The Royal College of Pathologists
Pathology: the science behind the cure

Part 1 examination

Genetics: First Paper

Tuesday 24 September 2019

Candidates must answer FOUR questions ONLY

Time allowed: Three hours

1. For the molecular diagnosis of many genetic disorders there is a move towards using whole genome sequencing (WGS) rather than exome sequencing or large NGS gene panels.

   What additional insights has WGS provided for the aetiology of genetic disease in rare disease and cancer? Discuss the advantages of the different testing strategies that can be used for WGS.

2. After a successful business case, you have been provided funding to implement a new test into your laboratory. Using a defined example of a test, describe the quality management process that you would undertake to bring this test into a routine clinical service.

3. Abnormal fetal structural anomalies which are detected by ultrasonography have a range of genetic causes. Discuss how whole genome analysis for prenatally diagnosed structural congenital anomalies has evolved over the years. In particular, discuss

   (i) the advantages and disadvantages of the differing technologies

   (ii) the challenges we currently face to ensure appropriate reporting of genetic findings within a prenatal setting

4. Chromosome 11 is gene rich. Cytogenetic and molecular aberrations involving this chromosome have been observed in both constitutional and acquired disorders.

   Give examples of 2 constitutional and 2 acquired disorders involving chromosome 11. For each of your choices, briefly describe the disorder and the genetic mechanism/s involved.

5. Discuss the significance and implications of germline findings in the context of molecular genetic testing in somatic cancer. Using examples, consider both laboratory and clinical aspects.

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Genetics: First Paper

Tuesday 25 September 2018

Candidates must answer FOUR questions

Time allowed: 3 hours

1. How might you evaluate the cost effectiveness of whole exome or genome analysis in clinical practice? Why might you want to do undertake such an evaluation and what would be the challenges?
2. Describe the structure, organisation and function of the human genome and use examples to illustrate how this has influenced analysis for the purpose of genetic diagnosis.
3. Describe with the use of examples the advantages and disadvantages of different test strategies available for dosage/quantitative analysis (of the genome) for the investigation of clinical genetic disorders.
4. You have been asked to write best practice guidance for genetic analysis of ONE of the areas listed below. Provide an outline of the topics to cover and any specific issues to address.

   Cystic fibrosis
   Chromosome 11p15 imprinting disorders
   Fragile X syndrome
   Haemaglobinopathies
5. You have been asked by your local Haematologists to give a presentation on current haemato-oncology genetic testing and what will impact on service provision over the next 5 years. Include current and future testing strategies, including the techniques, their advantages and disadvantages.

   OR

   You have been asked by your local neonatologists to give a presentation on current genetic testing and what will impact on service provision over the next 5 years. Include current and future testing options, including the techniques, their advantages and disadvantages.

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Part 1 Written Examination

Genetics

First Paper

Tuesday 26th September 2017

Candidates must answer FOUR questions

Time allowed: 3 hours

1. Compare and contrast with examples the following FOUR approaches for genetic diagnosis of inherited rare genetic disorders:

   (i) whole genome sequencing
   (ii) whole exome sequencing
   (iii) clinical exome sequencing
   (iv) next generation sequencing of a targeted panel of genes.

   Include the advantages and disadvantages of each approach.

   What is the expected impact on service provision for genetic diagnosis of inherited rare genetic disorders over the next 5 years?

2. Describe what is meant by epigenetic inheritance. Explain its relevance, with examples, to our understanding of human genetic disorders. Include analytical approaches used for studying such genetic disorders.

3. Analysis of tumours for mismatch repair deficiency detects cases with absent mismatch repair protein expression and/or microsatellite instability but no evidence of a germline mutation. Describe the possible explanations for this, how these may be investigated and the clinical relevance.

4. Describe with examples the ways in which the utility of a genetic diagnostic test may be assessed. What processes may be implemented to evaluate test performance and use.

5. Analysis of cell-free DNA from maternal blood is widely used to provide genetic information in pregnancies. It is proposed that NIPT should be implemented as an additional test within the current Down syndrome screening pathway for high risk mothers. Write a patient information leaflet for NIPT for this purpose. In addition explain why NIPT is a screening and not a diagnostic test.