National School of Healthcare Science

NHS England

IACC 2023 Case-based discussion (CBD) scenario

Specialty:	Genomics

CBD Scenario

CBD Scenario Title	DNA sequencing methods										
CBD Scenario Aim	To determine the trainee's technical knowledge of DNA sequencing methods and clinical applications										
CBD Focus (please provide the codes of the module(s) this scenario addresses)	*SLS 421*		*SLS 422*								
GSP Domains covered (enter X to indicate all that apply)	**GSP 1**	X	**GSP 2**	X	**GSP 3**		**GSP 4**	X	**GSP 5**		
CBD Scenario description	Using a genetic condition as an examples, describe a sequencing technology and how it works to a non-specialist healthcare professional. Describe a DNA sequencing technology which we may expect to see being used in genomics laboratories in the future.										
CBD Scenario model answer/ assessor guidance Detailed guidance that will be available for the assessors. Include guidance on what kinds of behaviours, actions, comments should secure a pass. What should the assessor expect to see? Assessors will be asked to plan questions in advance including links to trainee's IACC submission.	**Pass indicator** All of the following points discussed: - Provide example of a genetic condition which can be diagnosed through DNA sequencing - Ability to describe the technical details of the technique in a clear and concise manner. - Appropriate language for a healthcare professional with limited technical experience - Ability to demonstrate the advantages and limitations of the technique - - Good communication skills and demonstration of scientific knowledge										

	- Understanding of the future techniques and their uses within the laboratory Examples of sequencing techniques: • Sanger sequencing o Fluorescent chain termination o Single exon gene specific primers required, not high throughput, resolution of ~300-900bp but ~99% accurte o Capillary electrophoresis o Sequencing viewer software and comparison to reference sequence. • Exome sequencing / NGS o Target enrichment to capture regions of interest, complete exome (~20k genes) or clinical exome (~5000 genes), or panels of genes for NGS, clonal amplification of targets, o Sequencing by synthesis, usually Ilumina technology, on glass slide, short reads of ~100-150bp o reversible terminator bases and fluorescent detection and image capture o Short reads, accuracy much improved, base call accuracy of ~99% for most bases o Bioinformatics assembly and analysis of reads, may include CNV detection although not always robust o Panels often applied but may be open exome analysis o Bias in capture, CG rich regions underrepresented, or not covered, issues with pseudogenes o Introns not covered • Whole genome sequencing o Technology similar to WES more uniform coverage with no capture or PCR amplification steps o Detection of non-coding sequence variants o STR detection can be included in pipeline o CNV and structural variant calling o Panels often used but novel gene associations can be identified by additional analysis o Ethical considerations of incidental findings • For both WES/WGS: o Awareness of filtering options, e.g. trios in rare disease or comparison blood/ tumour o high throughput massively parallel sequencing o Data storage o Cost, although now more cost effective to do large panels or WGS compared to Sanger sequencing o Ethical considerations of incidental findings Future techniques • Single-molecule real-time sequencing (e.g. Pacific Biosciences)

	• Nanopore Sequencing
	  ○ Longer reads e.g., 30kb to 3Mb
	  ○ Less accurate compared to other technologies
	  ○ Moderate throughput but can be fast process, less sample preparation compared to other method
	  ○ Some technologies using small portable or handheld devices, potential for point of care testing
	  ○ Improved sequencing of repetitive regions and pseudogenes
	• The trainee may be aware of direct to consumer testing using sequencing technologies. May mention ethical implications and other limitations of DTC tests, e.g. interpretation, data sharing, privacy etc.
	
	Fail indicator
	- poor communication
	- language not appropriate for the audience
	- lack of understanding of the appropriate sequencing techniques for a disorder

Trainee instructions Please include any specific information to be provided to the trainee as part of the CBD scenario	N/A

Criteria being assessed by this CBD scenario

Aspect	Please indicate if this criterion is being assessed
1. Understands the clinical context of the scenario, including priority setting and testing strategies	
2. Understands scientific principles of scenario	X
3. Can discuss the relevant procedures involved in the scenario and associated health and safety issues	X
4. Understands and applies the appropriate test validation, IQC, EQA, relevant professional/clinical guidelines	
5. Understands and applies associated IT/bioinformatics and other appropriate resources	X

6. Is able to interpret and report patient results and provide appropriate clinical advice	
7. Can discuss the significance of patient results within the clinical context of the referral	X
8. Understands the ethical, legal and social implications of the scenario	
9. Is aware of the importance of audit and can use this tool effectively	
10. Output meets accepted laboratory/professional standards	X
11. Demonstrates awareness of the limits of responsibility and when to seek advice	
12. Consideration of patient/professionalism	
13. Overall ability to perform	