

PART A

TIME: 15 minutes

- Look at the four texts, A-D, in the separate Text Booklet.
- For each question, 1-20, look through the texts, A-D, to find the relevant information.
- Write your answers on the spaces provided in this Question Paper.
- Answer all the questions within the 15-minute time limit.
- Your answers should be correctly spelt.

Text A

DNA Sequencing Technologies

Past efforts at sequencing genes were painstaking, time consuming, and labor intensive, such as when Gilbert and Maxam reported the sequence of 24 base pairs using a method known as wandering-spot analysis. Thankfully, this situation began to change during the mid-1970s, when researcher Frederick Sanger developed several faster, more efficient techniques to sequence DNA. Indeed, Sanger's work in this area was so groundbreaking that it led to his receipt of the Nobel Prize in 1980.

Over the next several decades, technical advances automated, dramatically sped up, and further refined the Sanger sequencing process. Also called the chain-termination or dideoxy method, Sanger sequencing involves using a purified DNA polymerase enzyme to synthesize DNA chains of varying lengths. The key feature of the Sanger method reaction mixture is the inclusion of dideoxynucleotide triphosphates (ddNTPs). These chain-terminating dideoxynucleotides lack the 3' hydroxyl (OH) group needed to form the phosphodiester bond between one nucleotide and the next during DNA strand elongation. Thus, when a dideoxynucleotide is incorporated into the growing strand, it inhibits further strand extension. The result of many of these reactions is a number of DNA fragments of varying length. These fragments are then separated by size using gel or capillary tube electrophoresis. This procedure is sensitive enough to distinguish DNA fragments that differ in size by only a single nucleotide.

Text B

In the modern era, whole world has experienced tremendous boost in the field of molecular diagnosis by use of DNA sequencing technology. The human genome contains more than 3 billion base pairs that contain all the information about our health and well-being. The first whole genome sequence of human was published successfully before decades. It was very expensive and paid billion dollars to complete. The cost paid for, was much more worthy as it was providing the first fundamental understanding of the structure and biology of human genome and relation with diseases. Initially, Next Generation Sequencing technology was generated huge amount data of human variant later it was proved that this NGS technology is much more effective in the diagnosis human diseases by use of bioinformatic tools to select pathogenic variants. In present days, sequencing costs have dramatically declined and therefore it is now routinely using for diagnosis of many rare inherited diseases including hematology and blood disorder. Genome Wide sequence analysis is already playing an important role in the hematology field. This new sequencing technology is going to solve the challenges that researchers in the field of hematology are going forward.

Text C

Nowadays researchers are making disease-specific targeted NGS panel, which is helping more quickly and precise diagnosis of specific disease in the field of hematology. Keeping in mind the growing research in the area of molecular diagnosis, how genome-wide analysis has unlocked new avenues of research, diagnosis, and therapy for benign hematologic disorders. Recent advances in molecular technologies, mainly next-generation sequencing, inspire us to apply these technologies as a first-line approach for the identification of potential mutations and to determine the novel causative genes in patients with blood disorders. Researcher have started preparing targeted NGS panels for diagnosis of hematologic malignancies, Red cell congenital hemolytic anemia for diagnosis of all rare cause of hemolytic anemia which covers around 70-80 genes associated with hemoglobinopathies, which will cover gene related alpha (HBA1/2) and beta (HBB) globin gene locus analysis, HBD sequence analysis, gene related to RBC membrane protein disorders, RBC enzymopathies genes, congenital dyserythropoietic anemia (CDA) and the inherited bone marrow failure syndromes (IBMFS) are a group of rare genetic blood disorders in which there is usually some form of aplastic anemia associated with a family history of the similar disorder.

Text D

A panel of genes already identified by WES and association studies as responsible of CHA or modulators of the clinical course of the disease is already analyzed by mass sequencing methodology (NGS) including between 60-70 genes. Modifiers, related to sickle-cell formation, vascular adhesion to endothelium, tolerance to hemolysis and acute severe events, and the analysis of the RBC glycolytic enzymes are included. The variants obtained were studied by mapping in the GRCh38/hg38 version of the human reference genome. For the prioritization of variants, filters related to pathogenicity and population frequency according to the SnpEff v4.1 and Mutation Taster programs generally used for analysis. Some are previously used clinical databases of hemolytic anemia are Human Gene Mutation Database version Professional, ClinVar, Red Cell Membrane Database Mutations Database, Leiden Open Variation Database \pm PKLR. The allele frequency is generally assessed in the population (1000G and ExAC) and in the local database. Finally, most of the researchers generally used the 'in silico' predictions of pathogenicity and Sorting Intolerant from Tolerant (SIFT), PolyPhen-2, Mutation Taster, and Mutation Assessor

Questions 1-7

For each question, 1-7, decide which text (A, B, C or D) the information comes from. You may use any letter more than once.

In which text can you find information about;

1 Modern technologies of DNA sequencing

Answer _____

2 Determination of the precise sequence of nucleotides in a sample of DNA.

Answer _____

3 A source of inspiration

Answer _____

4 Early DNA sequencing technologies

Answer _____

5 Cost-effective solutions in sequencing

Answer _____

6 Clinical databases

Answer _____

7 Detection of the disease-causing genes

Answer _____

Questions 8-14

Answer each of the questions, 8-14, with a word or short phrase from one of the texts. Each answer may include words, numbers or both.

8 What is generally analyzed in a large population?

Answer _____

9 What is the term which defines a method in which an electric field pulls molecules across a gel substrate or hairlike capillary fiber?

Answer _____

10 Which term may mean "performed on the computer or via computer simulation?"

Answer _____

11 What is known to make up the backbone of the strands of nucleic acid?

Answer _____

12 What is characterized by failure of the bone marrow to produce blood?

Answer _____

13 Which method of sequencing usually comprises use of polymerase enzyme for the purpose of building different types of chains of varied lengths?

Answer _____

14 Which sequencing technology is regarded to be more result-oriented?

Answer _____

Questions 15-20

Complete each of the sentences, 15-20, with a word or short phrase from one of the texts. Each answer may include words, numbers or both.

15 Red blood cell _____ affect genes encoding red blood cell enzymes..

16 Today, researchers are busy developed targeted NGS panels which can effectively be used for the purpose of diagnosis of_____.

17 The variants obtained were studied by mapping in the _____ of the human reference genome.

18 The key feature of the Sanger method reaction mixture is the inclusion of_____.

19 _____ analysis is effective and can solve challenges which researchers grappling with

20 NGS is considered the _____ for detection of the disease.

PART B

In this part of the test, there are six short extracts relating to the work of health professionals. For questions 1-6, choose the answer (A, B or C) which you think fits best according to the text.

1 What does the report indicate?

- A There has been a recent increase in the incidence of myositis worldwide.
- B Infection of the skeletal muscles.
- C Most common in tropical areas but can also occur in temperate zones.

Primary infection of muscle

Primary infection of muscle is usually regarded as a tropical disease, and is rare although becoming more common in temperate climates. A review of the 230 cases of primary obturator myositis which have been reported, shows that 82% were in children under 18 years of age. The median age was 9.5 years (3 to 46), with a male:female ratio of approximately 3:2. The median duration of symptoms prior to presentation was three days, and the most common symptoms were fever, hip or thigh pain, and inability to fully bear weight. In 41% there was a history of recent trauma to the hip, such as a fall or strenuous exercise. Local trauma is a recognised initiating factor for pyomyositis and is documented in between 21% and 66% of cases.

2 According to the notice given, what is correct?

- A Treatment cost has not gone down yet.
- B CAR-T is considered more effective.
- C After chemotherapy, CAR-T is more reliable.

Food and Drug Administration (FDA) Notice

In the year 2017, Food and Drug Administration (FDA) announced the first approval of a CAR-T cell therapy for kids and young adults with B-cell ALL. This approval was much celebrated and brought new hope for a more specific and efficient therapy for ALL. This result has come through many years of research and is expected to improve the quality of treatment of patients. It is worth noting that in addition to side effects, the high cost of treatment is still an obstacle and the side effects. Although there are challenges to be overcome as in any innovative research, CAR-T cell therapy seems to be the most promising therapeutic tool against cancer, including ALL, since chemotherapy introduction in the 1940s.

3 Huntington's disease;

A may result in the death of brain cells.

B may result in loss of intelligence.

C may result in involuntary movements.

Huntington's disease (HD)

Huntington's disease (HD) is a genetic neurodegenerative disorder that results in chorea, balance and gait impairments, changes in behavior and declines in cognition. Cognitive decline occurs early in the disease course, occasionally preceding chorea and motor impairment, and continues to progress throughout the disease process. Cognitive deficits include difficulty with executive function including trouble with planning and organizing, problems with working, visual and verbal memory, and impaired concentration. While gait dysfunction is typically thought to arise primarily from damage to the motor circuitry of the basal ganglia, studies in elderly populations and other neurologic populations indicate that gait dysfunction may also be related to changes in cognitive function.

4 What is correct about Hypertension?

A For subjects with normal or subnormal hypertension, it can prevent or delay hypertension.

B BP can be well tackled with the use of BP specific medicine.

C Right changes in lifestyle can curtail down BP values more effectively than various other medical therapies.

Hypertension - Prevention or Treatment

Adequate changes in lifestyle are the cornerstone for the prevention and treatment of hypertension. Although rapid medical initiation is necessary for the patients in a high level of risk, lifestyle changes are fundamental for the therapy. According to the previous report, lowering effects for stable blood pressure can be equivalent to monotherapy of medicine. Contrarily, the weak point would be the low level of compliance or adherence associated with necessary time for adequate action. Adequate changes in lifestyle would be effective for some group of subjects. For grade 1 hypertensive patients, it can prevent or delay medical therapy. Moreover, for hypertensive patients continuing on medical therapy, it can contribute to BP reduction of blood pressure and allow reduction of the number and doses of antihypertensive agents. Appropriate changes in lifestyle would decrease other cardiovascular risk factors and improve several clinical conditions.

5 What does the table indicate?

A Major significant differences were observed in 24-h, daytime and nighttime SBP or DBP when using the conventional or custom-made pillow.

B No significant differences were observed in 24-h, daytime and nighttime SBP or DBP when using the conventional or custom-made pillow.

C There are significant changes in Systolic Blood Pressure and Diastolic Blood Pressure.

Comparison of 24-h blood pressure monitoring between conventional and custom-made pillows:

	Conventional pillow	Custom-made pillow	P value
24-h SBP, mmHg	111 ± 8	111 ± 7	ns
24-h DBP, mmHg	70 ± 5	69 ± 6	ns
Daytime SBP, mmHg	115 ± 9	117 ± 7	ns
Daytime DBP, mmHg	74 ± 6	73 ± 6	ns
Nighttime SBP, mmHg	101 ± 6	100 ± 7	ns
Nighttime DBP, mmHg	59 ± 5	58 ± 7	ns
Nocturnal BP fall, mmHg	11 ± 5	14 ± 4	<0.05

6 What does the report indicate?

A Jugular venous engorgement and diffuse pulmonary rales were not found.

B The electrocardiogram (ECG) showed broad R waves.

C The patient was dyspnoeic with SaO₂ 74%.

Events

Initial presentation at the emergency room

- 3-h chest pain
- Respiratory failure and the need for advanced airway support
- Electrocardiogram with broad R waves, 4 mm ST-segment downsloping in right precordial leads, right bundle branch block (RBBB), and ST-segment elevation in posterior leads
- Coronary angiography with total thrombotic occlusion in the proximal segment of the circumflex artery
- Bare metal stent was placed
- The patient developed cardiogenic shock and intra-aortic balloon pump was placed; norepinephrine, vasopressin, and dobutamine were administered with clinical improvement

48 h post-arrival

- Electrocardiogram with disturbance of repolarization only attributable to RBBB
- The patient developed acute renal failure and haemodialysis was initiated

After 5 days.

- During a haemodialysis session, he developed sustained ventricular tachycardia with degeneration in asystole
- CPR was initiated, there wasn't a return of spontaneous circulation
- Patient decease

PART C

In this part of the test, there are two texts about different aspects of healthcare. For questions 7-22, choose the answer (A, B, C or D) which you think fits best according to the text.

Text 1: Renal Artery Stenosis

Renal artery stenosis (narrowing) is a decrease in the diameter of the renal arteries. The resulting restriction of blood flow to the kidneys may lead to impaired kidney function (renal failure) and high blood pressure (hypertension), referred to as renovascular hypertension, or RVHT ("reno" for kidney and "vascular" for blood vessel).

Renovascular hypertension is as likely to occur with bilateral stenosis (when arteries to both kidneys are narrowed) as with unilateral stenosis (when the artery to one kidney is narrowed). The decreased blood flow to the kidneys impairs renal function. Renal artery stenosis may cause renal failure in some patients. There is no predictable relationship between renal failure and renal artery stenosis. Some patients have very severe bilateral stenosis and normal renal function. Most cases of renal failure are related to diabetes, hypertension, glomerular sclerosis, contrast nephropathy, drug toxicity and other causes.

The majority of renal artery stenosis is caused by atherosclerosis (hardening and narrowing of blood vessel wall from the inside) similar to the process that occurs in blood vessels in the heart and other parts of the body. Risk factors for atherosclerosis include high cholesterol levels, high blood pressure, age, cigarette smoking, diabetes etc. Less common causes of renal artery stenosis are fibromuscular dysplasia of the vessels (narrowing of the vessel due to internal thickening of the blood vessel wall), arteritis (inflammation of the blood vessel), or dissection (tearing and division of the blood vessel wall).

Narrowing of the kidney arteries is more common in individuals 50 years of age and older. It is estimated that some degree of narrowing (greater than 50%) is found in about 18% of adults between 65-75 years of age and 42% of those older than 75 years of age. This may be due to the fact that atherosclerosis is more common in this age group. In younger patients, the narrowing of the renal artery is usually due to the thickening of the

artery (fibromuscular dysplasia) and it is more common in women than in men. It is estimated that renal artery stenosis accounts for approximately 1% of mild to moderate cases of high blood pressure. It may be responsible for more than 10% of cases of severely elevated or difficult to treat high blood pressure (hypertension).

In general, renal artery stenosis is not associated with any obvious or specific symptoms. Suspicious signs for renal artery stenosis include high blood pressure that responds poorly to treatment; severe high blood pressure that develops prior to age 30 or greater than age 50; an incidental finding (discovered through routine tests or tests performed for another condition) of one small kidney compared to a normal sized one on the other side. Typically, unilateral (one-sided) renal artery stenosis may be related to high blood pressure whereas bilateral (two-sided) renal artery stenosis is more often related to diminished kidney function.

Several tests exist to detect any evidence of renal artery stenosis, which can be divided into imaging tests and functional tests. The imaging tests provide a picture of the blood vessel and its anatomy and reveal the degree of narrowing. The functional tests provide information about whether the narrowing is significant enough to cause the high blood pressure or kidney dysfunction. Each of these tests has advantages and disadvantages.

In bilateral (both-sided) and unilateral (one-sided) renal artery stenosis associated with high blood pressure, controlling the blood pressure with usual blood pressure medications is the first and the safest treatment. ACE inhibitors or ARB medications with or without a diuretic (water pill) may be tried first. In some patients, this approach may be associated with worsening of their kidney function. Therefore, kidney function needs to be followed closely and if worsening of kidney function is evident, these medications may need to be stopped. It is worth noting that if renal artery stenosis is found incidentally when performing a test for another disease and there is no evidence of kidney dysfunction or high blood pressure then no treatment may be necessary. Sometimes even significant stenosis may not be associated with high blood pressure or kidney dysfunction. In these situations, periodic monitoring of blood pressure and kidney function may be advised.

Text 1: Questions 7-14

7 Renovascular hypertension is likely to occur with;

- A Bilateral stenosis.
- B Unilateral stenosis.
- C Both bilateral and unilateral stenosis.
- D When arteries to one or both kidneys are narrowed.

8 Which one of these statements is true, according to paragraph 1?

- A The increase or decrease in blood flow leads to improper functioning of the kidneys
- B Renal failure and renal artery stenosis are closely connected to each other
- C A patient may have normal renal function even if there is higher bilateral stenosis
- D In some cases, bilateral stenosis may affect renal functions too.

9 Renal Artery Stenosis is caused by;

- A Hardening of the blood vessel wall from inside.
- B Hardening of the blood vessels similar to that of the blood vessels in the heart.
- C Narrowing and hardening of the walls like that of blood vessels in the heart. D
- Hardening and narrowing of the blood vessels from inside.

10 Thickening of the arteries is more common among;

- A Men
- B Women
- C Children
- D All of the above

11 According to paragraph 4, which one of the following statements is true?

A There are no specific symptoms of the renal artery stenosis.

B Higher BP which develops before the age of 30 or after the age of 50 can become the cause of the renal artery stenosis.

C Untreatable high BP can be the cause of the renal artery stenosis.

D Differences in sizes of the kidneys can be a major cause of the renal artery stenosis.

12 Functional tests provide;

A A clear picture of the blood vessels and functions.

B A clear idea of whether narrowing is significant to cause high BP or kidney dysfunction.

C Anatomy of blood vessels.

D A clear idea of the thickening of the blood vessels.

13 The best possible treatment for renal artery stenosis is;

A Controlling the blood pressure.

B Using ARB medications for the quality functioning of the kidneys.

C Improving the function of the kidney through proper medications.

D None

14 Renal artery stenosis is closely associated with;

A Kidney dysfunction.

B High blood pressure.

C Low blood pressure.

Text 2: Hematochezia

Rectal bleeding (hematochezia) is used to describe the presence of blood with a bowel movement. That blood, whether it fills the toilet bowl, or is a streak on the toilet paper when wiping, or just a few drops in the toilet bowl, is not a normal finding and should not be ignored. The source of bleeding can be anywhere in the digestive tract, from the nose and mouth to the rectum and anus. The color can range from bright red to maroon to black or any shade in between, depending on how much the blood has been exposed to the digestive juices. Anytime there is blood within the gastrointestinal system, it will eventually be excreted in stool (feces, bowel movement, BM). The color of the stool will depend upon the amount of blood, the source of the bleeding and how quickly the stool moves through the digestive tract. Sometimes, the bleeding is too little to be seen by the naked eye but can be tested for by a healthcare professional.

Depending upon where and why the bleeding has taken place in the digestive tract, the stool consistency and color may vary greatly: the stool color may be bright red, maroon, dark red or black. The bleeding might be hidden, unseen to the naked eye, but able to be detected by a fecal occult blood test. There may be blood just in the bowel movement or there may be associated feces. If the feces are formed, the blood may be mixed in with the stool or it may just coat the surface. The stool may be well-formed or it may lose and diarrhea like. It may be normal in shape in size or it may become pencil thin. There may be associated with abdominal pain or the bleeding may be painless.

Hemorrhoids are the most common cause of blood in the stool. Blood vessels located in the walls of the rectum can swell, become inflamed and bleed. Hemorrhoids can be caused by straining at stool, diarrhea, pregnancy, obesity and prolonged sitting on the commode. All these factors increase the pressure within the hemorrhoidal vessels, causing them to swell. The bleeding is often associated with anal burning or itching. Bleeding can also occur because of an anal fissure, or a split in the skin of the anus. Hard constipated stool may cause the skin to split; other causes include pregnancy and anal intercourse. Anal fissures are also associated with other diseases including inflammatory

bowel disease (Crohn`s disease, ulcerative colitis), cancer and infections. Anal fissures tend to be very painful, even when sitting. The blood in the stool can also be due to swallowed blood from a nosebleed, dental work, or other mouth injuries that cause bleeding.

Rectal bleeding is often diagnosed by history. The health care professional may ask questions about the circumstances surrounding the rectal bleeding including the color, the amount of bleeding, any associated symptoms and past medical history. A variety of medications and food can mimic blood in the stool. Iron supplements and bismuth (Pepto-Bismol, Kaopectate) can turn stool black, as can beets and licorice. Red food coloring and beets can turn stool into a reddish hue. Patients who take blood thinners (anticoagulation medications) are more prone to rectal bleeding. Examples of blood thinners include warfarin (Coumadin), enoxaparin (Lovenox), aspirin and other antiplatelet drugs including clopidogrel (Plavix), prasugrel and rivaroxaban (Xarelto).

Physical examination is important to assess the patient`s stability. Vital signs are important and may include orthostatic vital signs, where the blood pressure and pulse rate are taken both lying and standing. In a patient with reduced blood volume, the blood pressure may fall, the pulse rate may rise, and the patient may become lightheaded and weak when standing. Palpation of the abdomen is performed to look for tender areas, masses or enlarged organs, especially the liver and spleen. Rectal examination is performed by inserting a finger into the rectum, with the purpose of feeling for a mass or other abnormality. The stool color and consistency may be examined when the finger is withdrawn. The anus also may be examined. Blood tests may be considered if there is concern about the amount of bleeding or other associated diseases. A complete blood count (CBC) measures the number of red blood cells, white blood cells and platelets. Blood clotting tests include PT (protime), INR (international normalized ratio) and PTT (partial thromboplastin time). Depending upon the situation, other tests may be ordered to measure electrolytes, and kidney and liver functions.

Most diseases which cause rectal bleeding are likely preventable, but it is not often possible. Hemorrhoids can be avoided with proper diet and hydration to prevent constipation and straining to pass stool, but normal pregnancy increases the risk of hemorrhoid formation as does the patient with an acute diarrheal illness. Avoiding

constipation also decreases the risk of diverticulosis, outpouchings in the lining of the colon, and the risk of a diverticular bleed but this may be a consequence of a Western diet. Alcohol abuse increases the risk of rectal bleeding in a variety of ways, from directly irritating the lining of the GI tract, to decreasing clotting capabilities of blood.

Text 2: Questions 15-22

15 Rectal bleeding describes;

- A Blood in the bowels.
- B Blood in the digestive tract.
- C Blood in the stools.
- D Blood in the rectum.

16 Paragraph 2 talks more about;

- A Which symptoms are associated with rectal bleeding.
- B Causes of the rectal bleeding.
- C Variations in the color of the stools.
- D None

17 "Blood in the stool can originate anywhere in the gastrointestinal tract."

- A False
- B True
- C Not given
- D Sometimes true and sometimes false

18 Hemorrhoids can be well defined by which one of the following?

- A Swelling of the rectal walls.
- B Inflammation and bleeding of the rectal walls.
- C Straining
- D All of the above

19 Causes of anal fissure may include;

- A Formation of the constipated stool
- B Inflammatory bowel disease
- C Cancer and infections
- D All of the above

20 According to paragraph 4, which of the following statements is true?

- A Blood thinners can cause rectal bleeding.
- B Blood thinners may sometimes cause rectal bleeding.
- C It is not fully established that rectal bleeding is the direct result of the use of blood thinners.
- D None

21 Which one of the following statements is not included in paragraph 5?

- A Physical examiners will always look for orthostatic vital signs.
- B A patient may have low blood pressure with a higher pulse rate.
- C Palpitations of the abdomen is performed to look for tender areas.
- D Rectal bleeding is identified through taking a stool sample.

22 Which one of these is the preferred blood clotting test?

A PT

B INR

C PTT

D Not given