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

Part 1 examination

Molecular pathology: First paper

Autumn 2020

Candidates must answer FOUR questions ONLY

Time allowed: Three hours

Question 1

Describe how you would implement either a new solid cancer or haematology NGS panel into your laboratory. Ensure you briefly describe all stages of the process, including relevant examples and criteria.

Question 2

Describe the clinical utility and biological basis of either DPYD testing in colorectal cancer or TPMT testing in childhood acute lymphoblastic leukaemia. What do you think the main barriers are and what factors should you consider when establishing Pharmacogenomics testing services?

Question 3

NTRK gene fusions have become the essential testing targets for pan-cancer types and their detection is required to identify patients who may benefit from tyrosine kinase (TRK) inhibitor therapy.

a) Describe molecular characteristics of NTRK gene fusions, their incidence in different tumour types and TRK inhibitor therapy.

b) Discuss techniques that can be used to detect NTRK fusions in clinical samples and the optimal approach to facilitate the identification of patients with NTRK fusions in routine practice.

Question 4

The detection of minimal residual detection (MRD) has become important in blood cancers. Discuss the factors around the techniques, sensitivity and impact of MRD using a specific target loci for a given disease and using more than one disease as examples.

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Question 5

As oncology molecular pathology practice is expanding rapidly due to increasing number of targeted therapies, the use of large DNA panels for tumour somatic sequencing is becoming standard of care practice. Some of the pathogenic variants detected in a subset of genes may be difficult to confirm as either somatic or germline variants.

a) Explain the difference between “on-tumour” and “off-tumour” associations with the tumour type tested.

b) Provide examples of genes that are recommended to be included for a germline focused analysis when running somatic cancer panels. Why are these genes chosen?

c) Given the significant percentage of true germline findings with large DNA somatic panels, what steps are important to consider for the implementation of a standard approach to germline incidental findings into routine practice?

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FRCPath Molecular Pathology Part 1 Autumn 2021 Paper 1

Candidates must answer FOUR questions ONLY
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Question 1

PDL1 immunohistochemistry, tumour mutation burden and microsatellite instability are all tests used to select cancer patients for immune check point inhibitors.

a) Describe each test: PDL1 IHC, TMB and MSI in the context of oncology tumour testing. (21 marks)

b) Expand on the pros and cons for each method with regards to sample types, reporting and limitations. (6 marks)

Question 2

The introduction of NGS and WGS into routine clinical practice has the potential to identify both germline variants and clinically relevant incidental findings (also known as secondary findings or opportunistic findings).

a) Outline the different groups and pertinent genes found within the WHO 2017 classification of myeloid neoplasms with germline disposition category, the clinical features associated with each and which clinical indications might alert to a suspicion of a germline predisposition. (12 marks)

b) What are the considerations which should be taken into account (pros and cons) with looking for and reporting incidental findings unrelated to the clinical indication under investigation? (8 marks)

Question 3

Variant classification, interpretation & reporting is the cornerstone of the genomics medicine service. Classification requires systematic, objective evaluation of variants called using an NGS workflow. Clinical reports should be clear about the logic behind classification of the variant and pathogenicity evaluations must be reproducible and evidence based.

a) Describe the key steps involved in analysing variants for clinical reporting. (8 marks)

b) Discuss the process for classification of sequence variants and how a robust framework for variant classification and interpretation of pathogenicity is generated. (12 marks)

Question 4

Chromosomal aberrations play a pivotal role in the diagnosis and prognostication of most haematological neoplasms.

a) Describe the differences between common chromosomal translocation constructs and their pathogenic mechanism using specific examples of recurrent changes in both acute leukaemias and lymphomas. (6 marks)
b) Discuss techniques available for the detection of both types of structural variants including NGS-based approaches, indicating advantages and disadvantages for each approach. (14 marks)

Question 5

Business planning is essential for all NHS organisations to ensure the functioning of all services

a) Define and outline the purpose of a business continuity plan. (5 marks)

b) Describe a business continuity plan in response to the emergence of a pandemic severe respiratory virus, identifying all key phases. (10 marks)

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FRCPath Molecular Pathology Part 1 Autumn 2022 Paper 1

Candidates must answer FOUR questions ONLY
Time allowed: Three hours

Question 1

1. Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the Western world.

a) Describe the laboratory work-up in a case referred to your laboratory with a suspected diagnosis of B-CLL. Which molecular markers need to be assessed and what is their implication for prognosis and treatment choice? (60% of marks).

b) What are the different testing strategies/methodologies available for the assessment of the molecular aberrations in question (include the advantages and disadvantages for each approach)? (40% of marks).

Question 2

2. The WHO classification of the central nervous system tumours integrates the molecular classification of these tumours and provides a “histo-molecular” approach to allow for a more precise diagnosis.

a) What are the molecular abnormalities molecular pathologists should report and integrate in the diagnosis and classification of gliomas? Please list these abnormalities and briefly state how they affect the diagnosis and prognosis of these tumours. (70% of marks)

b) The new WHO classification, the 5th edition, has been published in 2021. Please provide a brief update on the changes recommended and list any new molecular targets that have been introduced in the classification in the “gliomas”. (30% of marks)

Question 3

3. Change control is an essential and systematic approach to managing change in laboratories.

Describe the steps that would be required to implement a new method or piece of equipment, considering all the different aspects of a service that will be covered. Illustrate your answer with examples.

Question 4

4. In recent years Whole Genome Sequencing (WGS) has become a widely used tool in genomic analysis of oncology samples.

a) Briefly describe the steps involved in generating the data used in paired tumour:germline WGS analysis. (30% of marks)

b) Describe the advantage and disadvantages of WGS versus traditional, targeted methods of variant analysis. (70% of marks)

Question 5

5. The gastrointestinal stromal tumours (GIST) are now recognised as malignant tumours, according to the latest 2020 World Health Organization (WHO) classification of soft tissue sarcomas (STS) and bone sarcoma, regardless of size, site of origin and mitotic index.

a) Describe the molecular abnormalities associated with GIST and paediatric GIST, and briefly describe the syndromes which are linked to paediatric GIST. (60% of marks)

b) Some GISTs are known to show no response to treatment (primary resistance) while others respond to treatment for a limited time when resistance emerges (secondary resistance). What are the mechanisms of primary and secondary resistance? (20% of marks)

c) Multiple clinical and pre-clinical studies have demonstrated a role for immunotherapy in soft tissue sarcomas. Briefly describe some of these potential immunotherapeutic strategies. (20% of marks)