HONG KONG ACADEMY OF MEDICINE
香 港 醫 學 專 科 學 院

BEST PRACTICE GUIDELINES ON GENETIC AND GENOMIC MEDICINE

Hong Kong Academy of Medicine
Professionalism and Ethics Committee
Task Force on Genetics and Genomics

Contents

Please cite as: Task Force on Genetics and Genomics, Professionalism and Ethics Committee, Hong Kong Academy of Medicine. Best Practice Guidelines on Genetic and Genomic Medicine. HKAM Press: Hong Kong, 2021.

Published by Hong Kong Academy of Medicine Press
10/F, HKAM Jockey Club Building
99 Wong Chuk Hang Road, Aberdeen, Hong Kong
https://hkampress.org/

Foreword

1

To further promote professionalism and ethical practice among Fellows and specialist trainees, the Hong Kong Academy of Medicine established the Professionalism and Ethics Committee in March 2019. The Committee is tasked to assist the Academy Council by providing advice on matters related to professionalism and ethical issues pertaining to the practice of specialty medicine and dentistry, public policy, and other Academy matters.

The Committee has established different task forces to cover specific areas in which relevant best practice guidelines will be developed, where appropriate, from the perspectives of professionalism and ethical clinical practice for medical and dental practitioners.

In May 2020, the Government of the Hong Kong Special Administrative Region published a report on "Strategic Development of Genomic Medicine in Hong Kong".[1] The Academy acknowledged the report's various recommendations and initiatives to support the development of genetic and genomic medicine with a coordinated and systematic approach. The Academy is committed to its statutory roles in specialist training and accreditation, including specialty development and training in genetic and genomic medicine. The Academy has been working with relevant constituent Colleges to provide and strengthen specialty training in the related areas and to develop respective subspecialties. The development of these Best Practice Guidelines on Genetic and Genomic Medicine provides timely recognition of the momentous development in this area of clinical practice and the Academy's responsibilities in providing relevant guidance to medical and dental practitioners.

In response to rapid advancements in genomic medicine and the wider application of relevant technologies in clinical diagnosis, therapeutics, and decision making, the Academy is looking forward to working with the Government and other professional bodies to enhance public education and awareness in this area.

The present document will be subject to regular review and update. Your input will be most valued and welcome.

Professor Gilberto Leung
Co-Chair
Professionalism and Ethics Committee
Hong Kong Academy of Medicine

Dr. James Chiu
Co-Chair
Professionalism and Ethics Committee
Hong Kong Academy of Medicine

2 Executive Summary

2.1 Background

This document is produced by the Task Force on Genetics and Genomics (G&G) established under the Professionalism and Ethics Committee of the Hong Kong Academy of Medicine with a view to providing a clear ethical framework for the sound adoption and application of genetic technology and the many benefits it brings.

2.2 General principles of best practice in genetic and genomic medicine

Valid written informed consent should be obtained when applicable from the patient before human G&G testing. Consent is considered valid if the person giving consent is mentally competent; sufficient and appropriate information is provided; and consent is given voluntarily. Minors and persons with psychiatric or neurological disorders are not necessarily incapable of giving consent and should be counselled by a qualified medical professional.

Unlike microbiological tests, G&G tests related to the diagnosis and management of solid or haematological malignancies are often performed without the need for additional specific consent. However, in some cases, the possibility of germline mutations may be revealed and informed consent is indicated.

G&G testing should be performed in accredited laboratories. In general, all results of G&G testing should be kept confidential and safeguarded against unauthorised or accidental access. Nevertheless, G&G information may be disclosed if the patient has provided explicit consent to disclose; disclosure is required by law or permitted under a statutory process; or disclosure is in the public interest.

2.3 Genetics and genomics in specific situations

Genetic testing to establish diagnosis

For inherited disorders, G&G testing should be limited to individuals with signs or symptoms of the index condition who have given consent. Care should be taken to narrow the scope of G&G testing, to improve cost-effectiveness and minimise incidental findings. The details of the genetic test should be made clear to the patient, including the scope and limitations of the proposed test, the possibility of uncertain results (such as variants of uncertain significance), the possibility of incidental findings, and how the interpretation of genomic results may change at a later date. Pre-test and post-test counselling by a qualified health professional with appropriate training is advisable.

Pre-symptomatic testing or predictive testing

For persons who have a family history of a heritable condition but do not currently show signs and symptoms of the conditions, G&G testing is indicated if knowledge of the test result is likely to benefit the patient medically. Pre-test counselling with a medical professional qualified in G&G is highly recommended. Potential risks of discrimination, stigmatisation, loss of privacy, and negative impact on family dynamics should be made clear to the patient before such testing. A genetic diagnosis for the patient may suggest that other family members might also have inherited the condition or trait, and this issue should be discussed with the patient.

Genetic carrier screening

Conventionally, genetic screening recommendations for heritable health conditions have followed an ethnic-based approach. This is being replaced by expanded carrier screening, a more universal approach that uses high-throughput next-generation sequencing. Pre-test counselling on expanded carrier screening to explain to the patient the different screening panels available, the timing of the test, confidentiality issues, and benefits and limitations of the test, as well as post-test counselling is recommended. Patients should be made aware that a screen negative result does not eliminate the risk of having an affected offspring.

Prenatal testing

Genetics and genomics have already become essential components of prenatal diagnosis. These "new algorithms" are based on advances in prenatal molecular diagnostics, including noninvasive prenatal testing, quantitative fluorescent-polymerase chain reaction, chromosomal microarray testing, whole-exome sequencing, and whole-genome sequencing. The purpose of prenatal testing is to maximise the amount of prenatal information available for pregnant women and their families to make choices for their next generations. However, a new spectrum of ethical issues and concerns (such as variants of uncertain significance or incidental findings) has emerged.

Pre-implantation testing

Pre-implantation genetics testing is a technique that combines *in vitro* fertilisation and genetic testing of embryos before transfer. This provides a means to avoid transmission of a genetic abnormality or disease to the offspring, including aneuploidies, monogenic defects, and chromosomal structural rearrangements. Service providers of pre-implantation genetics testing need to be familiarised with the Human Reproductive Technology Ordinance and the Code of Practice set by the Council on Human Reproductive Technology which provides guidance on the ethical principles, indications and the essential points in patient counselling.

Consent for genomic testing for children

There are two situations where G&G testing in children requires special consideration: where the child has the mental capacity to make a decision themselves, and where testing is for an adult-onset disease. Children should be involved in decision making if they have the mental capacity to do so. The competency of the child should be assessed on a case-by-case basis; there is no legally defined age cut-off. If there is a difference of opinion in consenting to G&G testing between a child and their parent or guardian, the clinician should review the situation for the definite necessity of such a test. The final decision for the test should be based on the principle of the best interest of the child. The consent process should be clearly documented.

2.4 Genome sequencing and population-based or large-scale disease screening

Best practices for genome sequencing

Proper counselling and consent of the patient are necessary before genomic sequencing. Family members affected by the same medical condition may also be invited for counselling and sequencing.

The counselling should include a review of the genetic diseases that may be responsible for the patient's condition, as well as the benefits and risks of a molecular diagnosis, medically actionable secondary findings, and the possibility of false-positive or false-negative diagnoses. The patient should understand that they are expected to inform family members who may be affected by the same conditions.

Informed consent for genome sequencing should include the patient's wishes to be (or not to be) informed of any secondary findings and also if future re-analysis reveals additional findings of clinical significance.

Requesting and reporting of clinical genome sequencing

Requests for genome sequencing should include relevant clinical and family history information, as well as DNA samples from informative family members, where available. In some cases, the genomics laboratory may request additional phenotype data (e.g., biochemical tests or imaging data) that may improve variant interpretation, so good communication should be maintained.

The clinical genome sequencing report should include a list of detected variants that are potential candidates for explaining the patient's clinical condition. Medically actionable secondary findings should only be reported if they are among the classes which the patient wishes to be informed about. Results indicating unexpected genetic relationships (such as non-paternity) should be excluded from the report unless there are exceptional clinical implications.

Counselling and further consultation after genomic sequencing

Counselling should be provided to the patient after genome sequencing to review the report of findings, including the list of genomic variants which may be responsible for the patient's medical condition, as well as medically actionable secondary findings. The potential implications of these findings, for the patient and for their family members, should be discussed. This should be followed by the formulation of an action plan, which may involve referral to appropriate qualified medical professionals for the diagnoses suggested by the findings.

Disease screening by population-based or large-scale genome sequencing

Individuals for whom screening is potentially beneficial should be counselled so that they understand the target medical conditions of the screening programme, the possible outcomes of the screening test and their implications, as well as the potential risks and benefits of the screening. Written informed consent should include the points covered by the counselling. The patient should be given appropriate advice on the results and any available resources and services.

2.5 Pharmacogenomics

The doctor should only consider pharmacogenomics testing when it is required in the drug label as approved by a regulatory authority, or when strong recommendations are given by regulatory authorities and the clinical benefits clearly outweigh the risks. For example, pharmacogenomics testing may be necessary for investigation of patients with drug reaction as well as their family members.

Where drug dosing adjustment is recommended, or where a particular drug may be contraindicated in patients with certain pharmacogenomics findings, the doctor should consider the potential benefits of pharmacogenomics testing together with the risks, limitations, and cost implications.

Clinical pharmacogenomics testing should be done in an accredited medical laboratory. The attending doctor should provide necessary information to the laboratory, including the drugs under consideration and clinical scenario, and sometimes the ethnic origin of the patient, which may affect the choice of risk alleles tested. Ethnicity information can be useful in test panels, especially in well-genotyped populations. However, the adoption of ethnicity as the foundation in determining the need for pharmacogenomics testing could be risky, particularly in populations which have not been comprehensively genotyped.

To facilitate the decision to perform clinical pharmacogenomics testing, an online database of information and guidelines is available from the Pharmacogenomics Knowledge Base (https://www.pharmgkb.org/).

For pharmacogenomics testing results provided by a patient, the attending doctor should consider whether the laboratory is appropriately accredited; whether the signatories are qualified medical professionals with experience in G&G; whether the methods employed, alleles tested, and limitations have been stated; and whether the patient has been unambiguously identified in the pharmacogenomics report.

2.6 Direct-to-Consumer Genetic Testing

For patients considering taking a direct-to-consumer genetic test, the doctor should explain the possible shortcomings of such tests, including the potentially lower clinical and analytical validity. The doctor should recommend pre-test and post-test genetic counselling by qualified medical professionals.

If the doctor chooses to recommend a direct-to-consumer genetic test, the proposed test should be explained to the patient by qualified medical professionals, including the potential results, the possibility of incidental findings, the scientific evidence, and the privacy implications of such tests. Pre-test and post-test genetic counselling should be provided and informed consent obtained.

Doctors are not advised to recommending direct-to-consumer genetic testing unless they have appropriate training and qualification in G&G, especially for children, pre-pregnancy testing, and pre-symptomatic testing of certain disease and conditions.

For direct-to-consumer genetic testing presented by patients, the doctor should provide or recommend genetic counselling by qualified medical professionals. For positive test results, the patient should be advised to adopt appropriate lifestyle modifications and, if clinically indicated, consult appropriate qualified medical professionals for proper evaluation. In contrast, for negative test results, the patient should be advised that although they are unlikely to have the disease, the possibility that they may develop disease in

the future cannot be excluded. The doctor should explain the possibility of genetic discrimination and the implication of genetic test results becoming part of the patient's medical record which may have bearing on future insurance coverage and employment.

In case of doubt, referral to qualified medical professionals with experience in G&G is appropriate.

2.7 Genomic Research and Data Banking

The general principles of good practice in clinical research also apply to genomics research.

A biobank should have the approval of the relevant research ethics committee(s). Standard and effective procedures should be established for the secure and ethical collection, processing, storage, handling, transfer, sharing, and destruction of samples and data.

Informed consent should be sufficiently broad to allow samples or data to be used in future studies, to maximise the potential benefits from a biobank, and to avoid the need for patients to re-consent. Because genomic research often involves international collaboration, it is advisable to include anonymised data sharing in the consent.

The usage of samples and data from older studies that obtained more restrictive consent should ideally be consistent with the specifications of the original consent. However, where there are compelling reasons for deviating from the original consent, and re-consenting is not feasible, an application for exemption can be considered by the relevant ethics committee or appropriate authority.

2.8 Conclusion

G&G testing is imbued with challenging ethical and legal concerns. Its adoption and application must therefore be grounded on sound ethical principles and legal doctrines, to maximise the many benefits it brings. This document aims to provide a general framework to guide and facilitate good practice in G&G medicine. As medical technology evolves, novel ethico-legal issues will likely follow, necessitating a continued and concerted effort in examining and re-defining our standard of practice.

About this Document

3

The information contained within this document is for guidance only and not intended to be prescriptive. It is developed from the perspectives of professionalism and ethics, on the basis of which medical and dental practitioners should exercise their clinical judgement, with regard to all clinical and other circumstances.

This document is compiled by the Task Force on Genetics and Genomics established under the Professionalism and Ethics Committee of the Hong Kong Academy of Medicine, with the following membership:

Convener
Prof. Gilberto Ka-kit Leung (Co-Chairman, Professionalism and Ethics Committee, Hong Kong Academy of Medicine)

Members
Prof. Annie Nga-yin Cheung (The Hong Kong College of Pathologists)
Dr. Calvin Yeow-kuan Chong (The Hong Kong College of Pathologists)
Dr. Wing-cheong Leung (The Hong Kong College of Obstetricians and Gynaecologists)
Prof. Chi-kong Li (Hong Kong College of Paediatricians)
Prof. Pak-chung Sham (The Hong Kong College of Psychiatrists)
Dr. Maureen Mo-lin Wong (Hong Kong College of Physicians)

Contributors
Dr. Kelvin Chan (Prenatal Diagnostic Laboratory, Tsan Yuk Hospital)
Dr. Heidi Cheng (The Hong Kong College of Obstetricians and Gynaecologists)
Dr. Anita Kan (The Hong Kong College of Obstetricians and Gynaecologists)
Dr. Raymond Li (The Hong Kong College of Obstetricians and Gynaecologists)
Prof. Ernest Ng (The Hong Kong College of Obstetricians and Gynaecologists)
Dr. Edmond Ma (The Hong Kong College of Pathologists)
Prof. Daniel Chan (Hong Kong College of Physicians)
Dr. Larry Baum (University of Hong Kong)
Dr. Clara Tang (University of Hong Kong)

Advisors
Dr. Bernard Lo (University of California San Francisco)
Mr. Woody Chang (Honorary Legal Advisor, Hong Kong Academy of Medicine)

4 Definitions

Definitions or interpretations of terms used in this document are given below:

DNA sequencing

DNA sequencing is a laboratory technique used in molecular biology to determine the order of bases (i.e., A, C, G, and T) in DNA.

Diagnostic genetic testing

According to the United States National Institutes of Health, diagnostic genetic testing is used to identify or rule out a specific genetic or chromosomal condition. In many cases, genetic testing is used to confirm a diagnosis when a particular condition is suspected based on physical signs and symptoms.

Direct-to-consumer genetic tests

Direct-to-consumer genetic tests are genetic tests directly marketed to consumers without involvement of healthcare providers.

Genetics

Genetics is the study of genes and how they are inherited.

Genetic counselling

Genetic counselling is the process of helping people understand and adapt to the genetic, medical, psychological, and familial implications of genetic contributions to disease.

Genome

Genome is an individual's complete genetic material, including the genes that provide the instructions for producing proteins (2% of the genome) and the non-coding sequences (98% of the genome).

Genomics

Genomics is the study of the genomes of individuals and organisms that examines both the coding and non-coding regions. This term is also used when talking about related laboratory and bioinformatics techniques. The study of genomics in humans focuses on areas of the genome associated with health and disease.

Genomic medicine

Genomic medicine is the use of human genomic information and technologies to determine disease risk and predisposition, diagnosis, and prognosis (i.e., a forecast of the probable course and outcome of a disease), and the selection and prioritisation of therapeutic options.

Pharmacogenomics

Pharmacogenomics is the use of genetic and genomic information to tailor pharmaceutical treatment to an individual.

Whole-exome sequencing

Whole-exome sequencing is a type of DNA sequencing targeting only a small part (around 2%) of the human genome, that is, the exome that directly codes for proteins. It aims to sequence all protein-coding regions of the genome.

Whole-genome sequencing

Whole-genome sequencing is a type of DNA sequencing targeting the whole genome, that is, every DNA base in the genome of an individual.

Existing Regulations 5

Relevant sections of existing Ordinances in Hong Kong (or relevant guidelines issued by relevant professional bodies) should be referred to where applicable, including (but not limited to) the following:

- Pharmacy and Poisons Ordinance (Cap. 138)
- Termination of Pregnancy Regulations (Cap. 212A)
- Supplementary Medical Professions Ordinance (Cap. 359)
- Consumer Goods Safety Ordinance (Cap. 456)
- Personal Data (Privacy) Ordinance (PD(P)O) (Cap. 486)
- Human Reproductive Technology Ordinance (Cap. 561)
- The four discrimination law ordinances implemented by the Equal Opportunities Commission:
  - Sex Discrimination Ordinance (Cap. 480)
  - Disability Discrimination Ordinance (Cap. 487)
  - Family Status Discrimination Ordinance (Cap. 527)
  - Race Discrimination Ordinance (Cap. 602).

6 Ethical Principles

Accelerated research in human G&G has drastically altered our understanding of health and diseases, and practices from diagnosis, treatment, prevention to strategic planning in health service provision. The specific nature of genetic information raises unique ethical concerns beyond those of the traditional realm and structure of clinical medicine. For instance, genetic information may affect not only the examinee but also their entire family; there may be medical, psychological, social, and economic implications; present choices and future scientific discoveries may impact generations in unpredictable ways. A clear ethical framework is essential for the sound adoption and application of genetic technology and the many benefits it brings.

Ethical judgements and practices in G&G medicine necessitate a considered appreciation of and respect towards the relevant interests of all parties concerned. The four principles of biomedical ethics proposed by Beauchamp and Childress[2] offer some helpful guidance:

Autonomy: underscoring an individual's right to self-determination whereby a person should be afforded proper education, consultation and respect before making an informed decision regarding genetic testing as well as the subsequent handling of genetic information.

Beneficence: ensuring that policies and practices are for the good of those undergoing genetic testing which goes beyond just medical benefits.

Non-maleficence: the requirement to do no harm, which, in the context of G&G medicine, may include present and future harm for family members of the patient.

Justice: fair and equitable access to treatment which means a scientifically established and affordable genetic test should ideally be made available to all.

In addition to these points is the principle set out in the 1997 Universal Declaration on the Human Genome and Human Rights[3]:

> *Everyone has a right to respect for their dignity and for their rights regardless of their genetic characteristics and that dignity makes it imperative not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity*

It is important that these principles should be upheld because genetic information could lead to stigmatisation or discrimination for a group or an individual.

It is well recognised that these principles could come into conflict with each other, not least in the practice of G&G medicine. For example, the exercise of the patient's right to privacy in refusing consent to the disclosure of genetic information may conflict with a doctor's duty to "do good" to others such as close relatives. Genomic research and data banking carried out in the public interest may potentially infringe upon individual autonomy. Parental "authorities" in performing genetic testing on children may similarly create tension with the latter's rights and welfare.

Presently, the absence of clear professional and legal guidance on some of these aspects poses particular challenges to healthcare practitioners when applying genetic technology. The “correct” decision in many instances is often context- and fact-specific, entailing a patient-centred approach in counselling, skilful communication, professional knowledge, an acute awareness of professional accountability, and, to a certain extent, value judgement. And it is with these onerous obligations and challenges in mind that the following sections are set out with a view to providing a working knowledge of G&G medicine, and some practical tips and reminders applicable to medical and dental practitioners.

7 General Principles of Best Practice in Genetic and Genomic Medicine

7.1 Requesting genetic tests

Genetic testing should only be offered to individuals who themselves or whose family members, now and in future, would likely derive clinical utilities and benefits from the findings. This may include disease diagnosis, assessment of individual disease risk, prediction of response to specific therapy, and disease prevention through pre-marital, pre-pregnancy, or pre-implantation (*in vitro* fertilisation) testing for carrier genes. The reliability and limitations of such tests, and the availability (or lack) of medical intervention in case of a positive finding should be discussed with the patient in an open and non-directive manner. Where no sickness or disability is involved, genetic testing should not be performed for merely promoting non-health related attributes or for the purpose of producing children with predetermined characteristics (e.g., sex selection unless a serious sex-based illness is in question).

Potential patients should be properly informed to enable them to decide whether they wish to undergo genetic testing and to help them manage the results of the test, particularly where this information pertains to their future health or that of their children. Healthcare professionals should be mindful of their competency and limitations in imparting such information and in interpreting test results and conducting post-test counselling; referral to qualified health professionals with appropriate training is needed where concern arises. Clinical G&G testing should be done in accredited medical laboratories under the direction of pathologists qualified in G&G.

At the core of good practice in G&G medicine is the issue of consent.

7.2 Consent

7.2.1 Why consent?

Obtaining valid patient consent before any diagnostic and interventional procedures, including G&G testing, is fundamental to the principle of autonomy and essential for the protection of patients' rights to self-determination. It is an obligation enshrined in law and professional code of conduct.[4] Valid consent must fulfil the following criteria:

- The person giving consent must be mentally competent.
- Sufficient and appropriate information must be provided.
- Consent must be given voluntarily.

Genetic and genomic testing is more than a routine blood test. Given the complex and far-ranging implications of a finding in G&G medicine, patient consent should be explicit (i.e., not implied) and given in writing (i.e., not merely verbally). Clear documentation is crucial.

7.2.2 Who can give consent?

Mental competence in medical consent is context- and task-specific. Whereas adults are presumed to be mentally competent until proven otherwise, it is the duty of healthcare professionals to ascertain and ensure that the patient understands the nature, purpose, and implications of the proposed test and is able to make and communicate the relevant

decision. Minors and persons with psychiatric or neurological disorders are not necessarily incapable of giving consent and should be counselled by qualified health professionals with appropriate training (see Section 8.4).

7.2.3 What information to provide?

Relevant and sufficient information should be provided to enable the patient to make an informed decision. A patient-centred approach should be adopted. Information should be explained using clear and appropriate language in a way that is understandable to the particular patient in question according to their background. Alternative options (e.g., somatic testing of the patient's tumour versus germline testing) should be discussed, and the patient should be allowed time for decision-making and the possibility to withdraw consent.[5]

The amount of information needs to be disclosed may vary, depending on the nature and the purpose of the proposed test, and is determined by what the particular patient may reasonably find significant rather than what professional opinion might suggest.[6]

The following case serves to illustrate the key principles:

Case study

A 45-year-old woman recalls a family history of breast cancer. The affected family members are not contactable and there is no information on their diseases. The patient has no breast lesion but would like to undergo testing for BRCA *gene mutations. Her healthy adult daughter would also like genetic screening of 'all her genes' so that she 'will know what to do'.*

What do they need to understand and consider?

The finding of a particular genetic signature such as *BRCA* mutation can have profound implications for not only the patient but also for their family members. The following should be discussed during the consent process:

- The scope and limitations of the test (i.e., what will and will not be tested for).
- The implications of a positive result for the patient and the prevention, screening, or treatment possibilities.
- The implication of a negative finding and its meaning in terms of disease risk.
- The same sets of implications for the patient's family members.

Genomic studies may generate additional and unexpected secondary findings, which may carry health-related and social implications for the patient and their family members. The key elements for discussion should include the following:

- Findings from genomic studies may be unclear and uncertain. Some variants may have unknown or uncertain clinical significance; others may be associated with diseases but by themselves would not be usefully predictive or diagnostic.

- The implications of a secondary finding in terms of future prevention, screening and treatment possibilities.
- Findings from genomic studies may reveal unexpected information such as paternity and ethnic origin or have bearing on health insurance, employment, and other social aspects of life.
- The patient would have to decide whether or not to be told about any unexpected findings, and whether or not to disclose relevant information to other family members.
- If *BRCA* mutation is found that has been documented to be associated with a high risk of breast, ovarian cancer with early onset, the patient should be strongly advised to allow first-degree relatives to be informed of their risk.
- In appropriate cases, clinicians may inform patients that, under specific circumstances, they will need to disclose relevant genetic information to her family members.

7.2.4 Follow-up evaluation and counselling

The interpretation of genomic findings may change over time with advancement in research. The significance of a particular genetic signature may be updated years after the initial testing and require re-evaluation and further counselling. What is considered "normal" or "abnormal" now might not be so later on. It is important for patients to be made aware of this dynamic nature of G&G testing results. Healthcare professionals should make reasonable efforts to provide follow-up counselling within the scope of their practices or take into account of expectations of the patients in this connection. There exists variation in recommendations on re-analysis and re-contact among different professional bodies in North America and Europe.[7,8] Although it is important to inform patients that they may be contacted in the future if the interpretation of their genetic findings changes, it is also important not to create an expectation that this will happen automatically if reliable systems are not in place to support this.

Case study

In the context of the case illustrated previously (Section 7.2.3), what is the appropriate action?

To refer the patient to qualified medical professionals for advice and follow-up counselling on the interpretation of genomic findings.

7.3 Confidentiality and disclosure

7.3.1 Duty of confidentiality

It is an ethical duty for healthcare professionals to respect and protect patient privacy. The importance of maintaining confidentiality in G&G medicine is underscored by the sensitive nature of test results, some of which may have a significant impact on the patient's life beyond health-related concerns. In practical terms, all results of G&G testing should be kept confidential and safeguarded against unauthorised or accidental access.[9]

However, the health professional's duty of confidentiality is not absolute, and G&G information

may be disclosed under the following circumstances:

- The patient has provided explicit consent to disclose.
- The disclosure is required by law or is permitted or approved under a statutory process.
- When disclosure can be justified in the public interest such as where disclosure is necessary to prevent serious harm to the patient or other persons.[10]

The principles behind consenting to disclosure are as those behind consenting to testing. The consent should specify the kind of information to be disclosed, to whom it will be disclosed, and the purpose of disclosure. The subsequent handling of disclosed information by other parties may involve complex legal issues; if in doubt, it is advisable to seek legal advice before disclosure.[11]

7.3.2 Disclosing information to relatives

Family members may benefit from knowing a particular test result (e.g., a positive finding of a hereditary condition) by pursuing the appropriate screening and prevention measures. Healthcare professionals should take active steps to seek the patient's consent so that such information can be disclosed to genetically relevant parties and appropriate counselling can be arranged for those parties. However, there may be circumstances where consent is not forthcoming.

Case study

A 40-year-old man has colonic cancer. Genetic studies reveal familial adenomatous polyposis. You raise the issues that some of his relatives may be at risk of developing colonic cancer and that genetic screening and routine colonoscopy can be helpful. He, however, refuses to let you discuss his diagnosis with any of his family members because he "just does not want to worry them".

What should be the appropriate response?

A failure to alert the family members could expose them to otherwise potentially avoidable health risks; in contrast, disclosure without consent contravenes the professional duty of confidentiality. It touches upon the controversial issues of whether a person's genomic information is in fact "shared" with certain family members, and whether the latter have the right to know. It is for these reasons that the issue of disclosure is best discussed before testing; post-testing counselling where the patient has refused disclosure should be handled with sensitivity and a careful explanation of the potential impacts on family members.

On occasions, family members may be approached and engaged in a discussion about the need for genetic screening because of family history, or because of other information that needs not be specified, without directly identifying the patient. The decision to undertake such an approach entails a careful balancing exercise between the harm of non-disclosure and that of disclosure. Where deemed necessary, a referral to a professional genetic counsellor should be considered. If the test result has been

documented to be associated with a high risk of cancer with early onset, the patient should be strongly advised to allow first-degree relatives to be informed of their risk. In appropriate cases, clinicians may offer to inform these relatives of the relevant risks they face with the disclosure of minimal information about the patient (preferably without disclosing the identity of the patient if possible). If the patient refuses to inform the family members and also refuses the offer to provide information to the relatives, legal advice may be sought on whether non-consensual disclosure could be justifiable in the circumstances.

(For further details, see Sections 7.2 and 7.3.)

7.3.3 'Duty to warn'

As mentioned in Section 7.3.1, the duty of confidentiality is not absolute and there are circumstances under which it may be justifiable for healthcare professionals to disclose G&G information without the patient's consent. In these circumstances, clinicians will have to decide whether disclosure against the patient's will is justifiable or not.

A more difficult question for doctors is, instead of whether a doctor is permitted to disclose genetic information to third parties without the patient's consent, whether there could be a positive duty on the doctors to disclose such information to third parties. This area, no doubt, involves complex ethical and legal considerations.

ABC v St George's Healthcare NHS Trust [2020] EWHC 455 (QB)

The above dilemma has been considered in a recent court case in the UK, ABC v St. George's Healthcare NHS Trust and others.[12] Further details of the case can be found in Annex A. In this case, the Claimant's father (XX) was detained in a hospital run by the 2nd Defendant as a result of being found guilty of manslaughter of the Claimant's mother. The defendants were three NHS Trusts which were involved in the care and treatment of XX. XX was diagnosed with a genetic disorder called Huntington's disease but he refused to give consent to the defendants to disclose such information to the Claimant, who had a 50% chance of developing the condition. The Claimant was pregnant at the time and it was only after she gave birth that she was found to have inherited the gene for the disease. The Claimant brought a negligence claim against all the defendants for failing to warn her of the risk that she had inherited the gene. The case was dismissed and it was found that the 2nd Defendant (but not the other two defendants) owed a duty of care to the Claimant because she attended family therapy sessions arranged by the 2nd Defendant, which were intended to offer therapeutic benefit to both the Claimant and XX. The duty recognised was a duty to "balance her interest in being informed of her genetic risk against her father's interest in preserving confidentiality in relation to his diagnosis and the public interest in maintaining medical

confidentiality generally". There was, however, no breach of such duty because the 2nd Defendant's decision was supported by a responsible body of medical opinion. The UK Court did not make any general ruling about the existence of a positive duty to warn a third party of genetic risks in the absence of the patient's consent.

The ABC case is relevant but it is not a Hong Kong court case. As such, the approach taken in the ABC case may or may not be adopted in Hong Kong. We are currently not aware of any Hong Kong court cases which discuss such duty to warn in the context of genomic medicine. However, as suggested by the ABC case, the Court will not lightly impose a positive legal duty on a doctor if the doctor has no special connection with the third party — it is only in exceptional circumstances that the Court would impose a positive legal duty on doctors to balance a third party's interests against the patients' interests.

In terms of genomic medicine, the present professional guidance in Hong Kong is silent on this issue but if a positive legal duty to warn could potentially arise under special circumstances, we cannot see why a positive ethical duty would not similarly arise in certain special circumstances.

At present, Section 32.3 of the Code of Professional Conduct provides that, in the exceptional circumstances of spouses or other partners being at risk of a serious infectious disease but the patient refuses to give consent to disclosure, the need to disclose the position to them might be more pressing and the doctor may, given the circumstances of the case, consider it a duty to inform the spouse or other partners.

Clinicians should therefore be mindful of these possible special circumstances so that they can act promptly and appropriately in those situations and more people can benefit from the application of genetic technology. When in doubt, legal advice should be sought.

7.3.4 Communication with other parties

Third parties such as insurance agents, employers, or schools may have reasons to want to know about the results of an individual's G&G testing. Healthcare professionals have no duty towards such parties. Disclosure should only be made with the patient's explicit consent. Laws in some jurisdictions expressly prohibit or limit the use of genetic testing results by insurance companies when determining product pricing but not in Hong Kong. An exception may be requested from the government or regulatory bodies which possess the authority of having the required information disclosed, as required by the applicable law.

8 Genetics and Genomics in Specific Situations

8.1 Genetic testing to establish diagnosis in adults

8.1.1 Introduction

Detailed history taking and elicitation of relevant physical signs remain the backbone in establishing the correct diagnosis in patients with suspected genetic disorders. Particular attention should be paid to features that might suggest a genetic basis such as family history or multiple organ involvement. Detailed attention to the family history, including a three-generation pedigree, is often helpful. G&G testing should only be requested after careful clinical assessment of the patient and the family and will be guided by such information.

Genetic disorders may be caused by pathogenic variants (mutations) which can be somatic or germline. **Somatic** genetic variations occur after birth in non-germline cells (e.g., mutations in cancers), and are normally not heritable by the offspring. **Germline** genetic variations are inheritable, meaning that they can be passed from the parents to the offspring. Some conditions may not be passable to the next generation (e.g., mitochondrial DNA mutations in a male patient).

Genetic diagnoses can be made through a variety of approaches in addition to G&G testing, including physical examination, imaging studies, and non-genetic pathology tests. In many cases the confirmation by genetic testing is not a prerequisite to the delivery of clinical management (e.g., familial hypercholesterolemia). For some conditions, public funding of treatment may require a genetic diagnosis.

In deciding whether to arrange genetic testing, doctors should weigh the potential benefits of the tests—taking into consideration the analytical or clinical validity (e.g., issues related to sensitivity, specificity, or predictive value) and clinical utility (e.g., demonstrable ability of a test to improve health outcomes) of the tests—against the potential risks or psychosocial ramifications of genetic testing. When considering the clinical utility of genetic testing for conditions without specific treatment at present, a broader definition which includes, for example, the avoidance of diagnostic odyssey and informing the patient to assist in reproductive decisions, may be applicable. Since genetic testing is often associated with psychosocial or ethical issues, professional genetic counselling is important for joint decision making.

8.1.2 Who should be tested for inherited disorders?

For inherited disorders, diagnostic genetic tests should generally be done in an individual with symptoms or signs of the said condition (see Section 9.2 for pre-symptomatic or predictive testing). Careful clinical assessment and other diagnostic modalities can be helpful in narrowing down the scope of genetic testing, improving cost-effectiveness, and reducing the chance of incidental findings.

Within a family, testing is usually initiated in the person most likely to harbour the pathogenic (disease-causing) genetic variant(s) who is often the one with the most severe clinical manifestations. If the preferred person for initiation of genetic testing is unwilling or unavailable, then genetic testing should be considered in family members

with unequivocal evidence of being affected by the suspected genetic condition.

Genetic tests for inherited disorders should be done after informed consent and, where appropriate, pre-test counselling. Where an adult patient is mentally incapacitated for the purpose of consenting to a genetic test, such testing should be done for the benefit of the patient, and only with the consent of the legal guardian (see Section 7.2).

Prior consultation with qualified medical professionals with relevant expertise in such diagnosis and subsequent management is helpful and advisable.

8.1.3 What kind of test should be used?

The choice of genetic test(s) depends on both the nature of the genetic disorder suspected in the patient and local availability. For example, small variants can be detected by Sanger sequencing or massively parallel sequencing (next-generation sequencing), and copy number variations can be detected by tests such as multiplex ligation-dependent probe amplification. Caution should be exercised in utilising tests with a broad scope such as whole-genome sequencing or whole-exome sequencing as additional issues such as incidental findings may arise. The most common type of specimen used for germline testing is EDTA whole blood. The use of other specimens may be indicated depending on the clinical condition of the patient or the type of disorder. For example, in a recently transfused patient, buccal swab specimen may be used instead of whole blood; and muscle biopsy and urine specimens may be preferred over blood for analysis of mitochondrial DNA. In contrast, somatic mutations can be tested on affected tissue such as biopsy specimens or with cell-free plasma.

8.1.4 What should the patients be told?

During pre-test consultation, three categories of information should be explained to the patient: the nature of the genetic disorder in the patient; details of the genetic test itself, and implications of a genetic diagnosis for the patient and their family (see Section 7.2).

For genomic testing of a disease, relevant guidelines from different professional bodies can be consulted, where available. Recommendations of guidelines may reflect the limitations of science and technology at the time, as well as local factors such as resource availability and value systems adopted in the society where it is developed, and advice to patients should consider these factors.

The details of the genetic test should be made clear to the patient, including the scope and limitations of the proposed test, the possibility of uncertain results (such as variants of uncertain significance), the possibility of incidental findings, and how the interpretation of genomic results may change at a later date. The possibility of uncertain results and incidental findings often arise in the context of massively parallel sequencing (see Section 7.2).

The possibility of uncertain results refers to the interpretation of genetic variants. There is sometimes insufficient evidence for the classification of a particular variant. In addition, the risk associated

with some variants may be small but statistically significant. One should also bear in mind the concept of penetrance, that is, the likelihood of carriers to develop the disease. For example, high penetrance genes for hereditary breast and ovarian cancer are *BRCA1* and *BRCA2*, while an example of moderate penetrance gene is *PALB2*, and there are low penetrance genes. In these cases, it may be helpful to refer the patient to a qualified medical professional for counselling.

Case study

Patient M is a 35-year-old man who developed hypertrophic cardiomyopathy in his twenties. He has a strong family history of sudden cardiac death. He has had a genetic test done and a novel variant of uncertain significance is found in his TNNT2 gene, which codes for cardiac troponin T. He asks if genetic testing should be performed in his relatives.

What is the appropriate response and action?

Mutations in this gene have been associated with familial hypertrophic cardiomyopathy as well as with restrictive or dilated cardiomyopathy. However, transcripts for this gene can undergo alternative splicing that results in many tissue-specific isoforms, and the nature of some of these variants has not yet been determined. Also, mutations of this gene may be associated with mild or absent hypertrophy and predominant restrictive disease with a high risk of sudden cardiac death. In view of the complexity, he is referred to qualified medical professionals for counselling; clinical, instead of genetic, screening for cardiomyopathies is recommended.

Here, **incidental findings** refer to information identified during the analysis of G&G test results that is unrelated to the initial reason for testing. There have been suggestions in the literature that certain genetic findings should always be reported on the basis that it is "clinically actionable". However, this approach is not universally accepted as there is no clear definition of what is "clinically actionable". The best time to discuss the possibility of incidental findings is at the time of arranging a genetic test.

As G&G represents a rapidly evolving branch of medicine, variant interpretation may change with time as more data become available. Also, limitations of genetic tests may become apparent later. The patient should understand that variant interpretation may change, and they may be contacted in the future for revision in interpretation. However, this would depend on the availability of an effective system for communication (see Section 7.3).

Refer to the above Case Study.

Three years after the initial genetic testing in Patient M, four relatives of Patient M have been diagnosed with hypertrophic cardiomyopathy, and they all carry the same genetic variant as Patient M. Also, the updated literature provides new evidence on the presence of this variant in patients with hypertrophic cardiomyopathy. The variant is reclassified as a pathogenic variant, and pre-symptomatic testing of other relatives is now possible. (For further details, see Sections 8.2.2 and 8.2.3.)

8.2 Genetic testing in pre-symptomatic adults

8.2.1 Introduction

Pre-symptomatic testing or **predictive testing** refers to genetic testing in persons who have a family history of a heritable condition but do not currently show signs and symptoms of the condition. The two terms are often used interchangeably but are slightly different. Pre-symptomatic testing is used when a finding of a familial pathogenic variant is almost certain to develop the familial condition during their lifetime, whereas predictive testing refers to the situation where the finding of the familial pathogenic variant would increase the risk of developing the familial condition.

The term **'consultand'** has been coined to refer to a person seeking pre-symptomatic or predictive genetic testing.

8.2.2 When should pre-symptomatic or predictive testing be used?

As with all other diagnostic tests, the use of pre-symptomatic testing and predictive testing should be based on a balance between benefits and risks to the consultand. This balance involves the assessment of short-term and long-term medical, psychosocial, and reproductive issues. The general rule is for the doctor to make recommendations according to the best interest of the consultand, who can then make an informed choice based on the information provided.

Pre-symptomatic and predictive testing is generally indicated if a positive test result is likely to result in **medical benefits** to the consultand. This is especially true if evidence-based screening program or pre-emptive treatment exists for the condition. In cases where the direct medical benefit is doubtful or non-existent, individual assessment is required. Consultation with a qualified medical professional with experience in G&G medicine is often helpful in these scenarios.

8.2.3 What are the implications for patients and their relatives?

Pre-symptomatic and predictive testing is only reliable when the genetic diagnosis within the family has been clearly established. In the case where the level of evidence is inadequate to conclude the pathogenicity of a detected variant in the affected family member (that is, a variant of uncertain significance), pre-symptomatic and predictive testing should be considered with utmost caution. In this context, thorough genetic counselling, and prior discussion with clinical geneticists and genetic pathologists is highly recommended.

Pre-test genetic counselling and consent is especially important in the context of pre-symptomatic and predictive testing (see Sections 7.2 and 7.3).

In addition to the medical benefits, predictive and pre-symptomatic testing may improve the **overall health** of the consultand through the removal of uncertainty about genetic status if it is positive, offers reassurance if it is negative, and allows decisions, such as lifestyle, career, and reproductive choices, to be made in light of the findings.

In contrast, **psychological or even psychiatric** sequelae may occur after, or even before, the disclosure of test results because of the immense stress associated with potentially life-changing results. Potential risks of discrimination, stigmatisation, loss of privacy, and negative impact on family dynamics should be made clear to the consultand before such testing. The issue that genetic material is shared within a family, and the implication that a genetic diagnosis in one person may suggest that others might also have inherited the condition or trait, should be discussed (see Sections 7.2 and 7.3).

8.3 Premarital, pre-pregnancy, prenatal and pre-implantation testing

8.3.1 Introduction

The objective of premarital and pre-pregnancy care is to detect and assess any specific health problems in the woman or her partner that may be relevant and can be managed before pregnancy. This covers assessment of lifestyle, environmental factors, medical health and medication use.

Preconception counselling can be provided to women or men at reproductive age, by optimising health to improve reproductive and obstetric outcomes, and to reduce modifiable risk factors.[13]

Preconception counselling can be provided by primary care physicians, midwives, and obstetricians. For women at increased risks of hereditary disorder, referral to pre-pregnancy genetic counselling is preferred to allow more reproductive options for consideration.

The process involves taking a thorough medical history including age, ethnicity, consanguinity, family history of congenital anomalies or intellectual disability, stillbirth, neonatal death, recurrent pregnancy loss, medical history of the woman and her partner, especially on disorders with possible underlying genetic causes.

Consanguinity, or consanguineous union, generally refers to a union between couples related as second-degree cousins or closer. It increases the risk of genetic disorders in offspring, especially for autosomal recessive conditions. There are also higher incidences of non-genetically confirmed structural abnormalities, stillbirth, developmental delay, and autism spectrum disorders.[14]

Conventional genetic disease screening starts with a comprehensive family health history assessment. It forms the basis of and plays a major role in genetic screening and assessment.

A three-generation pedigree through clinical history provides a pictorial representation of genetic disorders in a family. It is effective in assessing hereditary disorders and the mode of inheritance, guiding further investigations and management plans.

Table 1. Current carrier screening guidelines

Genetic conditions	Recommendations on genetic carrier screening				
	ACOG[15]	**ACMG**	**NSGC**	**SOGC-CCMG[16] (joint recommendation)**	**HGSA/RAZCOG[17,18]**
Haemo-globinopathies	Complete blood count with red blood cell indices for all women Haemoglobin electrophoresis if there is a suspicion based on ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent) or low mean corpuscular haemoglobin or MCV[19]	NA	NA	At-risk ethnic backgrounds, or MCV <80 fL, or abnormal haemoglobin type on electrophoresis	All pregnant women by a full blood examination at initial presentation Screening with specific assays for haemoglobinopathies should be considered in high-risk ethnic or population groups
Cystic fibrosis	Pan-ethnic screening	Pan-ethnic screening[20]	Pan-ethnic screening[21]	At-risk ethnic background, personal or family history, or clinical manifestation	Offer option of screening
Spinal muscular atrophy	Pan-ethnic screening	Pan-ethnic screening[22]	NA	Presence of family history	Offer option of screening
Fragile X syndrome	Family history of intellectual disability suggestive of fragile X syndrome, unexplained delay, autism, or primary ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years	Family history of fragile X-related disorders or undiagnosed mental retardation, premature ovarian failure[23]	Follows ACOG and ACMG guidelines[24]	Follows ACOG guideline	Offer option of screening
X-linked haemophilia	NA	NA	NA	Maternal family history of bleeding disorders in male relatives	NA

Table 1. (cont'd)					
Ashkenazi Jewish population	Tay-Sachs disease if either member of a couple is of Ashkenazi Jewish, French-Canadian, or Cajun descent), Canavan's disease, familial dysautonomia, Bloom's syndrome, familial hyperinsulinism, Fanconi's anaemia, Gaucher disease, glycogen storage disease type I, Joubert's syndrome, maple syrup urine disease, mucolipidosis type IV, Niemann-Pick disease, Usher's syndrome	Tay-Sachs disease, cystic fibrosis, Canavan's disease, familial dysautonomia, Niemann-Pick (type A), Bloom's syndrome, Fanconi's anaemia group C, mucolipidosis IV, Gaucher disease	NA	(Same as ACOG), with additional screening if presence of family history of dihydrolipoamide hydrogenase deficiency, nemaline myopathy, Walker-Warburg syndrome	Tay-Sachs disease, Niemann Pick disease type A, Fanconi's anaemia group C, familial dysautonomia, Bloom's syndrome, Canavan's disease and mucolipidosis type IV

Abbreviations: ACOG = American College of Obstetricians and Gynecologists; ACMG = American College of Medical Genetics and Genomics; CCMG = Canadian College of Medical Geneticists; HGSA = Human Genetics Society of Australia; MCV = mean corpuscular volume; NA = no guideline; NSGC = National Society of Genetic Counselors; RAZCOG = The Royal Australian and New Zealand College of Obstetricians and Gynaecologists; SOGC = Society of Obstetricians and Gynaecologists of Canada.

---

[15] Committee on Genetics. Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. 2017;129(3):e41-e55. PMID: 28225426. https://doi.org/10.1097/AOG.0000000000001952

[16] Wilson RD, De Bie I, Armour CM, et al. Joint SOGC-CCMG Opinion for Reproductive Genetic Carrier Screening: An Update for All Canadian Providers of Maternity and Reproductive Healthcare in the Era of Direct-to-Consumer Testing. J Obstet Gynaecol Can. 2016;38(8):742-762.e3. PMID: 27638987. https://doi.org/10.1016/j.jogc.2016.06.008

[17] Genomics Advisory Working Group & Women's Health Committee, Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Genetic Carrier Screening. Mar 2019. Available from: https://ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Genetic-carrier-screening(C-Obs-63)New-March-2019_1.pdf

[18] HGSA/RANZCOG Joint Committee on Prenatal Diagnosis and Screening, Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Prenatal Screening and Diagnostic Testing for Fetal Chromosomal and Genetic Conditions. July 2018. Available from: https://www.hgsa.org.au/documents/item/6110

[19] ACOG Committee on Obstetrics. ACOG Practice Bulletin No. 78: hemoglobinopathies in pregnancy. Obstet Gynecol. 2007;109(1):229-237. PMID: 17197616. https://doi.org/10.1097/00006250-200701000-00055

[20] Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med. 2004;6(5):387-391. PMID: 15371902. https://doi.org/10.1097/01.gim.0000139506.11694.7c

[21] Langfelder-Schwind E, Karczeski B, Strecker MN, et al. Molecular testing for cystic fibrosis carrier status practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2014;23(1):5-15. PMID: 24014130. https://doi.org/10.1007/s10897-013-9636-9

[22] Prior TW; Professional Practice and Guidelines Committee. Carrier screening for spinal muscular atrophy. Genet Med. 2008;10(11):840-842. PMID: 18941424. https://doi.org/10.1097/GIM.0b013e318188d069

[23] Sherman S, Pletcher BA, Driscoll DA. Fragile X syndrome: diagnostic and carrier testing. Genet Med. 2005;7(8):584-587. PMID: 16247297. https://doi.org/10.1097/01.gim.0000182468.22666.dd

[24] Finucane B, Abrams L, Cronister A, et al. Genetic counseling and testing for FMR1 gene mutations: practice guidelines of the national society of genetic counselors. J Genet Couns. 2012;21(6):752-760. PMID: 22797890. https://doi.org/10.1007/s10897-012-9524-8

8.3.2 Genetic carrier screening guidelines

Conventionally, various international bodies recommend genetic screening of different health conditions based on an ethnic-based approach. The current recommendations of genetic carrier screening are summarised in Table 1.[15-24]

This ethnic-based screening approach may be replaced by pan-ethnic universal screening in the near future. The major reasons for such change include evolving social structures and population mobility resulting in multiracial societies. These changes called for the replacement of ethnic-based carrier screening by a universal screening approach. Genetic carrier screening by high-throughput next-generation sequencing is termed **expanded carrier screening**.[25]

International bodies such as the American College of Medical Genetics and the American College of Obstetricians and Gynecologists have changing views on expanded carrier screening. The American College of Obstetricians and Gynecologists published the committee opinion in 2017 stating that ethnic-specific, pan-ethnic, and expanded carrier screenings are all acceptable strategies for prenatal and pre-pregnancy carrier screening.[26]

Special points to note[27,28]:

- Expanded carrier screening using high-throughput next-generation sequencing can screen for a panel of recessive genetic conditions, ranging from 3 to >200 genetic conditions depending on the panel used. Testing for Fragile X syndrome is added by using a different test methodology.
- The aims of detecting asymptomatic carriers in the pre-pregnancy or prenatal period are to reduce the chance of at-risk couples having an affected child, and to facilitate discussion on reproductive options including pre-implantation genetic testing or prenatal diagnosis.
- Ideally, pre-pregnancy screening would be preferred over prenatal screening, due to increased reproductive options and less time constraint on testing and counselling.
- Pre-test counselling on expanded carrier screening is important. There are choices of different screening panels available in the commercial market differing in the number, nature and severity of conditions to be tested. The majority of panels screen for autosomal recessive conditions, whereas some are on X-linked or autosomal dominant single-gene disorders.

- A screen negative result does not eliminate the risk of having an affected offspring. It remains difficult to give the residual risk for screen negative results for conditions with unknown prevalence.
- The timing of the test (test on one partner first or couple testing), confidentiality issues, benefits and limitations of the test and post-test counselling issues need to be addressed.
- Expanded carrier screening is currently not funded by the public health system in Hong Kong. The cost-effectiveness, acceptance, and uptake in the local setting remain unclear. Detailed pre-test counselling on the benefits and limitations of testing is important before implementation.[29]

8.3.3 Prenatal screening and diagnosis

Genetics and genomics have already become essential components of prenatal diagnosis. These "new algorithms" are based on advances in prenatal molecular diagnostics, including noninvasive prenatal testing (NIPT), quantitative fluorescent-polymerase chain reaction (QF-PCR), chromosomal microarray (CMA) testing, whole-exome sequencing (WES), and whole-genome sequencing (WGS). Its purpose is to maximise the amount of prenatal information for pregnant women and their families to make choices for their next generations (Figure 1).[30]

Some of the emerging ethical issues surrounding the additional information available to parents from prenatal molecular diagnostics include:

- Should genetics and genomics lead prenatal diagnosis, or vice versa?
- What are the ethical implications of false-positive and false-negative results?
- How should prenatal information of uncertain clinical significance be handled?
- Is there a case for withholding certain information, for example to avoid parental anxiety?
- What information should be included in pre-test counselling and consent as well as post-test counselling?
- Should incidental genetic findings, such as non-paternity, adult-onset diseases, low penetrance neuro-susceptibility loci, be disclosed?
- Should selective termination of pregnancy based on genetics and genomics be permitted?
- Could access to, affordability of, or willingness to pay for molecular prenatal tests affect equality in healthcare?
- What are the new medicolegal challenges associated with genetics and genomics?
- Are we practising **eugenics**, and where should we draw the line?

To facilitate a better understanding of these complex ethical issues, an outline of the new algorithms in prenatal diagnosis is provided in Annex B.

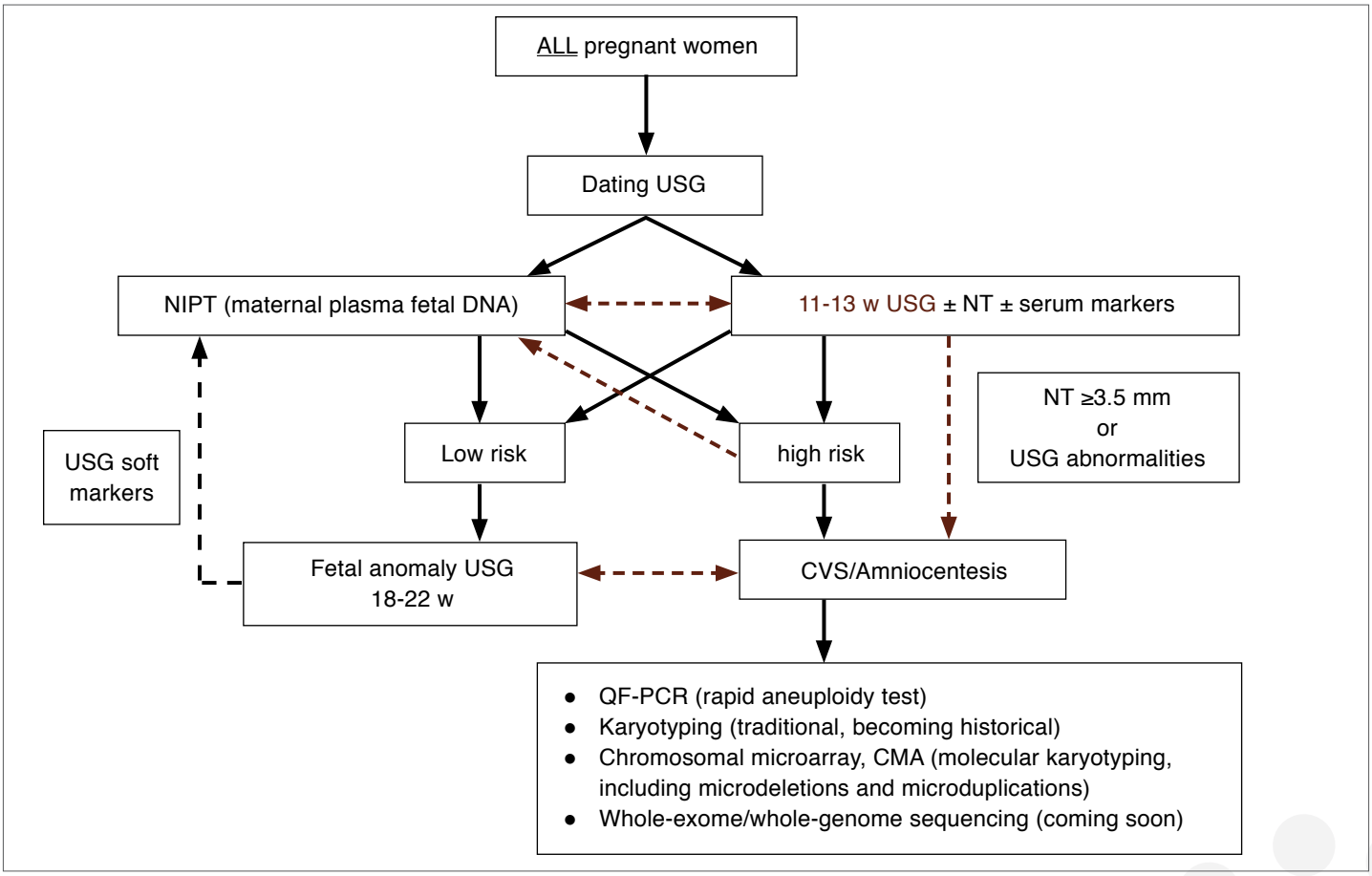

Figure 1. New algorithms in prenatal diagnosis (Adapted from: Leung WC. New algorithms in prenatal diagnosis. J Paediatr Obstet Gynaecol 2017;43:81-88)

Abbreviations: CMA = chromosomal microarray testing; CVS = chorionic villus sampling; NIPT = noninvasive prenatal testing; NT = nuchal translucency; QF-PCR = quantitative fluorescent-polymerase chain reaction; USG = ultrasonogram.

8.3.4 Pre-implantation Genetic Testing

Pre-implantation genetics testing (PGT) is a technique that combines *in vitro* fertilisation (IVF) and genetic testing of embryos before transfer. This provides a means to avoid transmission of a genetic abnormality or disease to the offspring.

In PGT, DNA from oocytes (polar bodies) or embryos (cleavage stage or blastocyst) is analysed for genetic abnormalities or for HLA typing. These include PGT for aneuploidies, monogenic defects, and chromosomal structural rearrangements.

As a form of assisted reproductive technology activity, PGT is permitted in Hong Kong by the Human Reproductive Technology Ordinance and is regulated by the Council on Human Reproductive Technology. Service providers of PGT need to be familiar with and adhere to the Code of Practice

and the other rules set by the Council on Human Reproductive Technology.[31]

More about PGT can be found in Annex C.

8.4 Consent for genomic testing for children

8.4.1 Introduction

Obtaining valid informed consent before G&G testing for a child is essential and should follow the same ethical principles that apply to obtaining consent from adult patients. The purpose of G&G testing is to establish the diagnosis which may help in the subsequent treatment of the child or decision making on the management path despite no curative treatment available in some conditions. At the same time, G&G testing also carries potential implications in genetic counselling for other family members or future pregnancies in the family. For a young child who does not have the competence to make a decision, the decision for G&G testing will be made by a parent or legal guardian. There are two situations where G&G testing in children requires special consideration: where the child has the mental capacity to make a decision themselves, and where testing is for an adult-onset disease.

8.4.2 Children with mental capacity to make a decision

Children such as teenagers may be mentally mature to the degree of understanding the needs and consequences of a medical investigation and can make a balanced decision on the G&G test. On the basis of the Gillick competence case,[32] these children should be involved in decision making, and their opinion must be taken into consideration.

There is no legally defined age cut-off for the capacity of making a medical decision. Healthcare professionals should assess the competency of the child on a case-by-case basis, considering the child's ability to understand and retain information, and to make rational decisions. Information provided to children and language used should be age-appropriate, to facilitate understanding and comprehension.

If there is a difference of opinion in consenting to G&G testing between a child and their parent or guardian, the clinician should review the situation for the definite necessity of such a test. The autonomy of the child should be respected if they can fully understand the significance of carrying the test. The final decision for the test should be based on the principle of the best interest of the child.

Clear documentation of the consent process should be made. Written assent of a child who is of the age that can understand and participate in the discussion is advisable.

As the implications of G&G testing may be complex, sufficient time should be allowed for the patient and their parent or guardian to discuss and consider before making a decision. It is always preferable to have consensus within the family when making the decision. A second or additional interview on the

decision of the test may be required in occasional cases.

8.4.3 Genetic test for adult-onset illness in a child

Some hereditary diseases may have onset of illness at adult age, such as Huntington's chorea. The diagnosis of the disease by genetic study will not provide benefit to the child if there are no preventive measures for the disease. The information on diagnosing an adult-onset condition will cause increased psychological burden to the parent or guardian and to the child. Physicians should inform the parent or guardian why the test is not recommended.

The diagnosis of such a condition should be made after the patient achieves adult age with full capacity to understand the condition and its implications. Each individual has the right to know or not to know the genetic cause leading to future medical illness. This decision should not be made by the parent or guardian when the child is young and cannot make a balanced decision.

Clinicians and laboratories may refuse the G&G tests to be performed if there are conflicts with ethical standards. There is no legal obligation that the clinicians or laboratories must perform the test.

8.4.4 Stored DNA samples after a genetic test done in a child

The samples are obtained with consent from the parent or guardian and will be stored for a period after completion of the test according to accreditation guidelines. Options for subsequent storage and use of any residue for quality assurance, research, or other purposes, should be discussed and agreed with the parent or guardian at the time of consent.

The following is a case for stimulating views and thoughts on this matter:

Case study

A baby was found to be a carrier of cystic fibrosis during neonatal screening. Her parents requested a genetic test for carrier status of the 9-year-old elder sister.

What do the parents need to understand and consider?

The finding of carrier status of cystic fibrosis in the neonate indicates that at least one of the parents carry the mutated gene. There is a chance that the elder sister also inherited the mutation. However, the 9-year-old sister is healthy and does not have any symptoms of cystic fibrosis; thus, performing the carrier screening has no benefit to the care of the sister. The sister may carry the mutated gene and has the chance of passing the mutation to the next generation or even to give birth to an affected baby if her partner is also a carrier of cystic fibrosis. However, the decision of screening for cystic fibrosis should be made by the sister when she achieves adulthood. Performing the carrier screening at childhood does not provide any benefit to the child.

8.5 Genetic tests for diagnosis and management of solid tumours and haematological malignancies

8.5.1 Introduction

Genetic testing on cancer cells is also termed somatic testing to distinguish from germline testing in constitutional disorders. The objectives of genetic testing in cancer can serve multiple clinical purposes, including disease diagnosis, especially in challenging cases that defy a definite diagnosis by morphology, special stains and immunohistochemistry; disease classification; prognostication and risk stratification; identification of actionable drug targets; and monitoring of treatment response and detection of drug resistance. Depending on the clinical need, somatic testing may range from single gene target or small panels, to comprehensive genomic profiling, and to whole-genome and whole-exome sequencing of cancer cells.

8.5.2 Pre-analytic considerations

Somatic testing is faced with the issue of mosaicism since the tumour sample usually contains an admixture of cancer cells and normal cells. As estimation of the tumour cell content by pathologist is recommended and enrichment of tumour cells may be considered if necessary, for example by microdissection of formalin-fixed paraffin embedded (FFPE) block sections of solid tumours. Advice from a pathologist should be sought to select the most appropriate sample (e.g., peripheral blood, bone marrow, or FFPE block of trephine or lymph node biopsy) for testing in haematological malignancies. Although FFPE tissue block is commonly used for genetic testing in solid tumours, the quality of test results may be confounded by DNA fragmentation or PCR artefacts due to fixation.

8.5.3 Spectrum of variants

Cancer is often considered a genetic disease and cancer cells can harbour a plethora of variants that include single nucleotide variant, small indel (<50 bp), large indel or genomic rearrangement, copy number variation and gene fusion. While cytogenetics, fluorescence *in situ* hybridisation and PCR methods are traditionally used to detect genetic changes in cancer, the comprehensive genomic profiling of cancer is increasing performed by next-generation sequencing (NGS). Regarding NGS-based oncology panels, guidelines on panel content selection, utilisation of reference materials for evaluation of assay performance, determining of positive percentage agreement and positive predictive value for each variant type, and requirement for minimal depth of coverage and minimum number of samples that should be used for assay validation are being developed.[33]

8.5.4 Variant annotation

In addition to standards and guidelines for variants, genetic testing in solid tumour and haematological malignancies should take into account the clinical significance of the reported variants in terms of applicability to guide treatment decision.[34] A four-tiered system is proposed to categorise somatic sequence variation based on their clinical

significance: Tier 1 variants of strong clinical significance, such as those targetable by FDA-approved therapy; Tier 2 variants with potential clinical significance, such as those targeted by FDA-approved therapy in another tumour type; Tier 3 variants of unknown clinical significance; and Tier 4 variants deemed benign or likely benign.

8.5.5 Germline variants detected by somatic testing

Cancer cells harbour somatic (acquired) genetic changes but, like other cells in the human body, they may also harbour germline (constitutional) genetic changes. Therefore germline variants may be detectable by virtue of somatic testing.[35] Whenever possible, it is advisable to test paired tumour and normal tissue by NGS-based oncology panels for the purpose of germline filtering. Written consent is usually unnecessary, and genetic counselling is not provided in the genetic testing of solid tumour and haematological malignancies for the aforementioned purposes. This is not expected to be a problem in tumours, for example lung cancer and lymphoma, without an obvious germline predisposition component. However, the issue becomes pertinent in other tumours such as ovarian cancer in which both germline and somatic variants of *BRCA1* and *BRCA2* genes are found and equally important as predictive markers for the use of Poly (ADP-ribose) polymerase (PARP)-1 inhibitor therapy.[36]

Although it is generally agreed that patients with ovarian cancer should have testing at the time of diagnosis, two alternative approaches can be undertaken. First, germline testing for *BRCA1* and *BRCA2* and other ovarian cancer susceptibility genes are performed and, for patients who do not carry a germline pathogenic or likely pathogenic *BRCA1* and *BRCA2* variant, somatic testing is performed. This approach requires intensive genetic counselling support and may prolong the lag time to test result. Second, in some places such as in Hong Kong, somatic testing is performed upfront or in combination with germline testing. This alleviates the stress and information overload to patients at the time of diagnosis, and is more cost-effective. However a disadvantage is that proper genetic counselling is not provided and cascade testing of family members is easily missed. In addition to ovarian cancer, this issue is also relevant to other cancers with homologous recombination defects, such as breast cancer, prostate cancer, and pancreatic cancer.

Case study

A 50-year-old Chinese woman had a history of metastatic ovarian cancer and received chemotherapy. She was referred by an oncologist to perform germline testing in the peripheral blood by a NGS gene panel for hereditary breast and ovarian cancer.

The results showed pathogenic variant c.4631delC p.P1544Hfs*4 of the BRCA1 gene at variant allele frequency of 36.2%. Another missense variant c.524G>A p.R175H of the *TP53* gene at variant allele frequency of 37.9% was also identified. The TP53 R175H variant was

not found in normal population database or in >1000 local patients with breast cancer screened in-house. However, it was previously reported in an extended family with Li–Fraumeni syndrome and thus interpreted as likely pathogenic in nature.[37]

To validate the two variants and to confirm germline nature, Sanger sequencing was performed on peripheral blood sample, buccal mucosa cells, and hair follicle cells. The *BRCA1* pathogenic variant was detectable in all samples tested at roughly 50% mutant level, which confirms germline nature and indicates heterozygous genotype. The patient is a candidate for PARP-1 inhibitor therapy.

The *TP53* missense variant was detectable in peripheral blood (mutant level by bidirectional Sanger sequencing: forward 46.6%, reverse 33.3%) and at a lower level in buccal mucosa cells (forward 26.9%, reverse 18.8%), but not in the hair follicle cells. The *TP53* missense variant was interpreted as likely somatic in nature, which may be induced by previous chemotherapy or related to somatic contamination from tumour origin, although no tumour testing is performed for confirmation. The low mutant level detectable in the buccal mucosa cells was interpreted as peripheral blood contamination.

8.5.6 Liquid biopsy

Liquid biopsy refers to genetic or genomic testing done on the circulating tumour DNA or less commonly circulating tumour cells in a blood sample. The scope ranges from single gene targets to panel testing by next-generation sequencing.

Liquid biopsy should not replace tumour biopsy. A negative liquid biopsy result does not preclude the presence of a mutation since the tumour may not shed DNA into the circulatory system. Whenever feasible, a negative liquid biopsy result should be confirmed by tissue biopsy. Liquid biopsy may identify mutations that are unrelated to the lesion of interest. A specific example is the detection of clonal haemopoiesis, which is a defect of the haemopoietic stem cells that affects the elderly population and predisposes to myelodysplasia and leukaemia.

This notwithstanding, liquid biopsy is applicable to patients in whom the tumour location is inaccessible, are poor surgical candidates or show contraindications to invasive procedures. Moreover, plasma EGFR detection is often adopted for management of non-small cell lung cancer to guide prescription of tyrosine kinase inhibitors. Currently the most common indication for liquid biopsy is in relapsed refractory disease to identify the mechanism of drug resistance and to detect new drug targets, but research into cancer screening and monitoring minimal residual disease are on-going.

Genome Sequencing and Population-based or Large-scale Disease Screening

9

9.1 Types of genome sequencing

Whole-genome sequencing (WGS) aims to sequence the entire genome, to identify disease-related DNA sequence variants in both protein-coding (exonic) and regulatory (intronic or intergenic) regions of the genome.

Whole-exome sequencing (WES) aims to sequence all protein-coding regions of the genome, to identify disease-related mutations that alter protein structure and function.

Targeted sequencing aims to sequence a panel of specific genomic regions (usually protein-coding genes) known to contain mutations related to a specific disease or diseases.

9.2 Diagnostic findings from genome sequencing

Genome sequencing is indicated for molecular diagnosis when a patient's clinical features are consistent with a genetic disorder, in the absence of a single strong candidate mutation that can be detected by a targeted genetic test. Genome sequencing is also indicated when there is evidence for its utility in guiding clinical management, such as molecular subtyping to assess prognosis or determine the most effective treatment target.

Genome sequencing, as with other forms of clinical investigations, does not always provide a definitive result. It is possible for genome sequencing to fail to identify a disease-causing mutation (false negative), to misidentify an irrelevant mutation as being the disease-causing mutation (false positive), and to identify mutations that have uncertain significance for the disease. Further biochemical or clinical investigations may be needed to confirm the molecular diagnosis.

Genome sequencing may identify medically-actionable secondary findings—DNA sequence changes that are unrelated to the patient's current medical condition but have potentially important implications for the patient's future health.

9.3 Potential benefits and risks from clinical sequencing

	Main findings	Secondary findings
Potential benefits	• Precise molecular diagnosis • Accurate determination of prognosis and treatment targets • Avoid diagnostic odyssey • Prevent transmission of disease mutation to future offspring (e.g., by pre-implantation screening)	• Identify future health risks that can be avoided or ameliorated (e.g., by risk reduction, early diagnosis, or personalised treatment)
Potential Risks	• Incorrect molecular diagnosis • Psychological distress from inconclusive or uncertain results • Patient not wishing to disclose the diagnosis to family members at risk of the same condition	• Distress or disadvantage to the patient or family members (e.g., discrimination in employment or insurance) • Unexpected genetic relationships (e.g., non-paternity) causing distress and family discord

9.4 Best practices for genome sequencing

9.4.1 Counselling before clinical genome sequencing

Proper counselling of the patient is necessary before genome sequencing. For patients who are intellectually unable to understand the counselling, a parent, responsible relative, or carer should be present. With the agreement of the patient, family members affected by the same medical condition may also be invited for counselling and sequencing, to help identify potential disease-causing variants that co-segregate with the medical condition in the family.

The counselling should include a review of the genetic diseases that may be responsible for the patient's condition, and how genome sequencing may provide a molecular diagnosis as well as medically actionable secondary findings. There should be a discussion of the potential benefits and risks of a molecular diagnosis, and broad classes of medically actionable secondary findings. The patient should be made aware that they are expected to inform family members who may be affected by the same conditions. The patient should understand that limitations in current knowledge mean that false positive and false negative molecular diagnoses are possible, and that future research may enable further medically actionable findings to be revealed from the sequencing data.

The informed consent for genome sequencing should include the patient's wish to be informed or not, of each broad class of secondary findings, if these are detected. It should also include the patient's wishes regarding the future usage of the sequencing data, including whether they wish to be informed if re-analysis reveals additional findings of clinical significance.

9.4.2 Requesting and reporting of clinical genome sequencing

Clinical genome sequencing should be done in an accredited medical laboratory under the direction of pathologists qualified in G&G. In the request for genome sequencing, relevant clinical information should be provided to facilitate the interpretation of sequence variants by the genomics laboratory. This should include clinical and family history information, particularly for those with syndromic presentation. The initial inclusion of a family trio—the index patient and parents—is common practice in clinical genome sequencing. Otherwise, where possible, DNA samples from informative family members should be obtained for follow-up genetic analysis, as evidence of segregation, *de novo* mutation, and phase configuration (whether two neighbouring variants disrupt both copies of the implicated gene (*trans*) or only one of the copies (*cis*)) may help resolve variants of uncertain significance in variant interpretation. In general, it is good practice to maintain communication with the genomics laboratory, to provide additional phenotype data (e.g., biochemical tests or imaging data) that may improve variant interpretation.

The clinical genome sequencing report should include a list of detected variants that are potential candidates for explaining the patient's clinical condition. The characteristics of each candidate variant should be summarised: the genomic location of the variant, the gene or genomic element which may be disrupted, the frequency of the variant in population databases, and the likely impact of the variant on gene function or protein product, as indicated by literature reports on the phenotypic effects of the same or similar variants, or predictions from bioinformatic tools. Medically actionable secondary findings should only be reported if they are within the classes which the patient wishes to be informed about. Results indicating unexpected genetic relationships (such as non-paternity) should be excluded from the report unless there are exceptional clinical implications.

9.4.3 Counselling and further consultation after genomic sequencing

Counselling should be provided to the patient after genome sequencing to review the report of findings, including the list of genomic variants which may be responsible for the patient's medical condition, as well as medically actionable secondary findings. The potential implications of these findings, for the patient and for their family members, should be discussed. This should be followed by the formulation of an action plan, which may involve referral to appropriate qualified medical professionals for the diagnoses suggested by the findings.

The patient may be advised that further consultations may be appropriate when there are future changes in the patient or their family, such as when a previously well family member develops the condition (which could alter the interpretation of genome sequencing data), or when the patient plans to start a family and wishes to have further counselling. The patient may be also advised that future re-analysis of the sequencing data may be useful when increased knowledge may alter the interpretation of genomic variants.

9.5 Disease screening by population-based or large-scale genome sequencing

Genome sequencing may be used for screening in healthy individuals, to detect those who are at an early asymptomatic stage of the development of a disease for which early intervention can improve outcomes or those who have a substantially elevated risk of a specific disease for which effective measures to reduce the risk or impact of the disease are available.

Such screening is only feasible when specific mutations, common variants, or other (epi)genomic markers have been identified, that allow the detection of early disease, or high-risk individuals, with sufficiently high sensitivity and specificity. Furthermore, it is important to ensure that necessary facilities and services are available to patients with positive screening results, to help them ameliorate their disease risks and improve their future health outcomes should be available. At the same time, it should be appreciated that a positive screening result may lead to anxiety and distress. The balance of cost and benefit from screening may thus differ for different individuals in the population.

Individuals for whom screening is potentially beneficial should be counselled so that they understand the target medical conditions of the screening programme, the possible outcomes of the screening test and their implications, as well as the potential risks and benefits of the screening. If the patient agrees to proceed with screening, written informed consent should be obtained, stating the points covered by the counselling. For patients who are too young, or who are unable to understand the screening program for other reasons, informed consent should be obtained from their parent or guardian. In the event of a positive test result, the patient should be informed accordingly, and given appropriate advice on follow-up action and information on available resources and services.

Pharmacogenomics 10

10.1 What is pharmacogenomics?

Pharmacogenomics (PGx) is the study of the role of the human genome in the interaction between the body and drugs. The interactions between the body and drug are grouped into two major fields of study: pharmacokinetics and pharmacodynamics. Pharmacokinetics represents the action of the human body towards a drug (absorption, distribution, metabolism, excretion), whereas pharmacodynamics represents the action of a drug on the human body (e.g., drug targets, signalling pathways).

Clinical PGx testing refers to the application of genetic testing to predict the effect(s) of pharmacologic treatment on a patient. Clinical PGx testing can be done when or before a drug prescription is contemplated.

10.2 When is clinical pharmacogenomics testing indicated?

The decision to perform clinical PGx testing should be based on a balance of benefits, costs, limitations, and risks. To facilitate this decision, information and guidelines can be obtained from various regulatory agencies (e.g., the United States Food and Drug Administration and European Medicines Agency) and professional societies (e.g., Clinical Pharmacogenetics Implementation Consortium, Dutch Pharmacogenetics Working Group). These guidelines have been curated in an online database, the Pharmacogenomics Knowledge Base (https://www.pharmgkb.org/).

The doctor should only consider PGx testing when it is required in the drug label as approved by a regulatory authority, or when strong recommendations are given by regulatory authorities and the clinical benefits clearly outweigh the risks.

Testing for HLA-B*15:02 is required by the United States Food and Drug Administration before prescription of carbamazepine in patients with ancestry in genetically at-risk populations (e.g., in Hong Kong Chinese), and testing of TPMT/NUDT15 is recommended by the United States Food and Drug Administration in patients with severe myelosuppression from thiopurines such as azathioprine. Guidelines for these gene-drug pairs are available from the Clinical Pharmacogenetics Implementation Consortium, the Dutch Pharmacogenetics Working Group and the Canadian Pharmagenomics Network for Drug Safety.

10.3 What do doctors need to consider?

The situation is less clear when clinical PGx testing is neither required nor recommended in guidelines and drug labels, but where drug dosing adjustment is recommended, or where a particular drug may be contraindicated in patients with certain PGx findings. For example, the European Medicines Agency recommends a downward dosing adjustment of aripiprazole prolonged-release formulation in patients who are CYP2D6 poor metabolisers without noting whether PGx testing is recommended. For drugs in this category, the doctor should consider the potential benefits of PGx

testing together with the risks, limitations, and cost implications associated with such PGx testing, as PGx testing for drugs in this category are naturally less well-developed and standardised.

10.4 Caveats in requesting pharmacogenomics testing

Clinical PGx testing should be done in an accredited medical laboratory with a quality system in place to ensure the quality of the report under the direction of pathologists qualified in G&G. The attending doctor should communicate with the pathologists in the laboratory to ensure that the method employed is appropriate for the patient and clinical scenario. The clinical information provided to the laboratory for PGx testing should include, for example, drugs under consideration, clinical scenario, and ethnic origin of the patient, which may affect the choice of risk alleles tested.

Case study

*Dr V was treating a new patient from South Asia, Patient H, who had been previously treated for biopsy-proven Crohn's disease. Dr V decided to perform genetic testing on thiopurine methyltransferase (TPMT) for Patient H. Dr V included the ethnicity of the patient in the clinical information provided to the laboratory. On the basis of this information, an extended panel of TPMT risk alleles were tested and the patient was subsequently found to be heterozygous for TPMT*3B, a risk allele not routinely tested for in East Asian patients.*

Ethnicity information can be useful in test selection particularly in well-genotyped populations. Nevertheless, the use of ethnicity as the sole basis in determining the need for PGx testing could be risky, particularly in groups which have not been extensively genotyped. Like all other genetic tests, PGx testing can be associated with the generation of unexpected secondary findings which may carry health-related and social implications. In some cases, PGx testing can yield results that are uninterpretable with the current state of medical science. These issues should be discussed by the attending doctor with the patient before testing.

10.5 Handling of pharmacogenomics information presented by patients

Doctors should exercise their professional judgement as to whether a PGx report provided by a patient can be used to guide further clinical management. The attending doctor should consider whether the laboratory is appropriately accredited; whether the signatories are qualified personnel with experience in G&G; whether the methods employed, alleles tested, and limitations have been stated; and whether the patient has been unambiguously identified in the PGx report.

PGx results can come in a variety of formats. A doctor should exercise independent judgement, to both the genetic findings and the interpretation.

Case study

Dr X considered the possibility of using irinotecan for colorectal cancer in Patient G. Dr X received

*from Patient G a genetic report which stated that the patient is homozygous for the UGT1A1*28 allele and Gilbert syndrome is therefore genetically confirmed.*

*Dr X read the drug insert of irinotecan, which states that dosage reduction is required in patients homozygous for UGT1A1*28.*

Case study

Dr Y conducted a follow-up examination for a patient with epilepsy, Patient L, who was currently taking phenobarbital. Dr Y received from Patient L a PGx report which stated that A/A genotype was detected in a known single nucleotide variant site rs17183814, located in the SCN2A gene. The report further stated that anti-epileptic drugs such as carbamazepine, phenobarbital, phenytoin, and valproic acid are contraindicated in the patient.

Dr Y reviewed the relevant literature in PharmGKB and found that although this genotype has been associated with a decreased response towards certain anti-epileptic drugs, no such association was found in two large cohorts and a meta-analysis. As the patient responded well, Dr Y decided to continue with the current regimen.

Where a report is deemed to be of questionable credibility, the doctor should explain the limitations of interpreting such reports to the patient and to arrange to repeat PGx testing in an accredited medical laboratory under the direction of pathologists qualified in G&G.

If the doctor considers the interpretation of a report to be beyond their professional practice, they should consult the reporting laboratory or refer the patient to a qualified medical professional with appropriate experience in G&G.

Case study

Dr Z received from Patient N a hyperlink containing raw data for a whole-genome sequencing study of Patient N performed in a commercial testing facility. No clinical interpretation was provided for the testing. Dr Z was asked what drugs Patient N should avoid in the future.

Dr Z had no prior experience in interpreting whole-genome sequencing data and referred Patient N to a qualified medical professional with experience in genetics and genomics for further assessment.

If a report is the result of direct-to-consumer testing, see also Section 11.

11 Direct-to-Consumer Genetic Testing

11.1 What is direct-to-consumer genetic testing?

Direct-to-consumer (DTC) genetic tests can be directly requested by a person without the involvement of a medical practitioner and can be purchased conveniently online or over the counter with self-collection and submission of samples.

These DTC genetic tests are appealing, apparently convenient, and sometimes marketed to provide information on health-related and non-health-related issues. Health-related DTC genetic tests attempt to provide diagnoses or carrier status for genetic diseases (e.g., thalassaemia, haemophilia, and spinal muscular atrophy), evaluation of genetic susceptibility for common diseases (e.g., diabetes, cancer, cardiovascular diseases) and pharmacogenomic evaluation to guide the decision on selection and dosage of drugs (see Section 10). Non–health-related tests may inform about lifestyle factors, kinship, ancestry, talents or nutritional needs. The actual genetic testing technology varies, but commonly involves the analysis of multiple single nucleotide polymorphisms, targeted sequencing of genes, or massively parallel sequencing. However, detection of variants is not equivalent to discerning their clinical impact, because the clinical interpretation of genetic variants depends on the context.

Some of these tests are offered by local companies and others are based and provided overseas as commercial kits or laboratory-developed tests. These DTC genetic tests are under different levels of regulation in various countries, ranging from codes of practice to legislation. In European countries such as Germany and France, DTC genetic tests are basically prohibited. Engagement of health professionals, genetic counselling, and obtaining informed consent are necessary for conducting genetic tests. Although there is no direct regulation of DTC genetic testing in the UK, use or analysis of human genetic data without the consent of the individual is regarded as an offence of DNA 'theft' according to the UK Human Tissue Act 2004. In the US, genetic tests are regarded as an *in vitro* diagnostic device and therefore require premarket review by the Food and Drug Administration.

The issue of DTC genetic testing may arise when a patient consults a doctor before DTC genetic testing or when a patient provides the attending doctor with a DTC genetic testing report and seeks advice upon it.

11.2 Concerns over direct-to-consumer genetic testing

11.2.1 Lack of medical supervision, informed consent, or counselling

Clinical genetic testing in Hong Kong, as for other tests for medical diagnosis and management, should only be done in medical laboratories by registered medical laboratory technologists upon referral by registered medical, dental or veterinary practitioners or by clinics with exemption in accordance with the Code of Practice of the Medical Laboratory Technologists Board and Supplementary Medical Professions Ordinance. In contrast, DTC genetic tests are currently unregulated in Hong Kong, and consultation with a medical practitioner is not required before testing. There is also no requirement

of informed consent regarding the carrying out of DTC genetic tests. Moreover, proper pre-test and post-test genetic counselling regarding the tests may not be available from the DTC genetic test provider. Consumers taking DTC genetic tests are often unaware of the suitability; the ethical, legal, psychological, and social implications; or the possible impact on insurance purchase of the genetic testing.

11.2.2 Clinical and analytical validity

Ample and often huge amounts of data from scientific studies are necessary to justify the clinical validity of predictive genetic tests. However, some DTC genetic tests may not be able to provide sufficient evidence based on an adequate volume of studies and data to justify their clinical validity. Moreover, limitations may not be mentioned and equivocal illustrations in marketing materials may be misleading. Interpretations of the DTC genetic test reports may not be provided by medical professionals who are suitably qualified in the field.

The predictive significance of a "disease-causing variant" is limited in a tested individual with no medical or family history of the corresponding disease. Many of the variants tested in DTC genetic tests are only weakly associated with conditions or traits tested. Most of the conditions and traits tested are polygenic and multifactorial, such that their development depends on multiple genetic and non-genetic environmental factors. There may be no currently available preventive means and test-positive individuals may not develop the disease.

False-positive results may occur due to suboptimal quality control of the DTC genetic tests, artefacts of the raw data, and the use of outdated databases for interpreting the clinical impact of data generated. For instance, it has been reported that the single nucleotide polymorphism–chip genotyping approach that many DTC genetic tests adopt is unreliable for evaluation of very rare disease-causing genetic variants. In contrast, some DTC genetic tests only screen for a small proportion of genetic variants of the disease-associated genes leading to false-negative results because a pathogenic variant which the tested individuals have was not included in the DTC test.

Moreover, there is currently no treatment for many of the conditions being tested for by DTC genetic tests on the market, or available treatments cannot be prescribed until clinical symptoms develop.

Therefore, out of clinical context consideration of positive DTC genetic test results indicating increased risk of a condition may lead to unwarranted anxiety of the tested individual. In contrast, false reassurance and reduced health awareness and practice may result from DTC reports indicating decreased risk of a disease.

11.2.3 Privacy and confidentiality

Consumers may be unaware of the privacy implications and potential risk of genetic discrimination associated with DTC genetic testing. They may not be conscious of the storage security of their genetic data or the extent to which these data may be shared, for instance with insurance

companies or employers. Some companies that offer DTC genetic tests make the genetic data of their clients available for sale as part of their business model.

11.3 Doctor's role in recommending direct-to-consumer genetic testing

Tips

- The doctor should try to understand what led the patient to consider taking the DTC genetic test. The doctor should explain to the patient that DTC genetic tests may not have acquired the same quality standards as tests performed in accredited medical testing laboratories, and as a result, DTC genetic tests may lack the necessary clinical and analytical validity and the results may be misleading, unclear, or inaccurate. If the patient insists on taking the test, the doctor should inform the patient of the importance of pre-test and post-test genetic counselling by qualified health professionals with appropriate training.
- The doctor should not recommend a DTC genetic test unless they have a clear understanding of the benefits, risks, validity, and limitations of the test in question, and the laboratory performing the test can guarantee the analytical and clinical validity of the results.
- If the doctor chooses to recommend a DTC genetic test, the doctor should explain the proposed DTC genetic test to the patient, including what the test can and cannot reveal about their health condition, the possibility of incidental identification of genetic variants beyond the intention of the test, the level of scientific evidence behind such tests, and the privacy implications of such tests. The doctor should ensure that appropriate pre-test and post-test genetic counselling would be provided to the patient by qualified health professionals with appropriate training and that informed consent has been obtained.
- The doctor should explain that even if a genetic diagnosis is found, preventive measures or treatments for the disease may not exist.
- The doctor should explain that a DTC genetic testing might lead to the possibility of genetic discrimination.
- If a genetic test is clinically indicated and the results are to be used in the clinical management of a patient, clinical genetic testing should be arranged with an accredited medical testing laboratory supervised by qualified medical professionals in place of a DTC genetic test.
- A doctor without appropriate training in genetics and genomics should refrain from recommending DTC genetic testing, especially for cases that fall onto one of the highly specialised areas (e.g., testing in children, pre-pregnancy testing, and pre-symptomatic testing of certain disease and conditions). In such cases, referral to an appropriate qualified medical professional should be made.

11.4 Handling of direct-to-consumer genetic testing presented by patients

Tips

- The crucial point is that DTC genetic tests should not be used as the basis of clinical decision making and healthcare provision without further validation of test results.

- The doctor should assess the reliability of the results in the DTC genetic report, and in light of this, should explain the results, limitation of the test including possible lack of analytical and clinical validity of the results, and their level of confidence in providing interpretation for the results. The doctor should provide, or recommend the patient to seek, appropriate genetic counselling by qualified medical professionals for the DTC genetic test(s) that has already been performed.
- For positive DTC genetic test indicating diagnosis or susceptibility to a genetic disease, the doctor should recommend early consultation of a specialist in the field since the severity and prognosis of the disease usually cannot be predicted by the DTC genetic test. The predictive accuracy for susceptibility to common diseases is usually low for DTC genetic tests. Tested patients should be advised to adopt appropriate lifestyle modifications and, if clinically indicated, consult appropriate qualified medical professionals for proper evaluation.
- In contrast, the doctor should advise test patients with a negative DTC genetic test result that while they are unlikely to have the disease, the possibility that they may develop the disease in the future cannot be excluded. The doctor should consider referral for patients with a medical or family history of genetic disease despite apparently "reassuring" DTC genetic test results.
- For patients with DTC genetic test results presenting with related symptoms, the doctor should assess and investigate as for other patients with the symptoms.
- If the DTC genetic test result would alter clinical management if correct, confirmation in an accredited medical laboratory supervised by qualified medical professionals is necessary. Clinical judgement is required.
- The doctor should explain the possibility of genetic discrimination and the implication of genetic test results becoming part of the patient's medical record which may have bearing on future insurance coverage and employment.
- In case of doubt, referral to a qualified medical professional with experience in genetics and genomics is appropriate.

12 Genomic Research and Data Banking

12.1 General principles of good clinical research

The general principles of good practice in clinical research also apply to genomics research. Good research should be purposeful, starting with the identification of an important problem. A thorough and critical literature review should be conducted to evaluate current knowledge, and to formulate key questions, hypotheses, and research objectives. A detailed research protocol should be carefully developed to address the research questions in the most efficient manner, to anticipate and circumvent potential problems, to minimise risks to the patients' welfare, and to maximise the validity, potential value and generalisability of research findings. The research should be approved by relevant institutions that have responsibility for the ethical conduct of research or the welfare of the patients. Research staff should receive adequate training for carrying out the project, and there should be mechanisms for monitoring progress, adverse events, or unexpected problems. Adequate measures should also be in place to maintain data security.

12.1.1 Consent for clinical research

Participation in clinical research should be voluntary. Informed consent implies that the patient is able to understand the project sufficiently to make an informed decision of whether to participate in the project, and to communicate this decision to the research team. The presence of neurological or mental disorders does not necessarily imply incapacity to consent. For patients who do not have the mental capacity to consent (e.g., unconscious patients), consent should be obtained from a parent or other responsible person. If even this is not feasible (e.g., where the study involves treatment that has to be given immediately to be effective), then exemption from informed consent may be considered by the appropriate ethical committees.

12.2 Features of genomic data relevant to research practice

Genomic data have features that require additional safeguards, but at the same time provide unique opportunities for research to improve population health and clinical care. Each person's inherited genome sequence is constituted at conception and changes little throughout life; it controls our development, physiological functions, and responses to the environment including pathogens, toxins, and drugs. Almost all human diseases, from rare monogenic conditions to common multifactorial disorders, are to some extent determined or influenced by an individual's inherited genome sequence. Somatic mutations of the genome sequence contribute to the development of diseases, in particular cancers. The expression of genes is altered by epigenetic modifications, which control cellular differentiation and responses to internal or external challenges. Modern technologies enable entire genomes to be characterised, including the inherited genome, the mutated (potentially cancerous) genome, and the dynamic (and cell-type specific) epigenome.

A patient's genome sequence can be used immediately for molecular diagnosis of a current medical condition, and for disease subtyping and patient stratification for precision medicine, and subsequently for evaluating future health risks to

guide personalised risk reduction and disease screening programs, and identifying drugs to be avoided because of idiosyncratic adverse effects. In addition, a person's mutated genome or epigenome may be informative for early detection of disease, and monitoring for relapse or progression of disease.

The pervasive and long-term impact of the genome on health and disease is the rationale for the establishment of genomic data banks to enhance patient care and research. Large genomic databanks can be used to establish correlations between genomic features and multiple health outcomes, by linkage to computerised medical records. The accumulation of such correlations will in turn increase the predictive power of genomic information, which can be used to promote population health and improve patient care. The realisation of the potential benefits of genomics for clinical medicine may require increasingly greater integration between research and practice.

12.2.1 Potential breach of anonymity

Each person's genomic sequence is unique (with the exception of monozygotic twins); thus, genomic data can be used for individual identification. Genomic information can be used to determine the sex, ethnicity and, to some extent, physical appearance (e.g., eye colour, skin colour, height, and weight) of an individual. Using Y chromosome markers, it may be possible to determine a man's male ancestry. Whole-genome sequencing data allows telomeric length estimation, which decreases with increasing age. Such features extracted from genomic data could be used to find matches with a database containing personal information, which could result in loss of anonymity of research patients. Loss of anonymity could lead to an individual's disease susceptibilities to be revealed, raising the risk of discrimination, for example, in employment or insurance.

12.3 Genomic material and data banking

Biobanks refer to collections of biological samples (such as blood and tissue samples, or extracted DNA or RNA), and to collections of data derived from the analysis of such samples, such as whole-genome or whole-exome sequencing data.

A biobank should have the approval by relevant research ethics committee(s), while its operational policies and implementation should be formulated, monitored and reviewed by a management committee. Standard and effective procedures should be established for the collection, processing, storage, handling, transfer, sharing, and destruction of samples and data, facilitated by the use of secured laboratory information management and database systems.

To maximise the benefits of biobanks, efforts should be made to include high-quality genomic samples or data from as many patients as possible, while respecting the right of individual patients to decline participation. Furthermore, samples or data should be destroyed if a participant asks to withdraw from the biobank, or if the management committee decides that the sample or data is no longer valuable.

12.3.1 Informed consent for biobanking

As for clinical research, participation of patients in biobanks should be voluntary. However, the pervasive and long-term impact of the genome on health and disease means that it is difficult to foresee all the potential uses of the materials or data in a biobank. Thus, informed consent should be sufficiently broad to allow samples or data to be used in future studies, to maximise the potential benefits from the biobank, and to avoid the need to re-consent patients, which may be not feasible.

Since genomic research often involves international collaboration, it is advisable to include anonymised data sharing in the consent.

The usage of samples and data from older studies that obtained more restrictive consent should ideally be consistent with the specifications of the original consent. However, where there are compelling reasons for deviating from the original consent, and re-consenting is not feasible, an application for exemption can be considered by the relevant ethics committee or appropriate authority.

References and Further Reading

13

Section	References
1	1. Steering Committee on Genomic Medicine, Food and Health Bureau, Hong Kong SAR Government. Strategic Development of Genomic Medicine in Hong Kong. Available from: https://www.fhb.gov.hk/en/press_and_publications/otherinfo/200300_genomic/index.html
6	2. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. Oxford University Press (New York), 1979. 3. Unesco. Universal declaration on the human genome and human rights (revised draft). Bull Med Ethics. 1997;126:9-11. PMID: 11660552.
7	4. Code of Professional Conduct, Medical Council of Hong Kong (2016), §2.1. 5. Code of Professional Conduct, Medical Council of Hong Kong (2016), §2.10. 6. Montgomery v Lanarkshire Health Board [2015] UKSC11 1 AC 1430. 7. Bombard Y, Brothers KB, Fitzgerald-Butt S, et al. The responsibility to recontact research participants after reinterpretation of genetic and genomic research results. Am J Hum Genet. 2019;104(4):578-595. PMID: 30951675. https://doi.org/10.1016/j.ajhg.2019.02.025 8. Deignan JL, Chung WK, Kearney HM, et al; ACMG Laboratory Quality Assurance Committee. Points to consider in the reevaluation and reanalysis of genomic test results: a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019;21(6):1267-1270. PMID: 31015575. https://doi.org/10.1038/s41436-019-0478-1 9. Code of Professional Conduct, Medical Council of Hong Kong (2016), §1.1. 10 Code of Professional Conduct, Medical Council of Hong Kong (2016), §1.4.2. 11. Personal Data (Privacy) Ordinance (Cap. 486) 12. ABC v St George's Healthcare NHS Trust [2020] EWHC 455 (QB)
8	13. American Society for Reproductive Medicine; American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice. Prepregnancy counseling: Committee Opinion No. 762. Fertil Steril. 2019;111(1):32-42. PMID: 30611411. https://doi.org/10.1016/j.fertnstert.2018.12.003 14. Siong KH, Au Yeung SKC, Leung TY. Parental consanguinity in Hong Kong. Hong Kong Med J. 2019;25(3):192-200. PMID: 31178441. https://doi.org/10.12809/hkmj187783 15. Committee on Genetics. Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. 2017;129(3):e41-e55. PMID: 28225426. https://doi.org/10.1097/AOG.0000000000001952 16. Wilson RD, De Bie I, Armour CM, et al. Joint SOGC-CCMG Opinion for Reproductive Genetic Carrier Screening: An Update for All Canadian Providers of Maternity and Reproductive Healthcare in the Era of Direct-to-Consumer Testing. J Obstet Gynaecol Can. 2016;38(8):742-762.e3. PMID: 27638987. https://doi.org/10.1016/j.jogc.2016.06.008

8	17. Genomics Advisory Working Group & Women's Health Committee, Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Genetic Carrier Screening. Mar 2019. Available from: https://ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Genetic-carrier-screening(C-Obs-63)New-March-2019_1.pdf 18. HGSA/RANZCOG Joint Committee on Prenatal Diagnosis and Screening, Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Prenatal Screening and Diagnostic Testing for Fetal Chromosomal and Genetic Conditions. July 2018. Available from: https://www.hgsa.org.au/documents/item/6110 19. ACOG Committee on Obstetrics. ACOG Practice Bulletin No. 78: hemoglobinopathies in pregnancy. Obstet Gynecol. 2007;109(1):229-237. PMID: 17197616. https://doi.org/10.1097/00006250-200701000-00055 20. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med. 2004;6(5):387-391. PMID: 15371902. https://doi.org/10.1097/01.gim.0000139506.11694.7c 21. Langfelder-Schwind E, Karczeski B, Strecker MN, et al. Molecular testing for cystic fibrosis carrier status practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2014;23(1):5-15. PMID: 24014130. https://doi.org/10.1007/s10897-013-9636-9 22. Prior TW; Professional Practice and Guidelines Committee. Carrier screening for spinal muscular atrophy. Genet Med. 2008;10(11):840-842. PMID: 18941424. https://doi.org/10.1097/GIM.0b013e318188d069 23. Sherman S, Pletcher BA, Driscoll DA. Fragile X syndrome: diagnostic and carrier testing. Genet Med. 2005;7(8):584-587. PMID: 16247297. https://doi.org/10.1097/01.gim.0000182468.22666.dd 24. Finucane B, Abrams L, Cronister A, et al. Genetic counseling and testing for FMR1 gene mutations: practice guidelines of the national society of genetic counselors. J Genet Couns. 2012;21(6):752-760. PMID: 22797890. https://doi.org/10.1007/s10897-012-9524-8 25. Cheng HHY, Kan ASY. Updates on screening for carriers of genetic diseases. MIMS JPOG. 2018;44(1):37-43. 26. Committee on Genetics. Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine. Obstet Gynecol. 2017;129(3):e35-e40. PMID: 28225425. https://doi.org/10.1097/AOG.0000000000001951

8	27. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol. 2015;125(3):653-662. PMID: 25730230. https://doi.org/10.1097/AOG.0000000000000666 28. Henneman L, Borry P, Chokoshvili D, et al. Responsible implementation of expanded carrier screening. Eur J Hum Genet. 2016;24(6):e1-e12. PMID: 26980105. https://doi.org/10.1038/ejhg.2015.271 29. Chan OYM, Leung TY, Cao Y, et al. Expanded carrier screening using next-generation sequencing of 123 Hong Kong Chinese families: a pilot study. Hong Kong Med J 2021;27:Epub 19 Feb 2021. PMID: 33602879. https://doi.org/10.12809/hkmj208486 30. Leung WC. New algorithms in prenatal diagnosis. J Paediatr Obstet Gynaecol 2017;43:81-88 31. Council on Human Reproductive Technology. Code of Practice on Reproductive Technology and Embryo Research. Jan 2013. Available from: https://www.chrt.org.hk/english/service/files/code.pdf 32. Gillick v West Norfolk and Wisbech [1986] AHA AC 112 ((HL)) 33. Jennings LJ, Arcila ME, Corless C, et al. Guidelines for Validation of Next-Generation Sequencing-Based Oncology Panels: A Joint Consensus Recommendation of the Association for Molecular Pathology and College of American Pathologists. J Mol Diagn. 2017;19(3):341-365. PMID: 28341590. https://doi.org/10.1016/j.jmoldx.2017.01.011 34. Li MM, Datto M, Duncavage EJ, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017;19(1):4-23. PMID: 27993330. https://doi.org/10.1016/j.jmoldx.2016.10.002 35. Konstantinopoulos PA, Norquist B, Lacchetti C, et al. Germline and somatic tumor testing in epithelial ovarian cancer: ASCO Guideline. J Clin Oncol. 2020;38(11):1222-1245. PMID: 31986064. https://doi.org/10.1200/jco.19.02960 36. Kwong A, Cheng KD, Hsue CV, et al. *BRCA* mutation testing for ovarian cancer in the context of available targeted therapy: Survey and consensus of Hong Kong specialists. Asia Pac J Clin Oncol. 2019 Mar;15 Suppl 2:20-31. PMID: 30838787. https://doi.org/10.1111/ajco.13116 37. Weitzel JN, Chao EC, Nehoray B, et al. Somatic TP53 variants frequently cofound germline testing results. Genet Med. 2018;20(8):809-816. PMID: 29189820. https://doi.org/10.1038/gim.2017.196

9	• Genetics/Genomics Competency Center: https://genomicseducation.net/competency • Bowdin S, Gilbert A, Bedoukian E, et al. Recommendations for the integration of genomics into clinical practice. Genet Med. 2016;18(11):1075-1084. PMID: 27171546. https://doi.org/10.1038/gim.2016.17 • Krier JB, Kalia SS, Green RC. Genomic sequencing in clinical practice: applications, challenges, and opportunities. Dialogues Clin Neurosci. 2016;18(3):299-312. PMID: 27757064. https://doi.org/10.31887/DCNS.2016.18.3/jkrier • Richards S, Aziz N, Bale S, et al.; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. PMID: 25741868. https://doi.org/10.1038/gim.2015.30 • Sequence Variant Interpretation Working Group, ClinGen. Sequence Variant Interpretation Guidelines. Available from: https://clinicalgenome.org/working-groups/sequence-variant-interpretation/ • Association for Clinical Genetic Science. ACGS Best Practice Guidelines for Variant Classification 2019. Available from: https://www.acgs.uk.com/media/11285/uk-practice-guidelines-for-variant-classification-2019-v1-0-3.pdf • Association for Clinical Genetic Science. General Genetic Laboratory Reporting Recommendations. Available from: https://www.acgs.uk.com/media/10758/acgs_general_genetic_laboratory_reporting_recommendations_2015.pdf • ClinGen. Gene-Disease Validity database. Available from: https://search.clinicalgenome.org/kb/gene-validity • Hunter JE, Irving SA, Biesecker LG, et al.; ClinGen. A standardized, evidence-based protocol to assess clinical actionability of genetic disorders associated with genomic variation. Genet Med. 2016;18(12):1258-1268. https://doi.org/10.1038/gim.2016.40 • Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(2):249-255. PMID: 27854360. https://doi.org/10.1038/gim.2016.190 • Hirschhorn K, Fleisher LD, Godmilow L, et al. Duty to recontact Genet Med. 1999;1(4):171-172. PMID: 11258354. https://doi.org/10.1097/00125817-199905000-00010 • Electronic Medical Records and Genomics (eMERGE) Network. Phase III eMERGE Consent Forms. Available from: https://emerge-network.org/phase-iii-consent-forms/

10	• Thorn CF, Klein TE, Altman RB. PharmGKB: the Pharmacogenomics Knowledge Base. Methods Mol Biol. 2013;1015:311-320. PMID: 16100408. https://doi.org/10.1007/978-1-62703-435-7_20 • Gammal RS, Dunnenberger HM, Caudle KE, et al. Pharmacogenomics Education and Clinical Practice Guidelines. In Pharmacogenomics. Elsevier; 2019:395-414. https://doi.org/10.1016/B978-0-12-812626-4.00015-2 • Goodman CW, Brett AS. Race and pharmacogenomics—personalized medicine or misguided practice? JAMA. 2021;325(7):625-626. PMID: 33492362. https://doi.org/10.1001/jama.2020.25473
11	• National Health and Medical Research Council, Australian Government. Discussing Direct-to-Consumer Genetic DNA Testing with Patients. A Short Guide for Health Professionals. Available from: https://www.nhmrc.gov.au/sites/default/files/documents/attachments/Discussing%20direct-to-consumer-genetic-dna-testing.pdf • Trent R. Direct-to-consumer DNA testing and the GP. Aust Fam Physician. 2014;43(7):436-439. PMID: 25006602. Available from: http://www.racgp.org.au/afp/2014/july/dna-testing/ • Horton R, Crawford G, Freeman L, Fenwick A, Wright CF, Lucassen A. Direct-to-consumer genetic testing. BMJ. 2019;367:l5688. PMID: 31619392. https://doi.org/10.1136/bmj.l5688 • Food & Drug Administration, United States Government. Direct-to-Consumer Tests. Available from: https://www.fda.gov/medical-devices/vitro-diagnostics/direct-consumer-tests • Canadian Medical Association. Direct-to-Consumer Genetic Testing. Available from: https://www.cma.ca/sites/default/files/2018-11/cma-policy-direct-to-consumer-genetic-testing-pd17-05-e.pdf • Ministry of Health, Singapore. Revised Code of Practice on the Standards for the Provision of Clinical Genetic/Genomic Testing Services and Clinical Laboratory Genetic/Genomic Testing Services. 2021. Available from: https://www.moh.gov.sg/docs/librariesprovider5/licensing-terms-and-conditions/moh-cir-no-234_2020_16dec20_genetic-testing.pdf • Clinical Genetic Service, Department of Health, Hong Kong SAR Government. Direct-to-Consumer Genetic Tests. Available from: https://www.dh.gov.hk/english/main/main_cgs/files/FHB_DTCGT_Web_ENG.pdf

12	• OECD Guidelines on Human Biobanks and Genetic Research Databases: Available from: http://www.oecd.org/science/emerging-tech/44054609.pdf • Campbell LD, Astrin JJ, DeSouza Y, et al. The 2018 Revision of the ISBER Best Practices: summary of changes and the editorial team's development process. Biopreserv Biobank. 2018;16(1):3-6. PMID: 29393664. https://doi.org/10.1089/bio.2018.0001 • Swiss Biobanking Platform. General Consent for Research—Best Practices. Available from: https://swissbiobanking.ch/website/wp-content/uploads/2018/04/SBP_Best-Practices-General_Consent_for_Research.pdf • Global Alliance for Genomics and Health. Regulatory & Ethics Toolkit. Available from: https://www.ga4gh.org/genomic-data-toolkit/regulatory-ethics-toolkit/

Annex A

In the case of ABC v St. George's Healthcare NHS Trust and others,[1] the Claimant's father (XX) was subject to a hospital order as a result of being found guilty of manslaughter of the Claimant's mother. XX was detained in a hospital run by the 2nd Defendant. The defendants were three NHS Trusts which were involved in the care and treatment of XX. While being detained, the Claimant started attending therapy sessions arranged by the 2nd Defendant because XX had killed the Claimant's mother. The sessions were intended to offer a therapeutic benefit to not only XX but also the Claimant herself. After the Claimant and XX started attending these sessions, XX was diagnosed with a genetic disorder called Huntington's disease which is an incurable neurodegenerative disorder which causes mobility, cognitive and psychiatric problems. There was a risk that the Claimant had inherited the gene for this disease but unfortunately, XX refused to give consent to the defendants to disclose such information to the Claimant. A child of someone with Huntington's disease has a 50% chance of developing the condition. The Claimant was pregnant at the time and it was only after she gave birth that she was found to have inherited the gene for the disease.

The Claimant brought a negligence claim against all the defendants alleging that they had failed to discharge their duty to warn her that she was at risk of inheriting the Huntington's disease gene, so that she would have the opportunity to consider whether or not to terminate her pregnancy. The High Court dismissed the negligence claim against all three defendants. As regards the 1st and 3rd Defendants, the Court held that they did not owe the Claimant a duty of care. In the case of the 2nd Defendant, however, the Court held the 2nd Defendant did owe a duty of care to the Claimant on the special circumstances of the case. The duty recognised was a duty to "balance her interest in being informed of her genetic risk against her father's interest in preserving confidentiality in relation to his diagnosis and the public interest in maintaining medical confidentiality generally". Although a duty of care existed in the case of the 2nd Defendant, the Court held that there was no breach of such duty because the 2nd Defendant's decision (i.e. not to disclose XX's genetic information to the Claimant in the circumstances of the case) was supported by a responsible body of medical opinion.

[1] ABC v St George's Healthcare NHS Trust [2020] EWHC 455 (QB)

Annex B

1. Conventional Down syndrome (trisomy 21) screening programme

First trimester (11-13 weeks) combined test: nuchal translucency + maternal serum markers (PAPP-A and free beta-hCG); detection rate 90%, screen positive rate 5%

Second trimester (16-19 weeks) biochemical test: maternal serum markers (alpha-fetoprotein, free beta-hCG, oestriol, and inhibin-A); detection rate 80%, screen positive rate 5%

Risks for trisomy 18 and 13 can also be estimated.

Those pregnant women with a high risk of T21, such as >1 in 250 will be offered a diagnostic invasive test (CVS or amniocentesis).

Down syndrome screening has been the focus in prenatal diagnosis and well known among pregnant women, but fetal Down syndrome only accounts for a small proportion of fetal chromosomal or genetic and structural abnormalities identified during Down syndrome screening, together with the 18-22 weeks fetal anomaly ultrasound examination.

A universal Down syndrome screening programme has been started in the public sector (HA) since 2010, providing a reasonable safety net to our local pregnant women.

However, the conventional Down syndrome screening programme is superseded by non-invasive prenatal testing (NIPT) on maternal plasma cell-free fetal DNA:

- Screen positive rate of 5% means 5% of screened pregnant women will be given a high-risk result, together with anxiety and the invasive procedure-related risk of miscarriage (although only 0.1%-0.2% for either CVS or amniocentesis from recent literature)
- The 90% detection rate of fetal Down syndrome is much less than the >99% detection rate by NIPT with a false positive rate <0.1%

2. Non-invasive prenatal testing

Fetal (placental) DNA accounts for 10%-15% of the total maternal plasma DNA. It is cleared from the maternal plasma hours after delivery of the baby. The use of maternal plasma cell-free fetal DNA for NIPT was pioneered by Prof. Dennis Lo from Hong Kong.[1,2]

[1] Lo YM, Lun FM, Chan KC, et al. Digital PCR for the molecular detection of fetal chromosomal aneuploidy. Proc Natl Acad Sci U S A. 2007;104(32):13116-13121. PMID: 17664418. https://doi.org/10.1073/pnas.0705765104

[2] Chiu RW, Akolekar R, Zheng YW, et al. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. BMJ. 2011;342:c7401. PMID: 21224326. http://doi.org/10.1136/bmj.c7401

A fetus with Down syndrome releases an extra amount of chromosome 21 DNA into the maternal plasma which can be detected by massively parallel sequencing (MPS). The detection rate is >99% and the false-positive rate (FPR) is <0.1%.[3]

Different laboratories use different MPS approaches, which may lead to different ranges of findings that need to be understood by end users:

- Whole-genome sequencing
- Targeted sequencing
- Single nucleotide polymorphism–based sequencing

Non-sequencing based NIPT is also available.

For the subgroup of pregnant women identified as high-risk by conventional Down syndrome screening test (either 1st or 2nd trimester, FPR 5%), second-tier NIPT (FPR <0.1%) can help avoid unnecessary invasive tests due to false-positive test results. Second-tier NIPT has been available in the private sector in Hong Kong since 2011 and in the public sector (HA) since December 2019 (where the initial phase reports on T21,T18, and T13 risk only).

Note that second-tier NIPT will not improve the detection rate of fetal Down syndrome (still 90%) unless the risk estimate cut-off value of the screening programme is adjusted, such as extend the offer of second-tier NIPT for the intermediate-risk group (e.g., 1 in 250 to 1 in 1200) or increasing the screen positive rate (or FPR) of the conventional Down syndrome screening test from say 5% to 15%-20%.

About 60% of women with high-risk conventional Down syndrome screening test will choose second-tier NIPT in order to avoid an invasive test (CVS or amniocentesis). In contrast, the detection rate and FPR of first-tier NIPT for low-risk pregnant women is as good as second-tier NIPT for high-risk women.

It is estimated that >50% of pregnant women in Hong Kong would have first-tier NIPT which is currently only available from the private sector.

In addition to detecting T21 (best performance), NIPT can also detect T18, T13, fetal sex, sex chromosomal abnormalities (e.g., monosomy X), rare autosomal trisomies (e.g., T9, T16, T22), and microdeletions (e.g., DiGeorge or 22q11.2 deletion syndrome, Cri-du-chat syndrome 5p-) and microduplications.

First-tier NIPT can replace the conventional Down syndrome screening test while the importance of ultrasonography should not be ignored. Early ultrasound examination allows proper dating and determination of the number of pregnancy, allow the detection of major structural fetal abnormalities such as anencephaly, holoprosencephaly, cystic hygroma, fetal hydrops, gastroschisis, megacystis,

[3] Chiu RW, Chan KC, Gao Y, et al. Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma. Proc Natl Acad Sci U S A. 2008;105(51):20458-20463. PMID: 19073917. https://doi.org/10.1073/pnas.0810641105

body stalk anomaly, major spine abnormalities and missing limbs. The ultrasound measurement of nuchal translucency at 11-13 weeks may yield additional information. Among fetuses with nuchal translucency >3.5 mm, 3.7% (>99th percentile) have pathogenic genomic imbalance which cannot be detected by NIPT. Therefore, direct CVS/ amniocentesis with chromosomal microarray (CMA) testing should be offered to this subgroup.[4]

NIPT can provide additional reassurance for ultrasound soft markers for common aneuploidies (T21, T18, T13) e.g., hypoplastic nasal bone, short long bones, choroid plexus cysts, intracardiac echogenic foci, tricuspid regurgitation, echogenic bowels, pyelectasis, single umbilical artery, in order to avoid an unnecessary invasive test.

However, nowadays when new ultrasound variants such as right-sided aortic arch, persistent left superior vena cava, persistent right umbilical vein, aberrant right subclavian artery, absent ductus venosus are detected, NIPT will not be able to cover the potential association between these new ultrasound variants with various microdeletions and microduplications, amniocentesis for CMA testing should be offered as an option.

Other special considerations for NIPT (vital knowledge to be acquired by end-users for pre-test and post-test counselling):

- Fetal DNA fraction (>4%) as a quality control parameter; that's why NIPT should not be performed <9 to 10 weeks gestation
- Failure to provide a reportable result (1%-2%)
- Confined placental mosaicism (CPM) – mosaic chromosomal abnormalities found in placenta but not in the fetus. Note that NIPT assesses the circulating DNA of placental origin in maternal plasma, which could give rise to false-positive NIPT results
- Abnormal maternal plasma DNA profiles (e.g., mosaic sex chromosomal aneuploidies, autoimmune diseases, cancer) will lead to false-positive NIPT results
- Multiple pregnancies – NIPT is feasible for twin pregnancies but need to inform the laboratory beforehand. Note that circulating DNA from a vanishing twin can affect the interpretation of the NIPT result for the surviving twin
- Most importantly, any abnormal NIPT result should be confirmed by CVS or amniocentesis before any decision for termination of pregnancy. Even for T21 with NIPT detection rate >99% and false positive rate (FPR) <0.1%, the positive predictive value (PPV) is only 50%

3. Invasive prenatal testing

Rapid aneuploidy test by QF-PCR

Rapid aneuploidy test by QF-PCR enables detection of common autosomal trisomies including

[4] Leung TY, Au Yeung KC, Leung WC, et al. Prenatal diagnosis of pathogenic genomic imbalance in fetuses with increased nuchal translucency but normal karyotyping using chromosomal microarray. Hong Kong Med J. 2019;25 Suppl 5(4):30-32

Table A1. Comparison of cytogenomic technologies					
	Traditional karyotyping	**Rapid aneuploidy test (PCR)**	**CMA**	**WES**	**WGS**
Sample	Cultured cells	DNA*	DNA*	DNA*	DNA*
Resolution	5-10 Mb	Targeted aneuploidy (21, 18, 13, X, Y)	≤100 kb	1 bp (base pair)	1 bp
Turnaround time	2-3 weeks	1-2 days	1 week	3-4 weeks	4 weeks
Laboratory	Labour intensive	High throughput	High throughput	Medium throughput	Medium throughput
Detect balanced rearrangement	Yes	No	No	No	No**
Detect triploidies	Yes	Yes	No Yes (SNP array)	No	No

Abbreviations: CMA = chromosomal microarray testing; PCR = polymerase chain reaction; SNP = single nucleotide polymorphism; WES = whole-exome sequencing; WGS = whole-genome sequencing.

* DNA extracted from either uncultured or cultured cells

** Potentially possible if increasing the sequencing read depth and/or special library preparation such as mate-pair sequencing

T21, 18,13, or sex chromosome aneuploidy including monosomy X. Around 30% of invasive tests performed for dysmorphic fetuses showed abnormal results which may lead to a decision to terminate the pregnancy.[5]

Traditional karyotyping

Traditional karyotyping could detect pathogenic unbalanced chromosomal rearrangements in another 5% of invasive tests performed for dysmorphic fetuses, and to supplement abnormal or inconclusive PCR and abnormal CMA test results.[5]

Chromosomal microarray–molecular karyotyping

Traditional karyotyping with its major drawback of low resolution (5-10 Mb) has been replaced by CMA testing in detecting CNV (copy number variations) with resolution as high as 50 kb (microdeletions and microduplications) after rapid aneuploidy exclusion for T21, T18, T13, sex chromosome aneuploidies by PCR. This prenatal diagnostic approach was found to be cost-effective in the local setting.[6,7]

[5] Best S, Wou K, Vora N, et al. Promises, pitfalls and practicalities of prenatal whole exome sequencing. Prenat Diagn. 2018;38(1):10-19. PMID: 28654730. https://doi.org/10.1002/pd.5102

[6] Chan KYK, Au SLK, Kan ASY. Development of cytogenomics for prenatal diagnosis: from chromosomes to single nucleotides: a review. Hong Kong J Gynaecol Obstet Midwifery 2019; 19(2):114-122.

[7] Chung CYC, Chan KYK, Hui PW, et al. Cost-effectiveness analysis of chromosomal microarray as primary test for prenatal diagnosis in Hong Kong. BMC Pregnancy Childbirth. 2020;20(1):109. PMID: 32059709. https://doi.org/10.1186/s12884-020-2772-y

Different laboratory platforms for CMA testing

- Oligonucleotide array comparative genomic hybridisation (aCGH)
- Single nucleotide polymorphism array
- Combination of the two

Available in the private sector, also available in the public sector (HA) from June 2019.

Unlike the application in postnatal settings such as paediatric examinations, interpretation of CMA test results in prenatal diagnosis can be difficult because of limited phenotype information from prenatal ultrasound examination.

Nevertheless, despite the rapid ongoing development in G&G in prenatal diagnosis, prenatal ultrasound (+ fetal MRI in selected cases) maintains a pivotal role in the new algorithms, being the link between the various tests inside the new algorithms.

The CNVs detected by CMA testing are usually categorised into three main types in the prenatal setting according to various publicly available databases (such as DECIPHER, ISCA, DGV, or CHOP) and published in-house datasets:

- No clinically significant CNV detected i.e., normal molecular karyotyping
- Clinically significant or pathogenic CNV – a chromosome imbalance harbouring genes or overlapping with a known syndrome (e.g., OMIM database). Parental studies (Trios) are necessary to further investigate whether the CNV is familial or de novo
- CNV of uncertain (or unknown) clinical significance – a chromosome imbalance which has not been reported in public or in-house databases or literature. Parental studies (Trios) are also recommended. This subgroup has created difficult scenarios in counselling and even medicolegal consequences

The higher the resolution of the CMA testing platform, the higher the resulting incidence of CNVs (both clinically significant or pathogenic CNVs and CNVs of uncertain (or unknown) clinical significance).

It is most important to include the above information into the pre-test counselling and consent before the invasive test or CMA test is performed, as well as for post-test counselling.

The detailed information for the CNV identified including literature search should be provided by the corresponding laboratory. Direct discussion on a case-by-case basis with the laboratory colleagues together with a clinical geneticist would be most useful.

Compared with traditional karyotyping, CMA testing can identify an additional 2% clinically significant CNV when the indications are advanced maternal age or positive Down syndrome screening result, and as high as an additional 6% when ultrasound fetal abnormalities are present.[8]

[8] Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med. 2012;367(23):2175-2184. PMID: 23215555. https://doi.org/10.1056/NEJMoa1203382

Low-pass genome sequencing (alternative to chromosomal microarray testing)

The performance of CNV analysis in low-pass genome sequencing can detect an additional 1.7% of clinically significant CNVs when compared with CMA testing.[9] For a comparable turnaround time, low-pass genome sequencing has a higher throughput, significant reduction in the technical repeat rate (0.5%), lower cost per sample, and smaller amount of DNA (50 ng) required for the assay. However, there is a slightly higher incidence of variants of uncertain significance (+0.6%).

Whole-exome sequencing and whole-genome sequencing

Both whole-exome sequencing (WES), which involves sequencing all the protein-coding genes in the genome, and whole-genome sequencing (WGS), in which the entire genome is sequenced, have already become part of the new algorithms of prenatal diagnosis.

Broad sequencing approach using WES and WGS versus targeted gene panels or single-gene testing based could be based on the clinical presentation.

WES can provide 85% of information from WGS (apparently making WES more cost-effective).

A cohort study on prenatal exome sequencing analysis (fetus-parental trios) in fetal structural anomalies detected by ultrasonography (PAGE) found that[10]:

- After excluding aneuploidies (by PCR) and CNVs (by CMA testing), a diagnostic genetic variant was identified in 8·5% of 610 fetuses assessed and an additional 3.9% fetuses had a variant of uncertain significance that had potential clinical usefulness
- Diagnostic genetic variants were present in 15.4% of 143 fetuses with multisystem anomalies, 11.1% of 81 fetuses with cardiac anomalies, and 15.4% of 65 fetuses with skeletal anomalies
- WES facilitates genetic diagnosis of fetal structural anomalies, which enables more accurate predictions of fetal prognosis and risk of recurrence in future pregnancies. However, the overall detection of diagnostic genetic variants in a prospectively ascertained cohort with a broad range of fetal structural anomalies is lower than that suggested by previous smaller-scale studies of fewer phenotypes

Another study in the United States examined 234 consecutive fetuses using a similar approach and demonstrated diagnostic variant in overall 10.3% of fetuses. Fetuses with multi-organ system

[9] Wang H, Dong Z, Zhang R, et al. Low-pass genome sequencing versus chromosomal microarray analysis: implementation in prenatal diagnosis. Genet Med. 2020;22(3):500-510. PMID: 31447483. https://doi.org/10.1038/s41436-019-0634-7

[10] Lord J, McMullan DJ, Eberhardt RY, et al. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. Lancet. 2019;393(10173):747-757. PMID: 30712880. https://doi.org/10.1016/S0140-6736(18)31940-8

involvement, skeletal, lymphatic or effusion, central nervous system, and renal anomalies had the highest diagnostic yield (from 16%-24%).[11]

The American College of Medical Genetics has published the latest statement for the use of fetal exome sequencing in prenatal diagnosis on pre-test and post-test considerations, fetal and parental incidental findings, targeted family testing as well as reporting and data re-analysis.[12]

WGS might fill the diagnosis gap for the >50% undetected genetic or genomic abnormalities from CVS or amniocentesis, for which CMA testing or low-pass genome sequencing could not provide the answers. with the main advantage of providing information on intronic changes, structural variants, and breakpoint that WES and CMA testing may not be able to provide.

Joint Position Statement from ISPD, SMFM and PQF on the use of genome-wide sequencing for fetal diagnosis (2018)[13]:

> *A current pregnancy with a fetus with a single major anomaly or with multiple organ system anomalies that are suggestive of a possible genetic etiology, but no genetic diagnosis was found after CMA; following a multidisciplinary review & consensus, in which there is a fetus with a multiple anomaly 'pattern' that strongly suggests a single gene disorder.*

[11] Petrovski S, Aggarwal V, Giordano JL, et al. Whole-exome sequencing in the evaluation of fetal structural anomalies: a prospective cohort study. Lancet. 2019;393(10173):758-767. PMID: 30712878. https://doi.org/10.1016/S0140-6736(18)32042-7

[12] Monaghan KG, Leach NT, Pekarek D, et al; ACMG Professional Practice and Guidelines Committee. The use of fetal exome sequencing in prenatal diagnosis: a points to consider document of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(4):675-680. PMID: 31911674. https://doi.org/10.1038/s41436-019-0731-7

[13] International Society for Prenatal Diagnosis; Society for Maternal and Fetal Medicine; Perinatal Quality Foundation. Joint Position Statement from the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) on the use of genome-wide sequencing for fetal diagnosis. Prenat Diagn. 2018;38(1):6-9. PMID: 29315690. https://doi.org/10.1002/pd.5195

Annex C

1. Basic ethical principles of pre-implantation genetic testing

Pre-implantation genetic testing must be conducted in accordance with the following basic ethical principles[1]:

- human life in all its forms warrants respect and special moral consideration;
- the welfare of the child is of paramount importance;
- personal autonomy, individual liberty and human integrity must be duly safeguarded;
- basic community values such as responsible parenthood, parental love and the family should be recognised; and
- use of resources must be based on the principles of care, equality, justice and accountability and a reasonable balance must be sought between individual and collective interests to protect vulnerable parties from harm or exploitation.

2. Indications of pre-implantation genetic testing

Pre-implantation genetic testing (PGT) should only be used for the detection of serious genetic conditions or abnormalities that significantly affect the health of an individual who might be born.[1]

Due attention should be given to the differing views in society about the seriousness of genetic conditions or abnormalities, and the potential development in medicine that may shift the boundaries defining the seriousness of genetic conditions or abnormalities.

PGT should not be used with the intention to enable parents to select a baby with some desired social, physical or psychological characteristics.

3. Counselling before pre-implantation genetic testing

Pre-implantation genetic testing should proceed only after discussion between the patient couple and the clinical team, which should consist of two doctors, one of whom should have proper training in clinical genetics or genetic counselling.[1,2]

The clinical team, having discussed with the patient couple and determined the condition to be sufficiently serious to warrant PGT, should follow the detailed reporting requirements as specified under the Human Reproductive Technology Ordinance, its regulations, and the legal notices and government notices issued from time to time by the Council on Human Reproductive Technology.[1]

---

[1] Council on Human Reproductive Technology. Code of Practice on Reproductive Technology and Embryo Research. Council on Human Reproductive Technology: Hong Kong, 2013. Available from: https://www.chrt.org.hk/english/service/files/code.pdf

[2] Harton G, Braude P, Lashwood A, et al. ESHRE PGD consortium best practice guidelines for organization of a PGD centre for PGD/preimplantation genetic screening. Hum Reprod. 2011;26(1):14-24. PMID: 20966460. https://doi.org/10.1093/humrep/deq229

It is also necessary for the clinical team to provide the patient couple with appropriate counselling and adequate information on the other reproductive options such as prenatal test, gamete donation, adoption, acceptance of risk, or to not conceive.

Genetic counselling should include a review of the genetic risk, availability and reliability of molecular or cytogenetic diagnosis and risk of misdiagnosis, the severity and variability of the condition and the limitations of genotype–phenotype correlation.

The counselling provided should be non-directive, enabling the patients to reach their own informed decision for treatment.

The chance of spontaneous conception while awaiting treatment, and the need for contraception, should be explained.

The possibility of having no embryos for transfer if all the embryos are genetically or embryologically unsuitable should be explained.

4. Other pre-testing considerations

The decision to provide treatment to specific couples should be discussed among a team of dedicated scientist and clinicians, including expertise in clinical genetics, molecular genetics or cytogenetics, clinical IVF specialists and embryologists, regarding the indication, technical feasibility and reliability of the test to be offered.[2]

The couple should be evaluated to exclude physical, psychological and social problems which would incur an unacceptable risk of medical or psychosocial complications during ovarian stimulation, oocyte retrieval or pregnancy, or may put the child born at risk of harm.

5. Pre-implantation genetic testing for monogenic defects

Pre-implantation genetic testing for monogenic defects (PGT-M) can be offered if the pathogenic genotype can be attributed to a single gene and there is sufficient family history to identify a haplotype of other microsatellite markers linked to the germline mutation.[2]

PGT-M should not be provided to couples where the genetic diagnosis or mode of inheritance is uncertain, or if the recurrence risk is low (e.g., <10%).

For autosomal recessive and X-linked recessive disorders, the transfer of carrier embryos should be discussed.

For X-linked diseases, the pros and cons of sexing (with subsequent transfer of females assumed to be unaffected) versus specific mutation detection can be discussed. The option of not revealing the embryo sexing should be discussed.

Exclusion testing can be considered for late-onset disorders, to avoid pre-symptomatic testing of the partner with a family history of the disease. However, PGT with non-disclosure of the direct test results to the couple is not recommended.

Prenatal diagnosis of an established pregnancy following PGT-M, or neonatal diagnosis by cord blood sampling, is generally recommended.

6. Pre-implantation genetic testing for mitochondrial disorders

PGT for mitochondrial disorders caused by mitochondrial DNA (mtDNA) mutations allows selection for embryos with an mtDNA mutation load below the threshold of clinical expression, providing an effective risk reduction strategy for heteroplasmic mtDNA mutations.

Embryos with a mutation load of less than 18% have a likelihood of more than 95% of being unaffected, irrespective of the mtDNA mutation and can be considered for transfer.

PGT is not indicated in the case of homoplasmy. However, it is acceptable to carry out sexing to reduce the clinical risk of the disease in the case of homoplasmic mutations showing sex-dependent penetrance. It should be noted that PGT in both instances is a risk reduction strategy, it does not eliminate it.

In cases where the causative mutation of the mitochondrial disease is encoded by nuclear DNA, testing is the same as for other monogenic disorders.

7. Human leukocyte antigen typing in conjunction with pre-implantation genetic testing

In appropriate situations, PGT can be used together with human leukocyte antigen (HLA) typing to identify embryos that match a living sibling with a genetic condition, with the intention that when the matched embryo develops into a baby, blood can be harvested from its umbilical cord to provide stem cells for transplantation to the sibling.

The service provider should follow the application and reporting procedures in accordance with the Code of Practice of the Council on Human Reproductive Technology.[1]

Appropriate pre-treatment and follow-up counselling should be provided to the couple to whom treatment is intended to be provided. All other treatment options should be covered in the counselling. The counsellor should clearly explain to the couple that if the child is wanted for their own worth, the treatment might be justifiable. If the child is conceived solely for the purpose of creating a donor of stem cells for an existing sibling, the child's dignity is violated, and the treatment is not justifiable.

Implication counselling should include the following:

- the motivation and level of understanding of the parents (in particular women undergoing IVF treatment) seeking to have an additional child;
- the condition of the existing child such as the degree of suffering associated with the condition of the affected child, the prognosis for the affected child in relation to all treatment options available;
- the possible consequences of the child to be born (such as the risks associated with embryo biopsy for the child to be born, the likely long term emotional and psychological implications for the child to be born, whether the treatment of the affected child is likely to require intrusive surgery for the child to be born);

- the family circumstances of the people seeking treatment such as the perception of the family on the consequences of the unsuccessful outcome, the issue which might arise when the birth of a child does not resolve the genetic condition of the existing child; and
- the extent of social support available.

8. Pre-implantation genetic testing for aneuploidy

The primary purpose of PGT for aneuploidy (PGT-A) is to improve IVF outcomes by reducing the impact of abnormal chromosome copy number (aneuploidy) in an embryo cohort.[2,3]

The following indications of PGT-A have been reported with an aim to improve the chance of pregnancy or live birth:

- Advanced maternal age
- Repeated implantation failure after multiple transfers of embryos
- Recurrent miscarriages
- Severe male factor infertility

There is currently inadequate evidence from randomised trials to elucidate the role and cost-effectiveness of PGT-A for these indications or as a universal screening for all IVF patients. Further large randomised studies, and possibly in combination with other genomic or metabolomic approaches, to enhance embryo screening and selection are needed to guide practice in future.

Cleavage-stage embryos or blastocysts can be tested for aneuploidy using array CGH, single nucleotide polymorphism arrays and next-generation sequencing (NGS) based methods. Use of these molecular techniques for 24-chromosome testing should be currently favoured to fluorescence *in situ* hybridisation (FISH) for the purpose of PGT-A. Using higher resolution NGS methods, segmental mosaicism can also be detected whereby small chromosome deletions or duplications (typically >10 Mb) are identifiable.

After IVF, fertilisation and embryo development should be reviewed, and this should be discussed with the patient about whether PGT-A should proceed.

9. Embryo biopsy

Since its first demonstration in 2005, trophectoderm biopsy on the Day 5-6 blastocyst is increasingly being adopted in favour of blastomere biopsy on Day 3 embryos.[4] Ideally, 5-10 cells are biopsied to give subsequent robust and balanced amplification. Trophectoderm biopsy is safer than blastomere biopsy in that embryo development

[3] Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. Fertil Steril. 2018;109(3):429-436. PMID: 29566854. https://doi.org/10.1016/j.fertnstert.2018.01.002

[4] McArthur SJ, Leigh D, Marshall JT, et al. Pregnancies and live births after trophectoderm biopsy and preimplantation genetic testing of human blastocysts. Fertil Steril. 2005;84(6):1628-1636. PMID: 16359956. https://doi.org/10.1016/j.fertnstert.2005.05.063

and implantation potential is negatively affected by blastomere biopsy but not trophectoderm biopsy.[5]

10. Transfer of mosaic embryos

Chromosome mosaicism refers to the presence, in a single embryo or blastocyst, of two or more cell lines with different chromosome sets. This occurs commonly in embryos at all stages of pre-implantation development. The incidence of reported mosaicism using NGS methods is typically between 5%-10%. The possibility of mosaic results and any potential risks in the event of transfer and implantation should be explained during pre-treatment counselling.[6]

Compared to euploid transfers, transfer of mosaic or mosaic segmental embryos may be associated with reduced implantation and higher miscarriage rates. Poorer outcomes were achieved with the transfer of complex mosaics where more than one chromosome was involved.

Transfer of mosaic embryos should be considered only after appropriate counselling of the patient and alternatives have been discussed, such as the option of initiating a further PGT-A cycle. Patients should be counselled that any biopsy piece analysed as mosaic may not accurately reflect the surrounding trophectoderm or the rest of the embryo. Prenatal diagnosis of the established pregnancy after any mosaic embryo transfer is highly recommended. To date, an evidence-based classification system for risk stratification of mosaic embryos is lacking. Clinicians should refer to the most updated guideline on their transferral from respective professional societies.

11. Newer developments

Detection and analysis of circulating cell-free embryonic DNA present in the blastocoel fluid or spent culture media has been studied as a non-invasive approach for PGT. This may have the potential to replace invasive embryo or blastocyst biopsy in future.[7]

---

[5] Scott RT Jr, Upham KM, Forman EJ, et al. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. Fertil Steril. 2013;100(3):624-630. PMID: 23773313. https://doi.org/10.1016/j.fertnstert.2013.04.039

[6] Cram DS, Leigh D, Handyside A, et al. PGDIS Position Statement on the Transfer of Mosaic Embryos 2019. Reprod Biomed Online. 2019;39 Suppl 1:e1-e4. PMID: 31421710. https://doi.org/10.1016/j.rbmo.2019.06.012

[7] Farra C, Choucair F, Awwad J. Non-invasive pre-implantation genetic testing of human embryos: an emerging concept. Hum Reprod. 2018;33(12):2162-2167. PMID: 30357338. https://doi.org/10.1093/humrep/dey314