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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Tuesday 24 September 2019

Candidates must answer FOUR questions ONLY

Time allowed: Three hours

1. Your pathology department has been designated as an Essential Services Laboratory/Local Genetics Laboratory (spoke laboratory) and all specialised testing (approximately 50% of the current workload) will be carried out at the Core/Hub laboratory (Genomics Laboratory Hub (GLH)) which is situated at the University Teaching hospital in a city 50 miles distant. Discuss the factors to consider in order to continue providing an excellent service for the local population.

2. Core quality metrics for pre-analytical and next generation sequencing analysis (NGS) stages are crucial to ensure the quality of the data for final variant interpretation. Briefly describe the methods used and quality metrics at the pre-analytical stage, raw data and alignment stages and explain why they are important.

3. Describe the clinical 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 pharmacogenetic testing services?

4. Genetic/genomic testing is routinely performed to identify and stratify cancer patients for treatment. In the context of the clinical setting in the UK, for either NSCLC or ALL:

   Describe

   a) which patients and what type of tumours should be tested;

   b) which genes should be tested, their common alterations and diagnostic, prognostic and therapeutic implications, and acceptable methods for testing; Please also discuss new and emerging genetic or genomic biomarkers for potential targeted or stratified treatment, why and how to test them.

5. One of the biggest advances in oncology is the emergence of immune checkpoint inhibitors that are currently used to treat various tumour types. Recent clinical trial data looked at and evaluated several biomarkers to select patients eligible for immune check point inhibitor therapy.

   a) What biomarkers do you have knowledge of and how are they used clinically to select patients for immune check point inhibitors?

   b) Discuss benefits and disadvantages of each of these biomarkers for a molecular pathology service.

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Part 1 examination

Molecular Pathology: First paper

Tuesday 25 September 2018

Candidates must answer FOUR questions ONLY

Time allowed: Three hours

1. Review the range of methodologies that are available to clinical laboratories for the detection of oncogene fusions. For each method given, describe the underlying principle of detection, provide an example of a clinical application where the method would be suitable and highlight the relative strengths and weaknesses of each methodology.

2. NGS gene panel testing is increasingly used for routine clinical work-up of myeloid neoplasms. You have been tasked with the development of an NGS panel to detect small somatic variants (SNV and indel) for diagnosis, prognosis and treatment of broad myeloid neoplasm including acute myeloid leukaemia, myelodysplastic syndrome and myeloproliferative neoplasmas. Describe your rationale behind the design of the panel. How would you plan to validate and implement the assay?

3. The interpretation of somatic variants to determine clinical actionability plays an increasingly critical role in the delivery of molecular pathology services. Describe the key considerations required in undertaking somatic variant interpretation and the principles, tools and resources that are used.

4. Recent clinical trial data suggests that tumour mutation burden (TMB) is a predictive biomarker of response to immune check point inhibitors irrespective of the PD-L1 expression status as tested by immunohistochemistry. Discuss potential issues around the implementation of TMB in clinical practice and challenges in the context of non-small cell lung carcinoma molecular testing.

5. There are several clinical applications of ctDNA as liquid biopsy: prediction of prognosis, early diagnosis, monitoring of therapies and therapeutic stratification on progressive disease. These are all of high clinical interest but there are challenges regarding the specificity and sensitivity of the current assays employed to deliver these tests. Please discuss pre-analytical issues affecting the ctDNA samples in patients with advanced lung cancer progressing on EGFR TKIs and address this in the context of technologies used for ctDNA testing with particular emphasis on the benefits and limitations for delivery in clinical practice.