants of *MYH7* and *MYBPC3* each account for about a quarter to one-third of disease. The diagnostic yield of sarcomere gene testing is about 60 - 70% in familial cases and ~30% in sporadic cases.[2] Approximately 5% of cases have two or more variants (compound or double heterozygotes); these cases may be associated with a more severe phenotype and earlier disease onset. It should be noted that a number of phenocopies of HCM may present with different inheritance patterns and/ or systemic features in addition to the cardiac features of HCM e.g. Wolff-Parkinson-White syndrome, Fabry's disease and Danon disease, Forbes disease and Noonan syndrome. Appropriate genetic testing should be arranged when these features are present.

Dilated cardiomyopathy (DCM)

DCM is a cardiomyopathy characterised by dilatation and systolic dysfunction of the ventricles, with a prevalence of 1 in 2,500. Causes of DCM are heterogeneous. Common examples of acquired causes are infection, alcoholism and drug effects. A significant portion is labelled as idiopathic. With advent of diagnostic genetics, it is now known that about 15 – 20 % of such idiopathic cases are familial with an underlying genetic aetiology. Patients with familial DCM can present with DCM alone or in combination with other clinical features such as conduction defects, valvular anomalies, congenital heart disease, left ventricular non-compaction, skeletal myopathy and hearing loss.[13] Familial DCM may be inherited in an autosomal dominant, autosomal recessive or X-linked manner. Most familial cases, probably 80 – 90%, appear to be autosomal dominant. There are more than 40 genes known to account for familial DCM. The diagnostic yield of genetic test in DCM patients is about 30%.[2]

Sudden arrhythmia death syndromes (SADS)

Primary arrhythmogenic disorders including LQTS, short QT syndrome, CPVT, Brugada syndrome and cardiomyopathies account for about one-third of sudden cardiac deaths in the young.[14] Identification of a pathogenic variant can solve the diagnostic mystery, bring relief to the family and enable family screening and counselling for other at-risk family members. Guidelines on molecular autopsy are available.[15,16] Our group has conducted the first local prospective study to determine the prevalence and types of sudden arrhythmia death syndrome underlying sudden cardiac deaths among local young victims through clinical and molecular autopsy of SCD victims and clinical and genetic evaluation of their first degree relatives. (http://www.sadshk.org/en/medical_research.php). To date, molecular autopsy is provided by the Clinical Genetic Service, Department of Health.

Next generation sequencing for cardiac disorders

Next generation sequencing (NGS) involves "massively parallel" amplification and sequencing generating hundreds of megabases to gigabases of nucleotide-sequencing output in a single analytical run. It can offer more cost-effective analysis in genetic conditions with huge gene sizes and with large genetic heterogeneity compared with the traditional method of Sanger sequencing. This approach also allows more comprehensive genetic screening as occasionally digenic mutations have been reported. It is important not to miss any relevant mutations especially in subsequent family screening. NGS can offer new possibilities for resolving cases with diagnostic difficulties. A gene panel targeted for specific genes according to the cardiac phenotypes is a commonly used effective way of genetic diagnosis. Gene list specific for a phenotype can reduce the chance of finding variants of uncertain significance which may cause more confusion to the clinicians and patients. For difficult cases, an exome approach (sequencing most if not all the protein-coding exons in the human genome) may be helpful to solve diagnostic mysteries in the search for genetic causes of rare inherited disorders. Since in most Mendelian disorders, disease-causing alleles mostly disrupt protein-coding sequence and a large fraction of rare mutations are predicted to be deleterious.

Genetic testing in clinical practice

Genetic testing plays an increasingly important role in the clinical management of cardiovascular disorders. It is recommended to follow the aforementioned international guidelines for the indications of genetic tests on individual conditions. Before requesting a genetic test, it is important to obtain a detailed pedigree analysis to determine the inheritance pattern in the patient's family as well as to estimate the recurrence risk of the at-risk family members. Normally, at least 3 generations should be plotted. It is not uncommon to have asymptomatic parents due to the incomplete penetrance and variable expressivity of mutations in cardiac genes, or sometimes due to germline mosaicism (the mutant allele is only present in the germ cells of the parent). Penetrance is usually incomplete and age-dependent in autosomal dominant cardiac disease. There is a large variable cardiac expression in terms of the age at onset, the degree of symptoms, and the risk of complications. A few phenotype–genotype correlations have been observed only, such as the specific triggering events (physical exercise, auditory stimuli, rest/sleep) leading to arrhythmia/syncope in LQTS. Both significant inter- and intra-familial variability in expressivity are observed.

Because of the well-known incomplete penetrance and variable expressivity in cardiac disorders, it is prudent to keep in mind that the finding of a genetic mutation means probabilistic rather than binary yes or no of having the symptoms and signs. Careful interpretation of the pathogenicity of genetic variants must be exercised. At-risk relatives should have regular cardiac examinations which normally have to be continued until the age when the penetrance is estimated to be nearly complete. Moreover, because of the limited sensitivity of genetic analysis on cardiac diseases, a negative genetic result does not rule out the hereditary basis of disease in the patients. Genetic counselling should be provided by specialists with experience on cardiac genetics.

It is not surprising to recognise a significant gap between the rapidly developing genetic knowledge of cardiac diseases and its applications in clinical practice. It is crucial to establish a closer working relationship between health care providers from cardiology, pathology and clinical genetics for the proper utilisation of genetic and genomic tests on the affected patients as well as the appropriate screening and follow-up of the relatives with careful consideration in various medical, psychological, ethical and social aspects.

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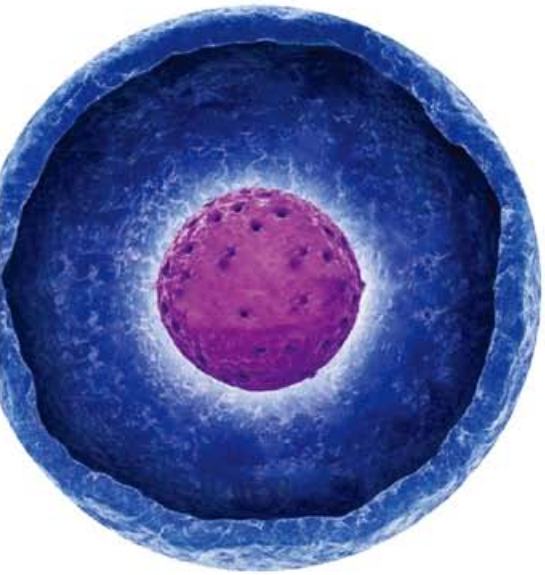

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Genomic approaches to prenatal and cancer screening

Dr Rossa WK CHIU

MBBS(Qld), PhD(CUHK), FRCPA, FHKCPath, FHKAM (Pathology)

Specialist in Chemical Pathology
Choh-Ming Li Professor of Chemical Pathology, Assistant Dean (Research), Faculty of Medicine, The Chinese University of Hong Kong

Introduction

Advocacy of disease screening is based on the notion that early disease identification may result in early management of the condition and hence, better outcomes. However, this notion is not always true. Whether disease screening brings benefits or not is dependent on a number of factors. The Wilson and Jungner criteria for disease screening, published in 1968, have stood the test of time[1]. These classical teachings indicate that the target disease should be an important health problem and acceptable treatments should be accessible. There should be an early stage of the disease assessable by a test acceptable to the testing population and the natural course of the disease from the early stage be known.

With the dawn of the genomics era, some consider that "screening" could take on a different meaning[2]. Whole genome analysis may identify rare conditions that are quite amenable to treatment. Just because these conditions are rare does not render them a problem too small to be considered candidates for screening in the appropriate context, for example in ethnic groups at high risk for such conditions. While genome-wide DNA analysis are currently expensive, there are strategies to help mitigate the costs and maximise its benefit. For example, identification of disease-relevant mutations among couples planning a pregnancy or are pregnant, termed carrier screening, has conventionally been applied to couples who are deemed to be at higher risks. Carrier screening of the thalassaemias is offered in parts of the world with high incidences of the thalassaemias or couples with a family history of affected family members[3]. The screening tests at the DNA level are gene-specific and usually mutation-specific. More recently, some centres advocate expanded carrier screening. The American College of Obstetricians and Gynecologists defines expanded carrier screening as programmes that assess a large number of genetic conditions, such as >100, and where the testing is applied to all couples regardless of genetic or ethnic background[4]. The diseases included in such panels may be rare individually but are of course more prevalent collectively.

On the other hand, genomic information of an individual has far-reaching implications affecting not only the tested person but also his / her relatives. As a result, when genomic analysis is used for disease screening, a person's wish to opt in or out of the testing needs to be respected. In fact, researchers have suggested some new elements to be included as the criteria for disease screening in the genomics era[2]. The newer elements include that the objectives of the screening as well as the target population be clearly defined. There should be scientific evidence to support the effectiveness of the screening strategy. The guidelines do not support the casual scanning for genomic features that have not proven to be well correlated with disease pathologies or been demonstrated to be associated with clinical benefit.

Genomic approach to prenatal screening

A number of genetic or genomic tests have attained technological maturity and gathered adequate evidence supporting their clinical implementation. One example is the non-invasive prenatal screening test for Down syndrome based on foetal DNA analysis from maternal blood[5]. During pregnancy, the natural cell-turnover process of the placenta results in small amounts of fragmented DNA to be distributed to the maternal circulation[6]. Such DNA fragments of 'foetal' origin contribute about 10% of the DNA content in the acellular portion of the mother's blood, namely the plasma portion. These DNA molecules are extracellular in nature and are termed, cell-free foetal DNA in maternal plasma. If a woman is pregnant with a foetus with Down syndrome, there would be an increased proportion of chromosome 21 DNA in her plasma with the added amount of chromosome 21 DNA contributed by the foetus. Because of the small amounts of cell-free foetal DNA in a mother's plasma, millions of plasma DNA molecules need to be analysed per sample in order to achieve high accuracy for the identification of foetal chromosomal aneuploidies. Thus, most of the non-invasive tests for foetal chromosomal aneuploidy screening are based on sophisticated molecular analysis approaches involving what is known as next-generation sequencing or massively parallel sequencing. Some testing approaches focus on the analysis of chromosomes 21, 18 and 13 for the purpose of identifying trisomies 21, 18 and 13[7]. Other testing approaches involve analysing DNA molecules from all chromosomes[8,9].

Shown by a number of large-scale trials[5,10,11], the non-invasive plasma DNA-based tests for foetal chromosomal aneuploidy screening could typically detect > 99% of the Down syndrome cases at about 0.1% false-positive rate. Due to its high performance that could be independently replicated by many centres, professional bodies, such as the American College of Obstetricians and Gynecologists, the National Society of Genetic Counselors of US, have since 2012 supported the

clinical adoption of the maternal plasma DNA tests for foetal chromosomal aneuploidy screening among high-risk women[12-14]. "High-risk" is determined based on conventional parameters such as maternal age, maternal serum testing and foetal ultrasonographic findings.

The tests were very soon widely adopted and became available in over 90 countries. At the same time, scientific evidence has emerged to show that the test offers 10 times improvement in positive predictive value even when testing is offered to women at low risk for foetal chromosomal aneuploidy[15]. Consequently, since 2015, some professional bodies have updated their clinical recommendation to support access of the maternal plasma DNA test for foetal chromosomal aneuploidy screening to be made available to women of all risk groups[16,17]. The main clinical value of the maternal plasma DNA test lies in its low false-positive rate (at about 0.1%) compared with conventional maternal serum biochemistry screening that has a false-positive rate of ~5%. One main consequence of the increasing adoption of the DNA-based non-invasive screening test was the reduction in the number of couples who had to be faced with the difficult decisions of whether to proceed with an invasive prenatal diagnostic tests, such as amniocentesis, or not. Some centres have reported a reduction in the number of invasive procedures by 30% since the introduction of the non-invasive DNA-based blood tests[18]. The technology continues to advance and now it is technically feasible to use cell-free foetal DNA in maternal plasma for screening a large range of foetal genetic diseases beyond foetal chromosomal aneuploidies[19]. However, whether these newer tests would become mainstream screening tests would depend on evidence demonstrating their clinical efficacy and cost-effectiveness.

Genomic approach to cancer screening

Extending beyond the prenatal context, it is now well appreciated that malignant tumours also release their DNA content into the circulation. Such DNA molecules are also cell-free in nature and circulate in the form of short fragments in human plasma. They are known as circulating tumour-derived DNA (ctDNA). ctDNA analysis has been used as liquid biopsies, namely to assess the genetic or genomic profile of tumours non-invasively through the analysis of a blood sample. For example, plasma DNA analysis in search for *epidermal growth factor receptor* (EGFR) mutations among patients with lung cancers facilitates clinical decision-making of whether the patient might benefit from the administration of tyrosine kinase inhibitors[20]. On the other hand, ctDNA analysis could also serve as a tool for post-treatment monitoring for tumour recurrence, such as has been demonstrated for nasopharyngeal carcinoma (NPC)[21].

Yet going beyond the liquid biopsy context, could ctDNA analysis serve as a means to screen for cancer among asymptomatic individuals and also enable early cancer detection? To test this hypothesis, our research group has conducted a study where over 20,000 healthy asymptomatic individuals were recruited from the Hong Kong community[22]. Blood samples were collected and the plasma samples were tested for the presence of Epstein-Barr virus (EBV) DNA. Cell-free EBV DNA fragments have previously been shown to be present in plasma and are derived from the tumour in NPC patients. By applying an EBV DNA assay optimised for screening, 309 (1.5%) of the studied cohort had detectable plasma EBV DNA when tested on two occasions 4 weeks apart. 300 of these participants underwent nasal endoscopy while 275 had magnetic resonance imaging. 34 participants were confirmed to have NPCs by nasal endoscopy and/or magnetic resonance imaging. 71% of the NPC cases identified by this screening study were of stages I or II which contrasted with historical data whereby only 20% of NPCs diagnosed under conventional circumstances were of early stage. After following up all study participants for a median of 22 months, one person, who had persistently positive plasma EBV DNA results but refused confirmatory workup, died of NPC 32 months after enrolling into the study. One other person was subsequently diagnosed with NPC within 1 year of having been tested negative for plasma EBV DNA. These results show that plasma EBV DNA analysis offered a sensitivity of 97.1% and specificity of 98.6% for NPC identification among asymptomatic individuals.

Among the 34 NPC cases identified through the study, 97% were surviving at 3 years. These data compared favourably with NPC patients recorded in the 2013 Hong Kong Cancer Registry where the 3-year survival was 70%. The hazard ratio for the screened cohort was 0.10 (95% confidence interval: 0.05 to 0.18). On-going follow-up of the 20,000 cohort is being conducted to affirm the notion if early identification of NPC translates to improved survival and better outcome. While these data are promising, they also spur questions of whether other screening tests could similarly be developed for the early identification of other cancers. To develop a more generic approach that might be applicable to the detection of more than one cancer type, our research group has been studying the use of approaches for genome-wide analysis of ctDNA[23,24]. The genome-wide approaches could be for the purpose of detecting chromosomal regions with gains or losses, abnormal DNA methylation profiles or aberrant RNA transcription profiles. The underlying hypothesis of such genome-wide strategies is that perhaps by capturing any genomic aberrations that might be associated with any sort of cancers, the tests might detect a wider spectrum of cancers.

Conclusion

Genomic technologies and bioinformatics are becoming more clinically accessible. The reliability of the technologies are improving and the costs are decreasing. However, it is reaching a state where it might be all too easy to perform genome-wide analysis on any DNA sample. However, as reviewed in this article, the use of genomic technologies for disease screening should still be performed for well-defined clinical needs with evidence in support of the ensuing clinical benefits. Studies and data are emerging to show that some genetic and genomic tests could indeed bring about improved clinical outcomes when performed at population scale. Examples in prenatal and cancer screening have been discussed. It is hoped that these early examples represent the start of a succession of such appropriately trialled and tested genomic tests that could help solve public health agendas.

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Dermatological Quiz

Dr Lai-yin CHONG

MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)

Specialist in Dermatology & Venereology

Dr Lai-yin CHONG

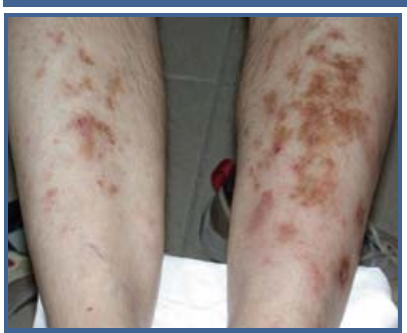

Fig.1: Bilateral pigmented purpuric lesions at the legs

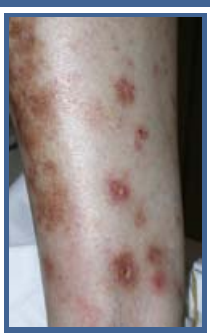

Fig.2: Ulcerations with tissue necrosis on close-up

A 35-year-old man presented with a one-year history of recurrent painful purpuric skin lesions at his legs (Fig.1). The lesions ulcerated (Fig.2) and healed with scars eventually. His thighs also showed bluish reticulated lesions. He was otherwise well. His past health was good. Skin biopsy reported by a junior pathologist as "cutaneous vasculitis". The lesions ran a wax and wane course despite treatment with oral steroid and azathioprine.

Questions

1. What other important diagnosis should you consider when reviewing the histopathology of his skin biopsy?
2. What are the other differential diagnoses of this disease?
3. What investigations will you order to search for the possible underlying pathogenetic cause?
4. What is the mainstay of treatment?

(See P.36 for answers)

FABRY DISEASE

*Data have indicated that **up to 5 family members** may be diagnosed with Fabry disease for every index patient*[1]

TEST THE PATIENT, TEST THE FAMILY, TREAT EARLY

A SIMPLE BLOOD TEST[2,3]

α-Gal A enzyme activity assay can be performed on a dried blood spot (DBS) sample. A positive result in males should be followed with DNA analysis to confirm Fabry disease and/or identify mutations in index cases

GENETIC TESTING[2,3]

DNA analysis for α-Gal A gene mutations is necessary to confirm a diagnosis of Fabry disease in females

FAMILY TESTING[1,2,4]

X-linked genetic condition with a high transmission rate testing may identify affected relatives early

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FABRY disease

A rare commitment to the Fabry community

For over 30 years, Genzyme has pioneered the development and delivery of patient-focused programs and services for individuals affected by rare and debilitating diseases. With a focus on rare diseases and multiple sclerosis, we are dedicated to making a positive impact on the lives of the patients and families we serve.

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SANOFI GENZYME

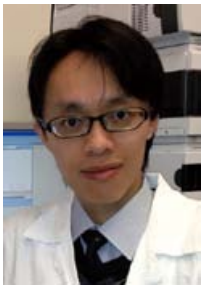
sanofi-aventis Hong Kong Limited
Units 706-710, Level 7, Core C, Cyberport 3,
100 Cyberport Road, Hong Kong
Tel: (852) 2506 8333 Fax: (852) 2506 2537

www.sanofigenzme.com

Undiagnosed diseases programme for ending diagnostic odyssey in rare diseases in Hong Kong, China

Dr Ching-wan LAM
MBChB (CUHK), PhD (CUHK), FRCP (Glasg), FRCPA, FHKCPath, FHKAM (Pathology)
Department of Pathology, The University of Hong Kong, Hong Kong, China

Dr Chun-yiu LAW
MBChB (CUHK), BMedSc, PhD (HKU), FRCPA, FHKCPath, FHKAM (Pathology)
Department of Pathology, The University of Hong Kong, Hong Kong, China

Dr Ching-wan LAM Dr Chun-yiu LAW

Background

Diagnostic odyssey refers to an extraordinary delay, in a matter of years, between the disease onset and the time of the final diagnosis. Diagnostic odyssey is mostly due to diagnostic challenges as a result of the rarity of the disease. According to the Rare list (http://globalgenes.org/rarelist/), there are approximately 7,000 rare diseases affecting 300 million people worldwide. However, the diagnosis of rare diseases is always difficult as most medical doctors have not been trained to diagnose rare diseases, and sophisticated laboratory investigations are often required; while public resources are mainly targeted at common diseases. Most rare diseases are genetic diseases. However, due to the diversity of rare diseases and the high likelihood that these patients will be undiagnosed or misdiagnosed, another name for rare disease is "orphan disease" because the health care system failed to provide a last resort to make sure that patients with rare diseases will be managed the same as patients with common diseases in terms of equal opportunity of receiving an accurate diagnosis and specific treatment.

According to the World Health Organization, a rare disease is one that affects a small percentage of the population, ranging from 0.65 to 1 in 1,000. A previous study estimated that there were about 10 million people in the China Mainland with a rare condition[1]. For the referrals that the authors have received in the past 25 years, most of the referrals came without a diagnosis or a diagnosis which was confirmed later to be erroneous. To help patients with rare diseases, the Office of Rare Disease Research, National Center for advancing Translational Sciences, National Institute of Health, USA, has set up the Undiagnosed Diseases Program (UDP) (http://rarediseases.info.nih.gov/research/pages/27/undiagnosed-diseases-program) to end the diagnostic odyssey of patients with rare diseases. In this programme, patients with a rare disease will be under the care of clinicians and physician-scientists / pathologists with experience with rare diseases. In Hong Kong, we have similar problems with the diagnosis of rare diseases. It is common for patients with rare diseases remained undiagnosed or misdiagnosed for decades. For example, a patient with treatable liver disease, Wilson disease, remained undiagnosed for 18 years and a patient received a definitive diagnosis of neonatal jaundice until the patient was 14 years old[2,3].

In the past 25 years, we had encountered a number of "rare" diseases locally (Table 1). We realised there is a strong clinical need to provide diagnostic service for rare diseases. With the support from the S. K. Yee Medical Foundation in 2014, we were able to set up the first Undiagnosed Diseases Programme (UDP) to end the diagnostic odyssey of patients suffering from rare diseases using Clinical Whole Exome Sequencing (CWES) and Clinical Whole Genome Sequencing (CWGS), and other advanced laboratory analysis, such as NMR-based metabolomics.

Table 1. Rare diseases encountered in previous years.

5-Alpha Reductase II Deficiency	6-Pyruvoyl-tetrahydropterin Synthase
Acetoacetyl-CoA Thiolase Deficiency	Acute Intermittent Porphyria
Antenatal Bartter Syndrome Type I	Antenatal Bartter Syndrome Type II
Arginase Deficiency	Argininosuccinate Lyase Deficiency
Ataxia Telangiectasia	Barth Syndrome
Basal-cell Naevus Syndrome	Butyrlcholinesterase Deficiency
Congenital Disorder of Glycosylation Type Ia	Carnitine-acylcarnitine Translocase Deficiency
Catecholaminergic Polymorphic Ventricular Tachycardia	Cerebrotendinous Xanthomatosis
Citrin Deficiency	Classical Late-infantile Neuronal Ceroid Lipofuscinosis
Congenital Adrenal Hypoplasia	Congenital Hyperinsulinism
Congenital Muscular Dystrophy	Microcephaly and Mental Retardation Due to Protein-o-mannosyl Transferase 1 Deficiency
Congenital Myasthenic Syndrome Type 1c	Congenital Nephrotic Syndrome
Cystinuria Type B	Darier Disease
Distal Renal Tubular Acidosis	Dopa-responsive Dystonia
Erythropoietic Protoporphyria; Fabry Disease	Familial Amyloidotic Polyneuropathy Type 1
Familial Dysalbuminemic Hyperthyroxinaemia	Familial Hypocalciuric Hypercalcaemia
Familial Hyperparathyroidism	Fumarate Dehydratase Associated Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome
Gaucher Disease	Gitelman Syndrome
Glutamate Dehydrogenase Deficiency	Glycogen Storage Disease Type Ia
Glycogen Storage Disease Type Ib	Glycogen Storage Disease Type II
Glycogen Storage Disease Type III	Glycogen Storage Disease Type IV
Glycogen Storage Disease Type IX	Hailey-Hailey Disease
Holocarboxylase Synthetase Deficiency	Hunter Syndrome
Hungtington Disease	Hurler Syndrome
Hyperekplexia	Hyperornithinemia-hyperammonaemia-homocitrullinuria Syndrome
Hypophosphatasia	Isovaleric Acidaemia Isolated Sulfite Oxidase Deficiency
Juvenile Parkinsonism	Kearns-Sayre Syndrome
Kelley-Seegmiller Syndrome	Kennedy Disease
Leber Hereditary Optic Neuropathy	Leigh Syndrome
Leopard Syndrome	Lipoprotein Lipase Deficiency
Long QT Syndrome Type 1	Malignant Infantile Osteopetrosis
Maroteaux-lamy Syndrome	Methylmalonyl Coa Mutase Deficiency
Methylmalonic Aciduria and Homocystinuria	MELAS
Mucolipidosis Type IIIa	Mucopolysaccharidosis Type IIIb
Myotonia Congenital	Nemaline Myopathy
Ornithine Transcarbamylase Deficiency	Pantothenate Kinase 2 Deficiency
Paramyotonia Congenital	Pendred Syndrome
Pearson Syndrome	Primary Hyperoxaluria I
Primary Hyperoxaluria II	Primary Torsion Dystonia
Progressive Familial Intrahepatic Cholestasis Type 2	Protein S Deficiency
Resistance to Thyroid Hormone Syndrome	Renal Hypouricaemia
Rett Syndrome	RYR1-related Myopathy
Sitosterolaemia	Spinal Muscular Atrophy
Steatocystoma Multiplex	Steroid 17 Alpha-hydroxylase Deficiency
Succinate Dehydrogenase Deficiency	Testicular Feminisation Syndrome
Tyrosine Hydroxylase Deficiency	Tyrosinemia
Variegate Porphyria	Very Long-chain Acyl-coenzyme a Dehydrogenase Deficiency
Xeroderma Pigmentosum Type C	X-linked Adrenoleukodystrophy

Objective

We are very affirmative that there is a need to set up an UDP in Hong Kong which is currently unavailable locally to end the diagnostic odyssey of patients with rare diseases. This initiative is the last resort for the patients, otherwise, the diagnostic odyssey will become endless and tragic for the patients and the families.

Significance

Ending diagnostic odyssey

In this exercise, we have handled over 100 cases. Various techniques, including biochemical testing, nuclear magnetic resonance (NMR) spectroscopy, microarrays, CWES and CWGS had been applied to end the diagnostic odyssey. The bioinformatics processing was based on our in-house filtering algorithm[4]. The overall clinical interpretation from pathologists was based on clinical presentation, laboratory findings, imaging results and pathophysiology. The disease entities identified in this UDP programme were highly heterogeneous and were summarised in Table 2.

We also realised that some of the "rare" diseases are not "rare", and the conditions had been encountered by us repeatedly, for example, early infantile epileptic encephalopathy 17 (EIEE 17), Allan-Herndon-Dudley syndrome, episodic kinesigenic dyskinesia, and coenzyme Q10-related conditions.

Importantly, we had successfully ended the diagnostic odyssey for some patients. For example, we identified a case of *POLG*-related mutation in a patient with sensory ataxia, neuropathy, ophthalmoparesis and stroke[5]. The patient first presented at 8 years old and she finally received the correct molecular diagnosis at 18 years old. She was initially thought to have mitochondrial disease and had been seen by various local and overseas experts. Multiple investigations (including whole mitochondrial genome analysis) and invasive procedures had been performed (including biopsy). A correct diagnosis, in this case, can help provide an appropriate genetic counselling to the family (autosomal recessive in this case rather than usual maternal inheritance in mitochondrial disease). This also brought direct benefits to the patient and the family because valproic acid, a common anti-epileptic drug would

Table 2. Cases solved in the current UDP.

Gene	OMIM	ORPHA number	DOID	Disease	Description
ABCD1	#300100	43, 139396, 139399	10588	Adrenoleukodystrophy	ATP-binding cassette, sub-family D (Ald), member 1
ADCY5	#606703	324588		Dyskinesia, familial, with facial myokymia	Adenylate cyclase 5
ATP2C1	#169600	2841	0050429	Hailey-Hailey disease	ATPase, Ca++ transporting, type 2C, member 1
ATP8B1	#243300	65682, 99960	1852	Benign recurrent intrahepatic cholestasis 1	ATPase, aminophospholipid transporter, class I, type 8B, member 1
BAAT	#607748	238475		Hypercholanemia, familial	Bile acid CoA: amino acid N-acyltransferase (glycine N-choloyltransferase
BRAF	#613706	1340	0060233	Cardiofaciocutaneous syndrome	V-RAF murine sarcoma viral oncogene homolog B1
C3	#612925	2134, 93575		Hemolytic uremic syndrome, atypical, susceptibility to, 5	Complement component 3
CDC25B				Cardiomyopathy	Cell division cycle 25B
CHRNA1	#601462	98913, 590	00110663	Myasthenic syndrome, congenital, 1A, slow-channel	Cholinergic receptor, nicotinic, alpha 1 (muscle)
COL12A1	#616471	610		Bethlem myopathy 2	Collagen, type XII, alpha 1
COL4A5	#301050	63, 88917	00110034	Alport syndrome, X-linked	Collagen, type IV, alpha 5
COQ4	#616276	457185		Coenzyme Q10 deficiency, primary, 7	Coenzyme Q4 homolog (s. Cerevisiae)
COQ6	#614650	280406	0050730	Coenzyme Q10 deficiency, primary, 6	Coenzyme q6 monooxygenase
DDX3X	#300958	457260		Mental retardation, X-linked 102	DEAD (asp-glu-ala-asp) box polypeptide 3, X-linked
EBF3	#617330			Hypotonia, ataxia, and delayed development syndrome	Collier/OLF1/EBF transcription factor 3; COE3
FGFR3	#146000	429		Hypochondroplasia	Fibroblast growth factor receptor 3
GATA1	#300835	363727		Anemia, X-linked, with/without neutropenia and/or platelet abnormalities	
GATAD2B	#615074	363686	0060307	Mental retardation, autosomal dominant 18	GATA zinc finger domain containing 2b
GLA	#301500	324	0014499	Fabry's disease	Galactosidase, alpha
GNAO1	#615473	1934	0050709	Epileptic encephalopathy, early infantile, 17	Guanine nucleotide binding protein (G protein), alpha activating activity polypeptide o
GRIN1	#614254	178469	0060307	Mental retardation, autosomal dominant 8	Glutamate receptor, ionotropic, N-methyl D-aspartate 1
GRIN2B	#613970	178469	0060307	Mental retardation, autosomal dominant 6; Intellectual disability, profound	Glutamate receptor, ionotropic, N-methyl D-aspartate 2b
GTPBP3	#616198	444013	0060286	Combined oxidative phosphorylation deficiency 23	GTP binding protein 3 (mitochondrial)
HUWE1	#300706	85328	0060811	Mental retardation, X-linked syndromic, Turner type	HET, UBA and WWE domain containing 1, e3 ubiquitin protein ligase
IFIH1	#615846	51	0050629	Aicardi-Goutieres syndrome 7	Interferon induced with helicase c domain 1
ITPR1	#117360	208513	0050978	Spinocerebellar ataxia 29, congenital nonprogressive	Inositol 1,4,5-trisphosphate receptor, type 1
KDM6A	#300867	2322	0060473	Kabuki syndrome 2	Lysine (k)-specific demethylase 6a
KIF1A	#614255	178469	0060307	Mental retardation, autosomal dominant 9	Kinesin family member 1a
KRAS	#615278	1340	0060233	Cardiofaciocutaneous syndrome 2	Kirsten murine sarcoma virus 2
KRIT1	#116860	221061		Cerebral cavernous malformations-1	KRIT1, ankyrin repeat containing
L1CAM	#307000	2182, 275543	10908	Hydrocephalus due to aqueductal stenosis	L1 cell adhesion molecule
MECP2	#300673	209370		Encephalopathy, neonatal severe	Methyl-CPG-binding protein 2
MVK	#610377	29	0050452	Mevalonic aciduria	Mevalonate kinase
MYH7	#160500	59135	11720	Laing distal myopathy	Myosin, heavy chain 7, cardiac muscle, beta
NDUFAF6	#256000	70474, 255210, 506, 255241	3652	Leigh syndrome due to mitochondrial complex I deficiency	NADH dehydrogenase (ubiquinone) complex I, assembly factor 6
PEX6	#614862	912		Peroxisome biogenesis disorder 4A (Zellweger)	Peroxisomal biogenesis factor 6
PIGO	#614749	247262		Hyperphosphatasia with mental retardation syndrome 2	Phosphatidylinositol glycan anchor biosynthesis, class O
POLG	#607459	70595, 254881		Mitochondrial recessive ataxia syndrome (includes SANDO and SCAE)	Polymerase (DNA directed), gamma
PRRT2	#128200	98809	0090053	Infantile convulsions and paroxysmal choreoathetosis, familial	Proline-rich transmembrane protein 2
PURA	#616158	438216, 438213		Mental retardation, autosomal dominant 31	Purine-rich element binding protein A
RAPSN	#616326	98913, 590	0110675	Myasthenic syndrome, congenital, 11, associated with acetylcholine receptor deficiency	Receptor-associated protein of the synapse
SCN9A	#613863	36387	0060170	Epilepsy, generalized, with febrile seizures plus, type 7	Sodium channel, voltage-gated, type IX, alpha subunit
SERPINF1	#613982	216812, 216820, 666	0110350	Osteogenesis imperfecta, type VI	Serpin peptidase inhibitor, clade F (alpha-2 antiplasmin, pigment epithelium derived factor), member 1
SLC16A2	#300523	280270, 59	0050631	Allan-Herndon-Dudley syndrome	Solute carrier family 16, member 2 (thyroid hormone transporter)
TBC1D24	#605021	352582		Myoclonic epilepsy, infantile, familial	TBC1 domain family, member 24
TOP2B				Autism	Topoisomerase (DNA) II beta 180KDa
TPK1	#614458	293955		Thiamine metabolism dysfunction syndrome 5 (episodic encephalopathy type)	Thiamine pyrophosphokinase
WT1	#194070	2154		Wilms' tumor	Wilms tumor 1

result in liver toxicity in POLG-carrier and should be avoided. Not only that, we had also successfully ended a 40-year diagnostic odyssey in a sibling who presented with Leigh-like symptoms by performing CWES which revealed a genetic defect in the *TPK1* gene. *TPK1* is responsible for encoding thiamine pyrophosphokinase (TPK), an important enzyme in thiamine metabolism and a genetic defect in *TPK1* gene would lead to episodic encephalopathy. Therefore, early dietary intervention/supplement may potentially reverse or slow down the disease progress[6] .

Treatable diseases

Through this UDP, we were able to identify potentially treatable conditions, for example, Allan-Herndon-Dudley syndrome, benign recurrent intrahepatic cholestasis (BRIC), coenzyme Q6 deficiency-related nephrotic syndrome, coenzyme Q10 deficiency, osteogenesis imperfecta type VII, steroid-resistant nephrotic syndrome, X-linked adrenoleukodystrophy, etc. We also identified novel treatment for GNAO1-related epilepsy.

Novel disease-causing gene discovery for neuromuscular diseases

We have identified the role of *AK9* in congenital myasthenic syndrome (CMS)[7]. In our works, we identified *AK9* as an important disease modifier and thus provided a new angle in the treating CMS[7]. We also identified *EBF3* as a new gene for Moebius syndrome. We proposed a genetic defect in *EBF3* would adversely affect the migration of facial branchiomotor neurons during early embryo development, and thus cause bilateral 6th and 7th cranial nerve palsies. Our works had been presented in the Diagnostic Challenge Session in the American Society of Human Genetics (ASHG) 2016 annual meeting on 20 October 2016 and also in a local public lecture, "Rare Diseases of the Newborn - Detection and Management" in Hong Kong on 12 March 2016 (available online - https://www.hkpl.gov.hk/mobile/en/extension-activities/event-detail/88251/rare-diseases-of-the-new-born-detection-and-management).

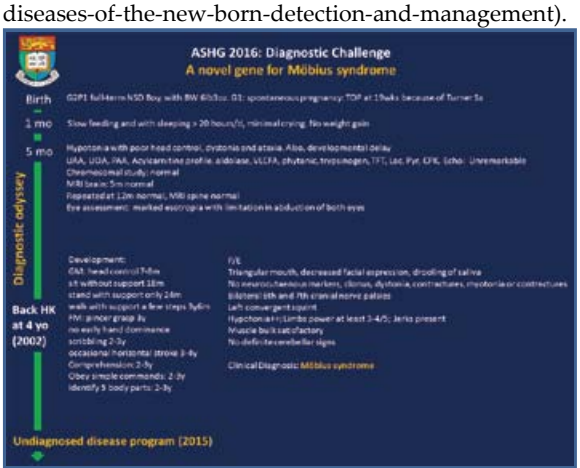


Fig. 1. Discovery of EBF3 as a new gene for Moebius syndrome.

Novel disease-causing gene discovery for autism spectrum disorder (ASD)

The team had also identified a new disease-causing gene for autism spectrum disorder (ASD). For example, *TOP2B* and *NEO1*[8,9]. This is the continuation of our work identifying MECP2 as the first disease-causing gene for non-syndromic ASD[10] (AUTISM, SUSCEPTIBILITY TO, X-LINKED 3; AUTSX3, OMIM # 300496).

Knowledge exchange

With the support from the S. K. Yee foundation, we were able to share our experience with other medical professionals and the public. These include seminars and public lectures (http://www.info.gov.hk/gia/general/201707/21/P2017072100308.htm) organised by the Government.

Discussions

A new diagnostic algorithm is proposed for all "rare" diseases. In the first tier, all newborns should receive expanded newborn screening to screen for treatable inborn errors of metabolism (IEM) in pre-symptomatic phase. With the support from the S.K. Yee Foundation, we had initiated the first territory-wide programme involving 3 regional hospitals and the University of Hong Kong.[11]

We recommended patients with acute metabolic decompensation (symptomatic) should all receive an urgent NMR-based urinalysis. This is a 15-minute test which allows quantitation of >100 urine metabolites in a single run. A rapid diagnosis will be very useful to the clinician to initiate appropriate treatment and guide further confirmatory tests.

Finally, all patients with an undiagnosed disease for more than 3 months should receive CWES/CWGS. In our experience, most patients can ultimately receive a correct molecular diagnosis through this approach (Fig. 2).

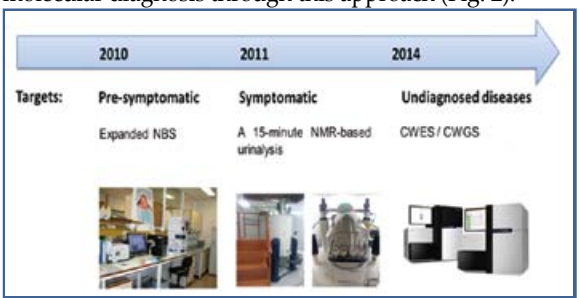


Fig. 2. Genetic services developed in 3 phases by the authors for the diagnosis of genetic diseases.

Conclusions

We had initiated the first UDP in Hong Kong. The disease spectrum is heterogeneous and we had successfully ended the diagnostic odyssey by providing a molecular diagnosis to the families. Importantly, some conditions are potentially treatable. The participation rate was encouraging. This reflected the improved public awareness of rare diseases. This also reflected the wishes of the patients and clinicians concerning the needs of undiagnosed diseases programme in future.

We recommend patients with undiagnosed diseases for more than 3 months should receive a CWES and CWGS. The interpretation of CWES and CWGS is challenging, requiring extensive knowledge and skills

in both laboratory medicine and clinical medicine. Inadequate experience in either side will easily lead to a false positive or a false negative result. Therefore, the analysis and interpretation of CWES and CWGS should be handled by pathologists and other specialists with adequate training in molecular genetics, for example, according to the recently implemented HOKLAS (The Hong Kong Laboratory Accreditation Scheme) Supplementary Criteria No. 30 (http://www.itc.gov.hk/en/quality/hkas/doc/SupplementaryCriteria/HOKLAS_SC-30.pdf).

Acknowledgement
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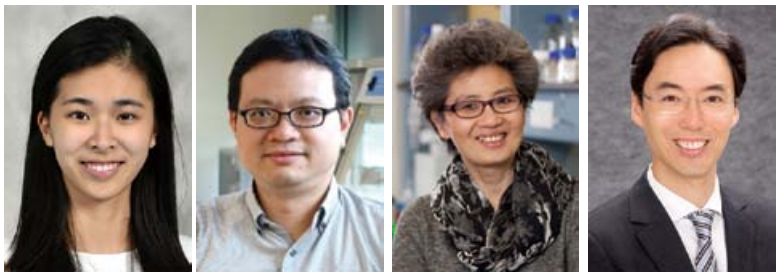
Genomic Medicine in Diabetes

Ms Rachel WC LAI[1]
Dr Cadmon KP LIM[1]
PhD, Registered MLT (Part I)
Prof Juliana CN CHAN[1,2]
MBChB, MD, FRCP (Edin), FRCP (Lond), FRCP (Glasg), FHKCP, FHKAM (Medicine)
Prof Ronald CW MA[1,2]
MBBChir (Cantab), FRCP (Edin), FRCP (Lond), FHKCP, FHKAM (Medicine)
[1]*Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong*
[2]*Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong*



Ms Rachel WC LAI Dr Cadmon KP LIM Prof Juliana CN CHAN Prof Ronald CW MA

Introduction

From the latest International Diabetes Foundation Diabetes Atlas, the Western Pacific region is estimated to have a regional prevalence of diabetes of 9.5% in 2017, which is predicted to increase to 10.3% in 2045[1]. Focusing on Hong Kong and the China Mainland, about 1 in 10 people have diabetes[1]. Meanwhile, Type 2 diabetes mellitus (T2DM) remains the most common form of diabetes in Hong Kong with its complications accounting for a major proportion of hospital admissions, blindness, renal failure, stroke and cardiovascular disease in the region[2,3].

The emergence of genotyping and sequencing technology, together with advances in genome-wide association studies (GWAS), have brought hope to deliver clues to the aetiology, treatment and prevention of T2DM, a disorder with significant heritability. But whilst there is a significant environmental component and significant gene-environment interaction in the pathogenesis of T2DM, in contrast, there is better understanding of the genetic basis of monogenic forms of diabetes, with corresponding clinical applications. With the continued surge in prevalence rates, coupled with the increasing plethora of different combinations of anti-diabetes therapies, there is an increasing emphasis on individualised treatment strategies in recent diabetes management guidelines, which often advocate personalised medicine[4]. This review article will discuss the current landscape of advancements in genomic medicine in relation to diabetes care, including updated genetic information on Maturity-onset diabetes in the Young (MODY) and Type 2 diabetes mellitus in Chinese and Asian populations.

Precision medicine refers to the tailoring of medical treatment to the individual characteristics of each patient. It relies on the ability to classify and stratify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment[5]. This definition by the National Research Council (US) Committee highlights the notion that medical science often evolves around the notion of taxonomy. For example, as far as 1,500 years ago, a group of Indian physicians had described different forms of diabetes, and the clinical distinction between insulin-dependent and non-insulin-dependent diabetes – in modern medical terms[6]. In the 1970s, scientists from England noted the strong association between the HLA genotype on chromosome 6 and insulin-dependent diabetes, but it was not until the discovery of autoantibodies to different islet antigens in the 1980s, which provided the tools to discriminate autoimmune Type 1 diabetes mellitus (T1DM) – and latent autoimmune diabetes in adults (LADA) in 1992, from other forms of diabetes clinically[7,8].

Table 1. Comparison among various types of diabetes and their genetic predispositions.
** with presence of at least 1 of 4 auto-antibodies to beta-cell antigens, islet cell antibodies, glutamic acid decarboxylase-65 antibody, insulinoma antigen-2 antibody, or insulin autoantibodies*

Overview on the development of precision medicine in diabetes

	Multifactorial Diabetes		Monogenic forms of diabetes	
Diabetes Subtypes	**Type 1 diabetes**	**Type 2 diabetes**	**GCK-MODY**	**HNF1-A MODY**
Age of onset	Children/ young adult	Typically after 40 years old	6 month-25 years	6 month-25 years
Mode of Inheritance	Non-Mendelian	Non-Mendelian	Autosomal dominant	Autosomal dominant
Genetic aetiology/ Causal Genes	Polygenic, > 40 known associated genomic regions (e.g. HLA region, INS, etc.)	Polygenic, >100 genomic regions (e.g. TCF7L2)	*GCK*	*HNF1A*
Clinical Feature	Islet autoimmunity*	Insulin resistance, progressive beta-cell dysfunction	Stable, raised fasting glucose.	Progressive beta-cell dysfunction. Glycosuria.
Preferred Treatment	Lifelong insulin	Metformin, sulfonylureas, glitazones, DPP4 inhibitors, SGLT2 inhibitors, GLP-1 agonists or insulin	Adjustment in diet, no drug treatment needed usually (though beware subjects can potentially carry additional common risks variants for T2DM)	Low dose of sulphonylureas

Nevertheless, the zero-to-one genetic breakthrough in diabetes classification relied on the taxonomy of Maturity Onset Diabetes of the Young (MODY, which will be discussed in the next section), with the discovery of genetic variants in glucokinase (*GCK*), hepatic nuclear factor 1 alpha (*HNF1A*), hepatic nuclear factor 4 alpha (*HNF4A*), and some rarer forms of MODY[9]. Another form of monogenic diabetes, neonatal diabetes mellitus, of which the first case in China dated back to 1986, has higher prevalence in the eastern and southern coasts[10]. Its genetic causes were identified by Professor Andrew Hattersley's group in Exeter, England with the realisation that the activating mutations in the gene encoding the Kir6.2 subunit of this channel

(*KCNJ11*) was a cause of neonatal diabetes[11]. Over the last two decades, clinical subtypes of this disease have been described by the 22 known genetic causes of neonatal diabetes with variants in 21 genes and methylation abnormalities at the 6q24 locus[12]. Such examples of improved understanding of pathogenesis has empowered more precise management – with 90% of diabetes cases caused by *KCNJ11* mutations switching to sulfonylurea therapy (which acts by closing of mutant KATP channels) experiencing improved glycated haemoglobin levels (from a mean of 8.1% pre-treatment to 6.4% 12 weeks post-treatment, P<0.001)[13]. As exemplified above, genomic advances in the field of monogenic diabetes has fulfilled the promise of precision medicine; in which exquisite definition of disease subtypes through genetic dissection of pathophysiology facilitates effective optimisation of disease management. Similar success has also been achieved in unraveling the genetic basis of MODY and in translating it to improve care[14].

Overview on MODY

Maturity onset diabetes of the young (MODY) is a type of monogenic and autosomal dominant form of inherited diabetes, presenting with early-onset (<35 years old) and non-insulin dependence[15,16]. To date, there are 14 sub-classifications of MODY according to the molecular defects, with mutations in *GCK* (MODY 2), *HNF4A* (MODY 1) and *HNF1A* (MODY 3) and hepatic nuclear factor 1 beta (*HNF1B*; MODY 4) being the most common genetic forms[17]. The prevalence of MODY in Chinese and Asian populations are not entirely clear, though an earlier study in Hong Kong suggested that around 14% of patients with young-onset diabetes and a positive family history may harbour mutations in the most common MODY genes[18]. Given that monogenic forms of diabetes may be more common than previously appreciated, there is increasing interest regarding the prevalence of MODY in early-onset diabetes in Chinese, and the potential of missed diagnosis in young patients[19].

Diagnosis of MODY and targeted treatment

With the identification of different genetic forms of the MODY subtypes, efforts to link the clinical presentations with the underlying aetiology have helped to guide treatment algorithms. For example, GCK-MODY is characterised by stable, elevated fasting glucose, and a low risk of long-term complications (Table 1)[20,21]. Initial clinical screening is hence critical in selecting patients for further molecular genetic testing of either the most likely gene or a panel of all genes[22]. However, it should also be noted that carriers of rare MODY mutations such as *GCK* can potentially also carry other type 2 diabetes risk variants.

Monogenic diabetes represents the archetypal example of precision medicine in diabetes. In monogenic diabetes, options of therapy are based on the results of genetic testing. For example, patients with *GCK*-MODY do not warrant pharmacological treatment usually, while low dose sulphonylurea is the recommended treatment to patients with *HNF1A*-MODY. Patients with MODY mutations are often reported to have been misdiagnosed with Type 1 diabetes earlier, as both forms of diabetes have early onset among young individuals. In the early 2000s, studies conducted in the UK identified MODY patients (who were often misdiagnosed with Type 1 diabetes) and had them transited from insulin to oral sulphonylurea therapy (with one proband having successfully been transferred off insulin to other medications after previously treated for 31-years with insulin treatment), together with encouraging improvement in glycaemic control[23]. This was followed by targeted therapies to hundreds of MODY 3 patients, and exemplified the potential application of stratified management utilizing genetic aetiology[24]. Advances in genomics can also potentially lead to discovery of new drugs and targets of pharmaceutical intervention, and this is an area of intense ongoing research efforts.

Implementation of screening and diagnosis of MODY in clinical setting

As illustrated above, precision medicine advocates targeted pharmaceutical interventions, with the prerequisite of a precise molecular diagnosis. Although early health economic studies confirm the cost effectiveness of genetic testing, it is currently unpractical to implement genetic testing for every potential patient with diabetes. Clinical screening is hence crucial to minimize false positive findings when patients have not been properly selected based on phenotype and identified with potential subgroups prior to genetic testing[25].

A MODY Probability Calculator was developed in 2012, with clinical prediction models for patients who may have MODY and are not insulin-treated. The calculator has been validated in Asian population, and is available at www.diabetesgenes.org/content/mody-probablilty-calculator and on "Diabetes Diagnostic" app for iOS and Android[19,26]. For patients who have been under insulin therapy and be potential cases of MODY, clinicians should apply the rule-out tests, whereby positive islet autoantibodies and/or C-peptide <200 pmol/l would be evidence against a diagnosis of MODY[20,27,28]. It is also worth noting that most of the clinical cases of familial diabetes in Chinese and Japanese populations do not harbour mutations in one of the 13 known MODY genes, and are classified by scientists as MODY X – highlighting the presence of MODY subgroups that remain to be defined[29,30]. A recent study in Hong Kong has highlighted that subjects with a family history of young-onset diabetes is at substantially higher risk of developing diabetes[31].

Applying genomic information in type 2 diabetes on prediction and risk assessment

While MODY is a monogenic form of diabetes, T2DM has a polygenic predisposition with clinical phenotype reflecting both genetic and environmental influences[32]. Since the first publication of genome-wide association studies (GWAS) in 2007, there are growing lists of loci reported to be associated with T2DM, with each risk allele associated with approximately

15 to 20% increase in risk[33]. All published associations are catalogued at the NHGRI-EBI (https://www.ebi.ac.uk/gwas/). Although scientists are striving to expand the benefits of technological advances in understanding of pathogenesis and pharmacogenetics to improve therapeutic management, current results have not been as rewarding as that demonstrated in monogenic diabetes. After all, known genetic variants for predisposition of T2DM are of comparatively small effect size. This implies modest discriminative accuracy of genetic profiling to perform individual-level prediction, as well as the extent of heterogeneity of common forms of diabetes[33,34]. One current approach of further investigation is to identify ethnic-specific risk loci and risk prediction for T2DM. This is particularly relevant in East Asian population, where there has been an explosion in diabetes prevalence, and where beta-cell dysfunction is a prominent feature in the pathophysiology of type 2 diabetes, and genetic findings from European populations may not be applicable[35,36,37]. Interestingly, the majority of loci associated with type 2 diabetes are believed to impact on beta-cell function[38].

The risk for diabetes can be substantially reduced in at-risk subjects through increase in physical activity and dietary changes, as supported by several landmark clinical trials[39]. It has therefore been hypothesized that individualized diabetes risk assessment based on genetic testing may motivate individuals to adopt a healthier lifestyle that can reduce their risk to develop diabetes[40]. The individualized genetic risk assessment can work by aggregating the genetic risk scores, adding up the genetic risk attributed to respective loci coupled with age, ethnic background and other phenotypic parameters. The ongoing discovery of additional loci for T2DM predisposition has improved the predictive ability. Recent research has highlighted that patients from different levels of genetic risk for T2DM can all benefit from intensive lifestyle intervention to reduce diabetes risk[39,41,42].

Genomic information and therapeutic outcome in type 2 diabetes

Advances in pharmacogenomics of T2DM are also emerging. There is inter-individual variation in the response to different oral hypoglycaemic agents (OHAs), and treatment failure is not uncommon. Only 53% of patients receiving OHAs achieve the therapeutic target of glycated haemoglobin of <7.0%[43,44]. For example, around one third of metformin users are poor responders, and 63% of them express gastrointestinal symptoms[45,46,47]. The underlying reasons for these observations remain poorly understood. Research studies have so far focused on genetic variations in the metformin transporters and their regulative transcription factors, as well as candidate genes in metformin pharmacodynamics. Regarding the therapeutic outcome of sulphonylureas, another commonly used oral glucose-lowering agent, the roles of genetic variants impacting on pharmacodynamics and pharmacokinetics have been widely reported, including genetic variants in the cytochrome P450 enzymes[44]. Translation of robust pharmacogenetic findings into genotype-guided treatment algorithms for metformin, sulphonylureas, meglitinides, glitazones and other medications represent one of the ongoing efforts to bring precision medicine in diabetes into the clinics. (See later section on pharmacogenetics)

Use of genomic information for diabetic complications

Diabetic complications can range from acute ones including diabetic ketoacidosis, hyperosmolar hyperglycaemic non-ketotic coma, and hypoglycaemia; to chronic complications such as macro- and microvascular disease, retinopathy, nephropathy, and neuropathy, which are mainly due to exposure of the vasculature to chronic hyperglycaemia[48]. A cross-sectional study conducted among primary care clinics has reported that glycaemic control among patients with diabetes in Hong Kong is comparable to other developed countries with a high prevalence of microvascular, thus calling for need for holistic management of all aspects of diabetes[49]. Analysis of secular trends in the rates of diabetes complications over the last 2 decades suggest recent reduction in incident rates of diabetic cardiovascular and renal complications[50]. Despite its relative infancy, our understanding in the genetic basis of diabetic complications has been improving with the advances in genotyping and sequencing technologies. Other ongoing areas of research include development of prediction models, delivering risk assessment based on genetic factors to subjects and providing genetic insights to therapeutic interventions.

A large number of earlier studies have highlighted the genetic susceptibility and hence heritability of diabetic complication, with the clustering of micro- and macrovascular complications and other disorders in families with diabetes[51]. While the heritability scores for diabetic retinopathy ranges from 18–27% in either T1DM or T2DM, the heritability of ischaemic heart disease in diabetes is approximately 50%[52]. A large number of candidate gene studies have been performed using genetic variants in genes implicated in the pathogenesis of diabetic nephropathy and coronary heart disease for T1DM and T2DM[53,54,55]. Recent hypothesis-free GWAS have identified some novel variants, though these discovery studies are currently still limited by rather modest samples sizes. Some examples of more consistently replicated variants associated with complications include those at *ELMO1* and *VEGF*, associating with nephropathy retinopathy, respectively[55,56,57]. Of note however, very few variants have been shown to be strongly associated with diabetic complications, or at levels of statistical significance required for GWAS.

In Hong Kong, an increasing trend of early-onset T2DM (i.e. onset before age 40) has put these patients at substantially higher risk of cardio-renal complications when compared with patients with onset after the age of 40 years, partly as a result of longer exposure to hyperglycaemia[51,58]. The increasing burden of young-onset diabetes may lead to increasing burden from diabetic complications in the city. The ability to identify subjects at increased risk of diabetic complications may facilitate more intensive management of these high-risk individuals.

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Utility of genetic information in management of type 2 diabetes

From pharmacogenetics to clinical applications

With advances in the development of treatment options for type 2 diabetes, there has been a marked increase in the choices of therapeutic agents, and increased prescription of incretin mimetics, dipeptidyl peptidase 4 inhibitors (gliptins), and sodium/glucose cotransporter 2 inhibitors (gliflozins)[4]. On the other hand, there has been a decreasing trend in the use of α-glucosidase inhibitors, sulphonylureas, meglitinides (glinides), and thiazolidinediones (glitazones), partly related to different treatment side effects, which may be heritable[59]. As discussed in the earlier sections, investigation of the adverse effects and efficacy of various types of antidiabetic drugs represent an active area of pharmacogenetic studies. Research in this area in relation to diabetes include identification of genetic variants that impact on treatment response, non-response, as well as variants associated with adverse drug reactions.

One of the earlier studies in this area identified carriers of the *TCF7L2* risk allele to have greater response to metformin than sulfonylureas[60]. More recent research has demonstrated how therapeutic interventions (α-2A adrenergic receptor antagonist yohimbine) can be guided by genetic testing of a risk variant (rs553668 at *ADRA2A*) in the related pathway[61]. Despite being early days, these examples foretell the potential role of genetics in future diabetes management, and whereby treatment decisions should be complemented by genetic information regarding individualised response.

Utility of genetic risk assessment in the management of type 2 diabetes

The benefit of utilising genetic information to improve diagnosis, risk assessment and treatment has been demonstrated through some examples of monogenic diabetes – which has been the main focus of genomic medicine in diabetes over recent years. With ongoing research, there is increasing interest to utilise genome-wide data including common genetic variants to create personal genomic profiles that would estimate an individual's risk of common forms of diabetes and their complications. The expansion of focus from monogenic forms of diabetes to a multifactorial, polygenic disorder is based on the assumption that knowledge of an increased estimated lifetime risk of a given disease, supported by genome-wide profiling, has the ability to motivate subjects to adjust their lifestyle and hence reduce their risk of onset or to begin early intervention[62]. Several early studies which explore the impact of genetic risk assessment to multifactorial diseases seem to show limited changes to behaviour in the short-term, though the impact of genetic testing on patient empowerment, mood, risk factor control and prognosis over the longer-term warrant further research[63-66]. Emerging results do provide useful experience towards how best to deliver the genetic counselling, evaluate patient response, and engage patients and health care providers in order to guide future development of precision medicine in diabetes.

Conclusions

Despite the fact that monogenic forms of diabetes comprise only approximately 2% of total cases in T2DM, the translation of genomic advances in diabetes has so far been limited mainly to the personalised management of monogenic and syndromic forms of diabetes[67]. In the past decade, there have been significant advances in our understanding of the genetic basis of common forms of diabetes, their complications, and treatment responses. Through ongoing efforts to translate these findings, it is believed that genomic information would become increasingly important for developing personalised approaches to the prevention, diagnosis, treatment and prognostication of people with diabetes.

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	* HKMA Council Meeting 2	3	4	* Joint Surgical Symposium – Asymmetrical Eyelids 5	6
7	8	* FMSHK Officers' Meeting 9	* Hong Kong Neurosurgical Society Monthly Academic Meeting –Diagnosis and management for blister aneurysm * HKMA-Central, Western & Southern Community Network DH-Centre for Health Protection - Antibiotic Stewardship Programme in Primary Care 10	* HKMA New Territories West Community Network – New Class of Injectable for Hypercholesterolaemia – What Patient will it be Benefit Most? * HKMA HKS&H CME Programme 2017-2018 –"Update in Medical Practice" 11	12	* Refresher Course for Health Care Providers 2017/2018 * 13th HKMA Sports Night 13
14	15	* HKMA Kowloon West Community Network - Update on Rheumatic Diseases - Common Important Presentation of Uncommon Diseases * HKMA Tai Po Community Network - Fatty Liver 16	17	* "A small leak will sink a great ship" & "Dr, I request MRI for my "Lung Mass"" * FMSHK Executive Committee Meeting 18	* HKMA Kowloon City Community Network - Antibiotic Stewardship Programme in Primary Care with ARNI 19	20
21	22	* HKMA Tai Po Community Network - Antibiotic Stewardship Programme in Primary Care 23	* HKMA Central, Western & Southern Community Network - Advancement of Immunotherapy Against Cancers 24	* HKMA Hong Kong East Community Network - Advancement of Immunotherapy for the Treatment of Lung Cancer * HKMA Kowloon East Community Network - SGLT2 is for Primary Care Doctors and Family Practitioners * FMSHK Foundation Meeting 25	26	27
28	29	30	31			

Date / Time	Function	Enquiry / Remarks
2 TUE 9:00 PM	**HKMA Council Meeting** Organiser:The Hong Kong Medical Association; Chairman: Dr. CHOI Kin; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
5 FRI 8:00AM - 9:00AM	**Joint Surgical Symposium – Asymmetrical Eyelids** Organizers: Department of Surgery, The University of Hong Kong & Hong Kong Sanatorium & Hospital ; Chairman: Dr. Vincent KWAN; Speakers: Dr. Gordon MA, Dr. Richie CHAN; Venue: Hong Kong Sanatorium & Hospital	Department of Surgery, Hong Kong Sanatorium & Hospital Tel: 2835 8698 Fax: 2892 7511 1 CME Point (Active)
9 TUE 8:00PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
10 WED 7:30AM	**Hong Kong Neurosurgical Society Monthly Academic Meeting –Diagnosis and management for blister aneurysm** Organiser: Hong Kong Neurosurgical Society; Chairman: Dr WONG Kai Sing, Alain; Speaker: Dr LI Ronald; Venue: Conference Room, 2/F, Block F, Queen Elizabeth Hospital	1.5 points College of Surgeons of Hong Kong Dr. LEE Wing Yan, Michael Tel: 2595 6456 Fax. No.: 2965 4061
1:00 PM	**HKMA-Central, Western & Southern Community Network** **DH-Centre for Health Protection - Antibiotic Stewardship Programme in Primary Care** Organiser:HKMA-Central, Western & Southern Community Network; DH-Centre for Health Protection; Chairman: Dr. TSANG Chun Au; Speaker: Dr. LAM Tin Keung, Edman; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	Ms. Candice TONG Tel: 2527 8285 1 CME Point
11 THU 1:00 PM	**HKMA New Territories West Community Network – New Class of Injectable for Hypercholesterolaemia – What Patient will it be Benefit Most?** Organiser:HKMA New Territories West Community Network; Chairman: Dr. TSUI Fung; Speaker: Dr. Adrian CHEONG; Venue: Pak Loh Chiu Chow Restaurant, Shop A316, Level 3, Yoho Mall II, 8 Long Yat Road, Yuen Long	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA HKS&H CME Programme 2017-2018 –"Update in Medical Practice"** Organiser:The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. CHAN Chun Yin, Johnny; Venue: Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	HKMA CME Dept. Tel: 2527 8285 1 CME Point
13 SAT 1:00 PM	**Refresher Course for Health Care Providers 2017/2018** Organiser:Hong Kong Medical Association; HK College of Family Physicians; HA-Our Lady of Maryknoll Hospital; Speaker: Dr. Wai Sing LEUNG; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin	Ms. Clara TSANG Tel: 2354 2440 2 CME Point
7:00 PM	**13th HKMA Sports Night** Organiser:The Hong Kong Medical Association; Chairman: Dr. CHAN Hau Ngai, Kingsley & Dr. IP Wing Yuk & Dr. YEUNG Hip Wo, Victor; Venue: Craigengower Cricket Club, 188 Wong Nai Chung Road, Happy Valley	Ms. Ellie FU Tel: 2527 8285
16 TUE 1:00 PM	**HKMA Kowloon West Community Network - Update on Rheumatic Diseases - Common Important Presentation of Uncommon Diseases** Organiser:HKMA Kowloon West Community Network; Chairman: Dr. TONG Kai Sing; Speaker: Dr. YU Ka Lung, Carrel; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chuen, Mei Foo	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:45 PM	**HKMA Tai Po Community Network - Fatty Liver** Organiser:HKMA Tai Po Community Network; Chairman: Dr. CHOW Chun Kwan, John; Speaker: Dr. CHEUNG Sai Wah; Venue: Chiuchow Garden Restaurant, Shop 001-003, 1/F, Uptown Plaza, No. 9 Nam Wan Road, Tai Po	Ms. Hannah LEE Tel: 6620 0185 1 CME Point
18 THU 18:30 – 20:00 PM	**"A small leak will sink a great ship" & "Dr, I request MRI for my "Lung Mass""** Organizer: Hong Kong Thoracic Society; Venue: Lecture Theatre, LG1, Ruttonjee Hospital; Speakers: Dr. TSENG Cee Zhung Steven, Dr. Chan Ming Chiu; Chairman: Dr. NG Lai Yun, Dr. Lee Sing Hang Derek	CME Accreditation (College): HKCFM, HKCP, CSHK Dr Grace Lam, Tel: 25956499 lamsm2@ha.org.hk
8:00 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
19 FRI 1:00 PM	**HKMA Kowloon City Community Network - Antibiotic Stewardship Programme in Primary Care with ARNI** Organiser:HKMA-Kowloon City Community Network DH-Centre for Health Protection; Chairman: Dr. CHIN Chu Wah; Speaker: Dr. LAM Tin Keung, Edman; Venue: President's Room, Spotlight Recreation Club, 4/F, Screen World, Whampoa Garden, Hung Hom	Ms. Candice TONG Tel: 2527 8285 1 CME Point
23 TUE 1:45 PM	**HKMA Tai Po Community Network - Antibiotic Stewardship Programme in Primary Care** Organiser:HKMA Tai Po Community Network; DH-Centre for Health Protection; Chairman: Dr. CHOW Chun Kwan, John; Speaker: Dr. LAM Tin Keung, Edman; Venue: Chiu Chow Garden Restaurant, Shop 001-003, 1/F, Uptown Plaza, No. 9 Nam Wan Road, Tai Po	Ms. Candice TONG Tel: 2527 8285 1 CME Point
24 WED 1:45 PM	**HKMA Central, Western & Southern Community Network - Advancement of Immunotherapy Against Cancers** Organiser:HKMA Central, Western & Southern Community Network; Chairman: Dr. LAU, Kevin Chung Hang; Speaker: Dr. WONG Hiu Yan, Hilda; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	Ms. Candice TONG Tel: 2527 8285 1 CME Point
25 THU 1:00 PM	**HKMA Hong Kong East Community Network - Advancement of Immunotherapy for the Treatment of Lung Cancer** Organiser:HKMA Hong Kong East Community Network; Chairman: Dr. KONG Wing Ming, Henry; Speaker: Dr. CHAN Siu Hong, Oscar; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Kowloon East Community Network - SGLT2 is for Primary Care Doctors and Family Practitioners** Organiser:HKMA Kowloon East Community Network; Chairman: Dr. SHIU Ka Lok, Ivan; Speaker: Dr. HO Chung Ping, MH, JP; Venue: V Cuisine, 6/F, Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak St, Tseung Kwan O	Ms. Candice TONG Tel: 2527 8285 1 CME Point
8:00 PM	**FMSHK Foundation Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Nancy CHAN Tel: 2527 8898

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Fare: **HKD14,795up**

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London (Southampton), England | Guernsey (St. Peter Port), England | Cork, Ireland | Dublin, Ireland [Overnight] | Belfast, Northern Ireland | Glasgow (Greenock), Scotland | Invergordon, Scotland | Edinburgh (South Queensferry), Scotland | Paris/Normandy (Le Havre), France | **London (Southampton), England**

2018 departure date: 1, 13, 25* May | 6^, 18*, 30 Jun | 12^, 24^ Jul | 5^,17,29* Aug

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^will not stay overnight at Dublin, will call to Liverpool, port order may vary

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Answers to Dermatological Quiz

Answer:

1. Livedoid vasculopathy (LV) (also known as occlusive vasculopathy)
   LV is a hyalinising vascular disease with thrombosis in the lumen, in contrast to inflammatory diseases like leukocytoclastic vasculitis. It is primarily an occlusive thrombogenic disease due to hypercoagulopathy. Skin biopsy should be done preferably at the early stage of skin lesion. It should be deep to the subcutaneous tissue and include both the bed and edge of the lesion. Clinically LV presents with painful purpuric macules and papules over the legs, which eventually ulcerate and form scars, resulting as atrophie blanche. In the early phase, sometimes it may manifest as livedo reticularis. Strangely LV often worsens in summer instead of winter.

2. Other differential diagnoses include ulcers due to polyarteritis nodosa, stasis eczema, arterial insufficiency and collagen vascular diseases. Livedoid vasculopathy is a distinct condition. Usually it is not the result of other diseases as originally thought. However, links with antiphospholipid syndrome and systemic lupus erythematosus had been reported.

3. Special investigations (if available) for hypercoagulopathy in occlusive vasculopathy include protein C, protein S, beta-2-glycoprotein, lupus anticoagulant, anti-cardiolipin, cryoglobulin, homocysteine, antithrombin III, factor V leiden and prothrombin gene mutation study.

4. Treatment of LV is mainly antithrombotic (drugs such as aspirin, dipyridamole, pentoxyfylline, etc.) rather than anti-inflammatory (drugs like systemic steroid or immunosuppressive). Nevertheless, sometimes inflammatory and thrombotic features can occur together. In this situation, combination of both can be given.

Dr Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology & Venereology

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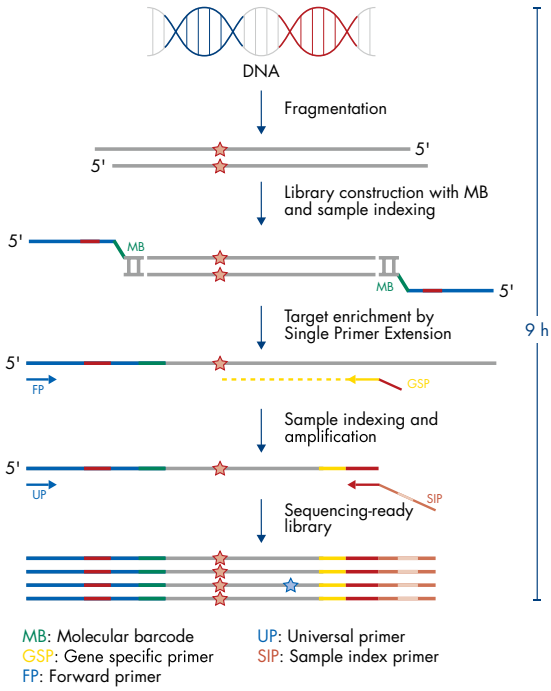

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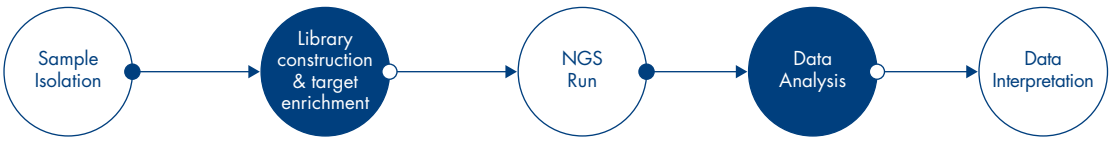

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