Clinical Sample Processing

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On this assay, the pathway of a glucose sample from a patient will be monitored throughout the laboratory, from reception to disposal.

Table of context

1. Sample reception

1.1 Sample arrival

Figure 0: Van used by the porters to transport samples.

The samples are transported to the laboratory by the porters, vans (see figure 0) or the pneumatic tube (red pod) system. This red pod system requires all specimens placed in the correct specimen bag and sealed appropriately. It is then loaded with the samples inside the red pod and sent to the laboratory. The following specimens should not be sent through this system:

- Blood gas samples
- Any specimens for cellular pathology
- Any CSF samples for xanthochromia
- Blood and blood products for transfusion
- Any samples with ice (no dry packs)
- Samples from suspected MERS coronavirus or VHF cases.

Any samples delivered from wards should be transported by a secondary leak proof carrier. In addition, laboratory vans have specific and strict scheduled times to ensure the specimens arrive to the laboratory in a safe and timely manner.

1.2 Booking in process and prioritisation

On March 27th 2023, a grey top sample arrived through the pneumatic system (see figure 1) from Accident and Emergency (A&E). The pod was opened, and the sample was taken out to be booked in. It came in a plastic bag (see figure 2) with a bag label to facilitate the booking process. This sample was scanned by a clinical support worker (see figure 3) working in the emergency bench and the patient details were displayed in Labcentre.

Figure 1: red pod with bags containing samples.

Figure 2: plastic bag containing the sample.

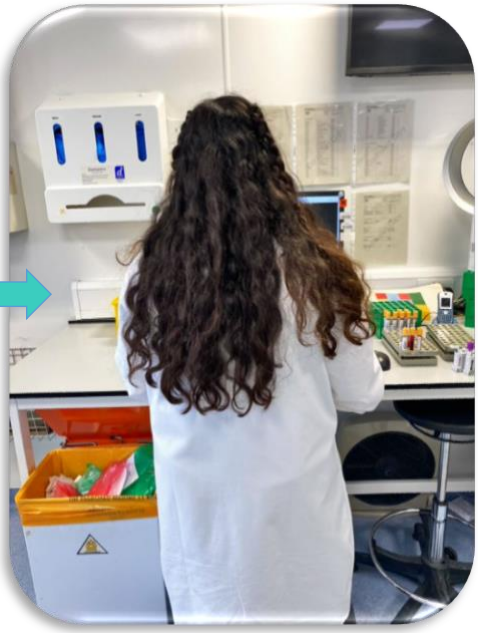


Figure 3: Clinical support worker booking in the sample.

As indicated by the grey top and the test requested on Labcentre (see figure 4), this was a glucose sample. The clinical details of the 71-year-old male patient showed fainting episodes and prostate cancer. It was an urgent test, so it was accelerated, and a cross was marked on the lid of the grey top sample. The laboratory has a turnround time of 1 hour for urgent samples.

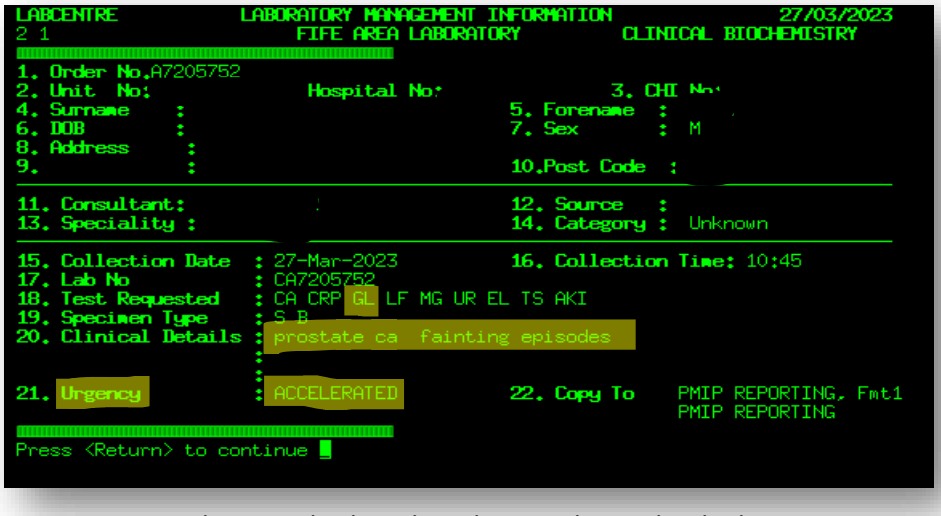


Figure 4: Labcentre display when the sample was booked in.

Before accepting the sample, it is essential to check the minimum data set on the sample label and Labcentre. The minimum data set needed to accept the booking of a patient sample requested via TrakCare or CyberLab electronic requesting system includes the following:

	Option A	Option B
Mandatory	Patients full name and date of birth	Patients name or identifier and CHI number
Recommended	Date and time, and source	Date and time, and source

Table 1: Minimum data set needed to accept the booking of a patient sample.

Once the minimum data set criteria and the required test have been checked, the sample is accepted into Labcentre. After the glucose sample is booked in, it is pre-centrifuged in central reception (see figure 5) and placed into the emergency rack in biochemistry (see figure 6), waiting to be loaded onto an analytical line.

Figure 5: Machine where the samples are centrifugated.

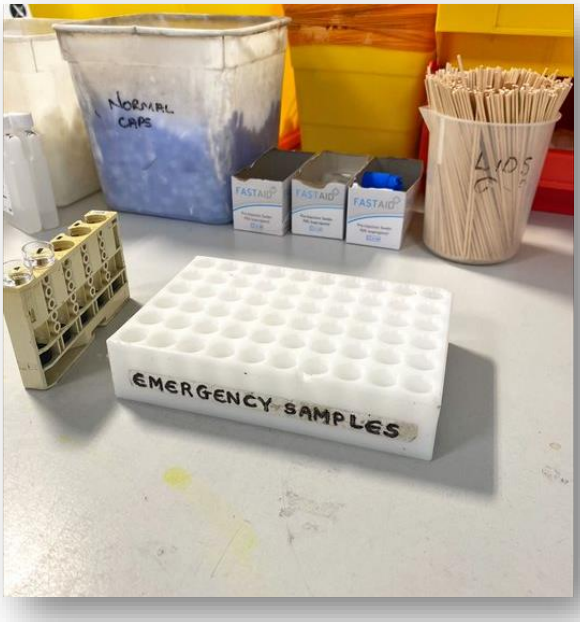


Figure 6: emergency samples track located in biochemistry.

The blood science south laboratory in Kirkcaldy provides a service 24 hours a day, 7 days a week. There are different timetables and shifts to make sure the workload is managed effectively and prioritizing urgent specimens (See figure 7). The urgent samples must be processed immediately, and the results should be available within 1 hour of receipt. All urgent requests should be reported to staff in reception so they can keep a record of the name, location, time of call, test and code needed in the urgent request recording sheet. From 8am to 8pm Monday to Friday, the requests will be received by specimen reception staff, outside those times the Duty BMS will receive the samples following procedure.

WEEK 5	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
Sendaways	FC am	FC am	FC am	FC am	FC am
Emergencies	LD	JG	LDEV	BM	SN
Urines/Fridges/Forms	BM	LDEV	JG	SN	LD
Track	AM	AM	AM	AM	AM
Duties/Stores	JG	LD	SN	LDEV	BM
Floater	LDEV	SN	BM	LD	JG
Lateshift	GP				

Figure 7: shift schedule showing the different tasks allocated to staff in specimen reception.

1.3 Health and safety

There is a contamination risk when handling infected samples if there is a specimen leaking on the receipt. The sample should be disposed in a yellow sharp safe box and any spillage cleaned. If the size of the spillage is bigger than the size of a hand, it would then be cleaned with the biohazard kit and discarded into a yellow sharp safe container with a yellow lid. If the spillage is small, it would be contained with folded paper or absorbent material. It would then be saturated with a Chemgene solution, cleaned with paper, and discarded into a to orange bag. If this were to be a precious sample (e.g. CSF) the duty Biochemist should be informed. In addition, the use of PPE such as disposable gloves, masks, safety glasses, and a plastic apron is key to preventing any health and safety issues.

Figure 8: Biohazard spill kit located in specimen reception.

2. Sample screening

2.1 Pre-examination

2.1.1 Method principle

The test performed on the glucose sample is UV test. It is an enzymatic reference method that involves hexokinase to catalyses glucose to glucose-6-phosphate by using ATP. The rate at which NADPH is generated during the reaction is directly proportional to the concentration of glucose, and this can be measured photometrical. Glucose-6-phosphate dehydrogenase oxidizes glucose-6-phosphate in the presence of NADP to gluconate-6-phosphate.

$$\text{Glucose} + \text{ATP} \xrightarrow{\text{HK}} \text{G-6-P} + \text{ADP} \qquad \text{G-6-P} + \text{NADP+} \xrightarrow{\text{G-6-PDH}} \text{gluconate-6-P} + \text{NADPH} + \text{H+}$$

Glucose monitoring is highly recommended when a patient is undergoing an androgen deprivation therapy (ADT) as a treatment for prostate cancer. ADT reduces the level of androgens in the body which help to slow down the growth of prostate cancer cells. These male hormones also play a role in monitoring blood sugar levels, so a decrease of androgens in blood can lead to developing diabetes. Routine glucose monitoring can detect abnormal changes in blood sugar levels and aid the medical team to adjust the treatment.

2.1.2 Equipment

The equipment consists of different analytical modules, and it is built with a core unit, a clinical photometric chemistry module (Cobas c702 module), an ISE unit (Cobas ISE module), a mid-volume throughput clinical photometric module (Cobas c 502) and the immunoassays modules (Cobas e 602 module). This line (see figure 9) is linked to the Cobas 8100 track system which deliver samples to the individual modules and a P501 fridge. The c8100 is connected to analytical and storage modules through multiple connecting modules. These components come together to form an integrated analyser system for NHS Fife.

Figure 9: Line B of Cobas 8000 modular analyser series.

2.1.3 Health and safety

The operation and maintenance of the Roche Cobas 8000 modular lines can present a risk during preparation of the substance as there can be a possible spill when changing reagents. It does not present a risk when substances are stored, when the analyser is performing the task and during

maintenance operations. However, the substances used have been identified as risk during transportation and disposal of the reagent. PPE and Spillage kits are provided to minimise those risks. In addition, it is essential that the staff handling these substances are aware of the corresponding SOPs containing detailed work instructions. The calibrator used for the glucose samples (see figure 16) is not a hazardous substance or mixture. The auxiliary reagents used by Cobas c702 present different hazard natures (See table 2)

Substance	Hazardous substance	Nature of hazard
COBAS 8000 Sample Cleaner 1 (12 X20ML) 0535299119	Sodium hydroxide	May be corrosive to metals. Causes severe skin burns and eye damage.
COBAS 8000 SAMPLE CLEANER 2 (12 X 20ML) 05968828190	R1 citric acid	Causes severe skin burns and eye damage
ECO-D 06544410190 (12 X 59ml)	Not a hazardous substance or mixture.	N/A
COBAS 8000 SYSCLEAN 11298500	Sodium hydroxide Sodium Hypochlorite	May be corrosive to metals. Causes severe skin burns and eye damage.
COBAS 8000 ACTIVATOR 04663632	Not a hazardous substance or mixture.	N/A

Table 2: COSHH assessment of the auxiliary reagents used by Cobas c702.

2.2 Examination process

2.2.1 Maintenance

Maintenance is key to provide high quality results. It does not matter the quality of the equipment or the samples if the analyser is not looked after. Maintenance prevents cross-contamination, enhances accuracy, saves unnecessary costs and waste, extends the lifespan of analyser, reduces downtime, and helps processing samples quickly. Maintenance procedures are required to be performed at different stated time intervals: daily, weekly, monthly, two-monthly, three-monthly, six-monthly, and as-required. The only maintenance required for Cobas c702 module was the daily maintenance and it was carried out in the morning following the SOP. The different tasks of the daily maintenance can be seen in the table below and figure 10.

	List of tasks
Daily	
	Run green rack and check masking
	Print reagent load list
	Load reagents and consumables
	Manual cleaning
	Clean ISE Drain Ports
	Clean sample and reagent probes
	Check cell rinse nozzles
	Clean PC/CC Pipes
	Press STOP
	Reset
	Drain MSB degasser (c702 only)
	Reagent registration (c702 only)
	Request Cal/QC & print loading list
	Daily pipe
	View photometer check
	Check parameter download
	Backup and delete data and print history

Table 3: a table listing the different tasks included in the daily maintenance of Cobas c702.

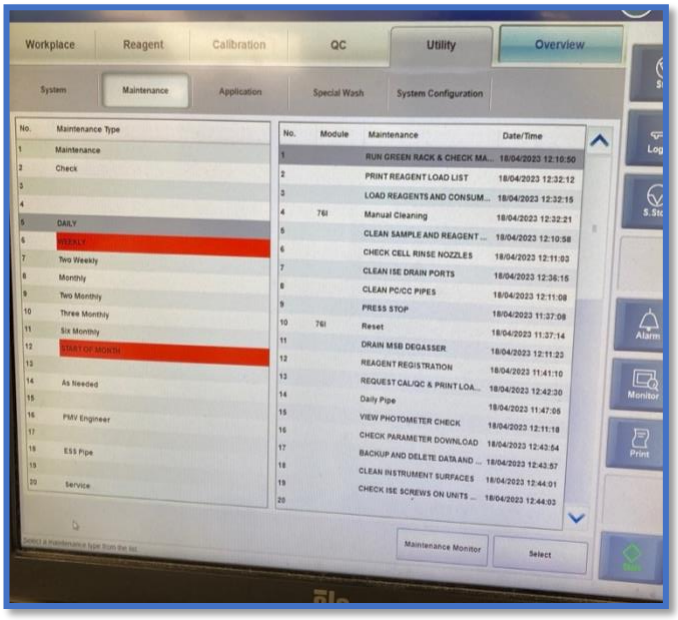


Figure 10: Cobas 8100 computer showing the daily maintenance list.

2.2.2 Reagents

During daily maintenance, the corresponding reagents get loaded according to the reagent load/unload list (see table 3). There are commercially prepared packaged reagents for individual chemistry channels and the one used to perform this test is GLUC3 (See figure 14). Further information about this reagent can be found in table 4.

Short code	Analyte	Analyser Module	Reagent Storage Temperature	Storage Location	Sample Type
GLUC3	Glucose	C702	2-8C	Cold room (See figures 11 and 12)	FLOX Plasma

Table 4: a table showing the characteristics of the reagent needed to perform the UV test on the glucose sample.

Figure 11: cold room entry

Figure 12: cold room

Figure 14: reagent stored in the cold room

2.2.3 CALIBRATION

Calibration is important to ensure accurate measurements which are fundamental to the safety, quality, and innovation of most of the services and products we rely on to process patient samples. It is one of the first processes needed to keep instrument accuracy as it configures the analyser to provide a high-quality result for a sample within an acceptable range. Calibration of an assay is needed after maintenance scheduled activities are done, an expired calibration, unacceptable quality control or a new lot number of reagent. It usually involves analysing the sample of one or more known values (calibrators, in this case CFAS) using the instrument and generating a calibration curve. There are different tests that require daily calibrations like glucose, urea, albumin, total protein, sodium, and bicarbonate. One of the maintenance tasks is to print a calibrator and QC loading list.

cobas 8000 Roche HITACHI

Calibrator Load List Operator ID: bmserv 27/03/2023 11:13

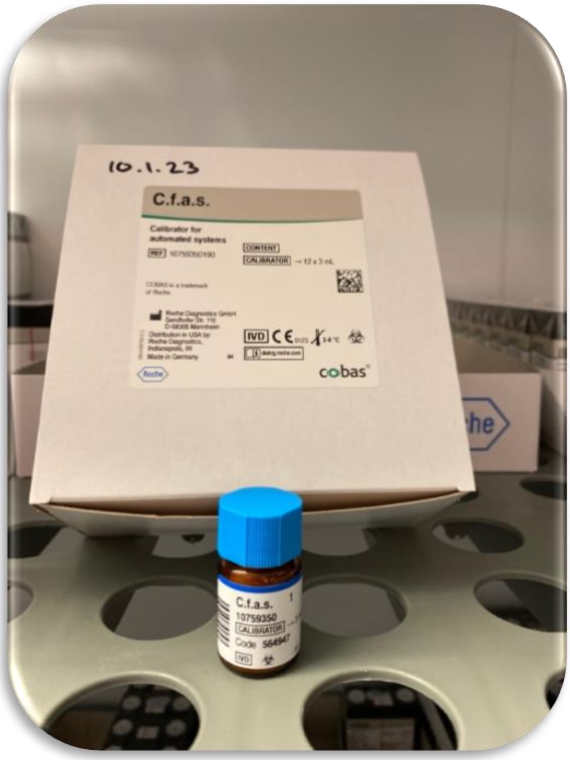
Module Specific Rack

Module	Rack Range
A1	-
A2	-
A3	-
ISE	-

Calibrators

Calibrator	Code	Lot ID	Rack No. - Pos.	Event	Volume
ACETA	00686	410422	C20003-2	1	5
ACETB	00687	410422	C20003-3	1	5
AMM-S	00688	638127	C20002-5	1	4
CFAS	00401	564947	C20002-2	15	68
ISEHIGH	00503	653847	C20001-2	6	90
ISELOW	00502	653849	C20001-1	6	90
PSTDM1-A	00691	674727	C20004-1	1	4
PSTDM1-B	00692	674727	C20004-2	1	4
PSTDM1-C	00693	674727	C20004-3	1	4
PSTDM1-D	00694	674727	C20004-4	1	4
PSTDM1-E	00695	674727	C20004-5	1	4
PSTDM1-F	00696	674727	C20005-1	1	4
H2O	00901	999999	C20002-1	17	106
S3	00763	99999	C20001-3	6	90
A-HBS 2-L1		631779		1	80

Figure 15: calibrator load list.



A calibrator load list can be seen in Figure 15. Here it is shown all the calibrators that are required for calibration in the next 24 hours, the code and lot ID, the appropriate rack and rack position, and the volume needed to successfully complete the calibration. The calibrators highlighted in blue are the ones needed to perform the test in the glucose sample (see figure 15). In use calibrators can be found in the fridge (See figure 17); however, fresh calibrators are located in the cold room (See figure 12). The lot number of calibrator on the list should be the same as the ones in use. It is important that the calibrator goes in the appropriate rack number and position, and that the lot number is checked.

Figure 16: C.f.a.s calibrator used to calibrate the analyser to perform the UV test on the glucose sample.

A test can be masked when the calibration or QC is failing to stop analysing samples in a non-precise and effective way (See figure 18). There are three types of masking:

1. Test mask. It does not allow the analysis of a specific test; this could happen when there is no reagent for a test, so no samples can run.
2. Patient mask allows the analyser to do calibrations and QC but will not do any patient test; this can be used when one specific calibration and QC are failing but the analyser is in operation.
3. Unmask means that the analyser is working as usual, and every sample of that test is being processed and analysed.

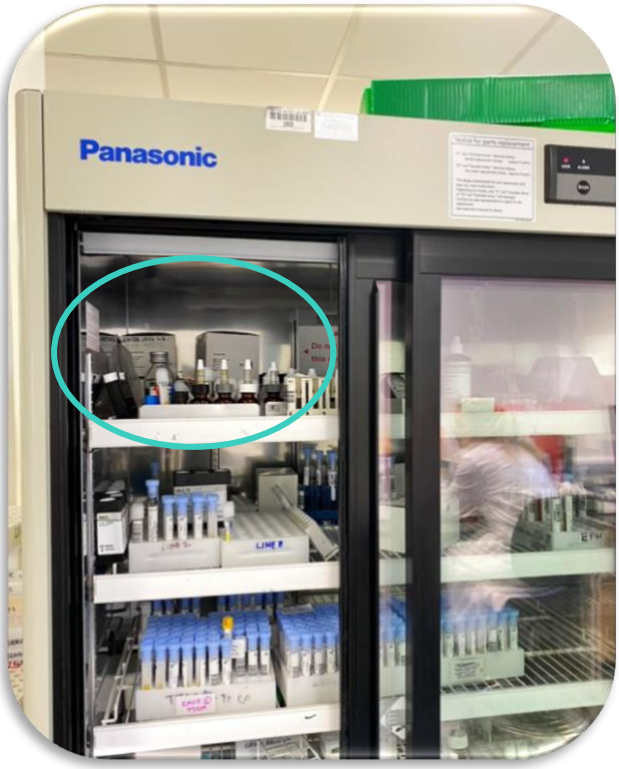


Figure 17: fridge located in biochemistry.

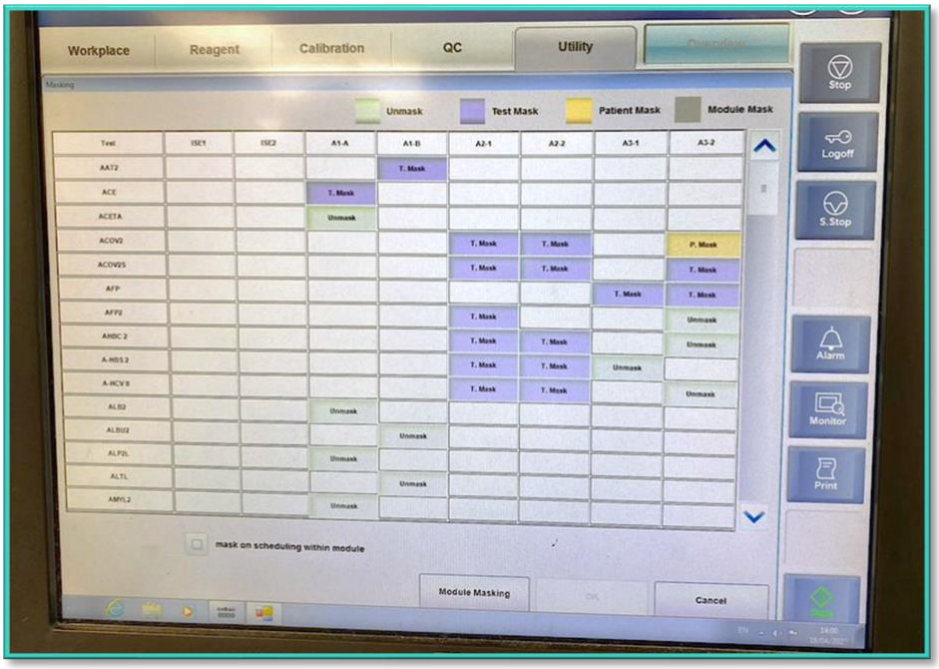


Figure 18: Cobas 8100 computer showing the tests that are test masked, unmasked and patient masked.

2.2.4 QUALITY CONTROL

After the calibration is done, the quality controls (QC) of the different levels (usually level 1,2,3) are analysed. QC is the process of monitoring the quality of your work, ensuring that there are no errors and fixing them where necessary. It is a real-time indicator of analytical performance and a monitoring tool for problems and trends which may become apparent over time. Routine in use quality controls are kept in the fridge (See figure 17), however, fresh ones can be found in the -40^{O}C freezer (See figure 19). Fresh ones should be defrosted and mixed before use. The controls needed for testing the glucose sample are highlighted in blue (See figure 20).

Figure 19: Quality controls used by Cobas 8000. Level 1, 2 and 3.

cobas 8000 Roche HITACHI

QC Load List Operator ID: bmserv 27/03/2023 11:13

Automatic QC Rack	-
Module Specific Rack	
Module	Rack Range
A1	-
A2	-
A3	-
ISE	-

System QC

Control	S. Type	Material No.	Lot ID	Rack No. - Pos.	Event	Volume
PC AHBS1	Ser/Pl	00012	664734		2	80
MULTIS1	Ser/Pl	25004	510201	Q30001-1	50	206
MULTIP	Ser/Pl	25007	450032	Q30001-4	4	29
MULTICSF1	CSF	25114	810201	Q30004-1	3	10
MULTIS2	Ser/Pl	25005	510202	Q30001-2	46	177
MULTICFS2	CSF	25115	810202	Q30004-2	3	10
PC AHBS2	Ser/Pl	00013	664737		2	80
PC ACOV2S1	Ser/Pl	00671	646835		1	20
PC AHBC1	Ser/Pl	00008	549457		1	40
PC ACOV2S2	Ser/Pl	00672	646836		1	20
PC ACOV2 1	Ser/Pl	00669	689536		1	20
PC ACOV2 2	Ser/Pl	00670	689534		1	20
MULTIS3	Ser/Pl	25006	510203	Q30001-3	50	206
PC AHBC2	Ser/Pl	00009	549461		1	40
PC HIV1	Ser/Pl	00014	643861		1	39

Figure 20: QC load list.

When the analyser has tested the calibrators and QC, the results are displayed in Infinity so the BMS can validate them. If the results of the controls do not match the target mean ± 2SD when validating, the test is considered to be out of control and should be further reviewed with the Senior BMS or BMS

Manager. Further investigation and/or appropriate changes should be conducted, and the QC material should be re-analysed. Only when the QC results are within acceptable range should patient outcomes be validated. The result status is indicated by a green tick when the result is passing QC and calibration rules and a red exclamation mark when the result is failing QC rules at that level. The QC and calibration results were within acceptable range, and therefore, patient samples could be analysed.

Figure 21: Green wash rack, calibrator, and QC in the BRF module.

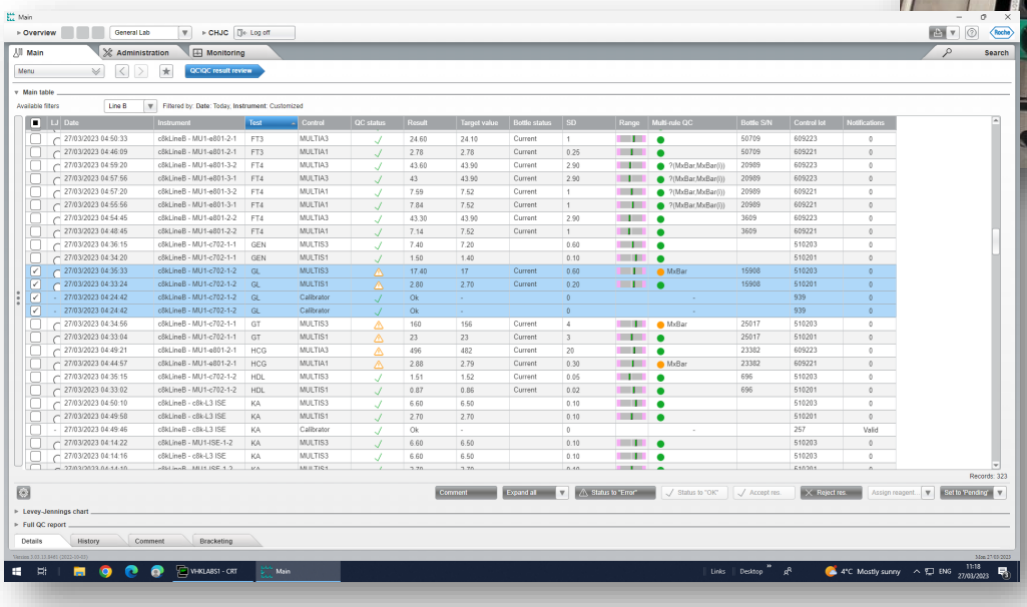


Figure 22: Calibrators and QC result showed in infinity.

This shows that the glucose sample was performed in a safe and a compliant environment and consequently, the test results were accurate.

2.2.5 Method performance

Once maintenance, calibration and the quality control have passed, it is then possible to process patient samples. The sample was spun in reception, checked for bubbles and then it was ready to be tested. The glucose specimen was manually frontloaded in a red rack into the core unit of line B (See figure 24 and 13) because it is an urgent specimen and any racks loaded in the core module are treated as a priority. This is done to avoid any delays and issues that may raise within the line such as a track malfunction to guarantee the sample will be tested within the time limit (1 hour). When the green light is on, all racks should be placed in a handbag which can be orientated in one way only into one of the two input positions on the core module (See figure 25). After pressing the standby button to start a run (see figure 26), the Cobas 8000 will move from standby to preparation and then to operation mode. The Cobas 8000 series analyser is connected to C8100 to help them deliver samples to the individual modules. Samples and aliquots move through the c8100 track in single- sample holders (see figure 23). The sample was then moved to the Cobas c702 where the test was performed. The Cobas c702 is a high throughput clinical chemistry module that can perform photometric assays test for a large range of analytes. Automatic reagent cassette decapping and unloading/loading during operation is possible because the analyser is fitted with a reagent manager. The Cobas c702 can perform up to 2000 test per hour, ensuring the analyser handles heavy workloads and provides efficiency.

Figure 23: Single sample holder. (Roche Diagnostics, 2017).

Figure 24: Core unit module.

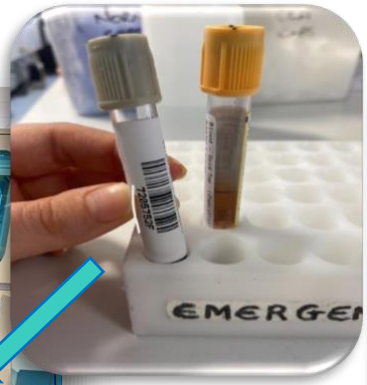


Figure 13: Patient sample in the emergency rack waiting to be front loaded.

Figure 25: red rack containing the glucose sample.

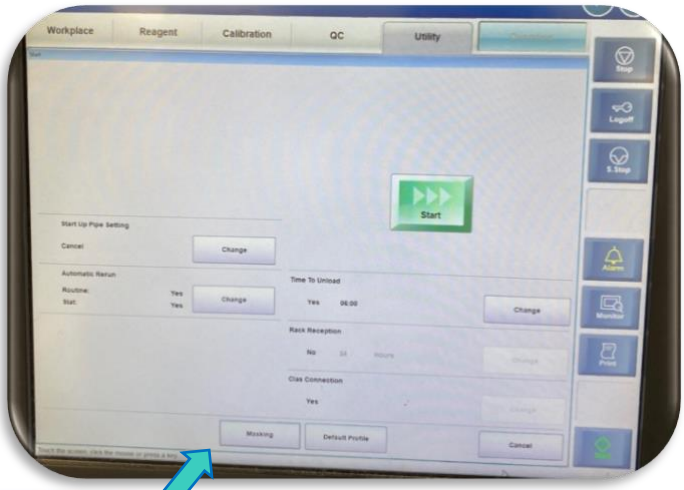
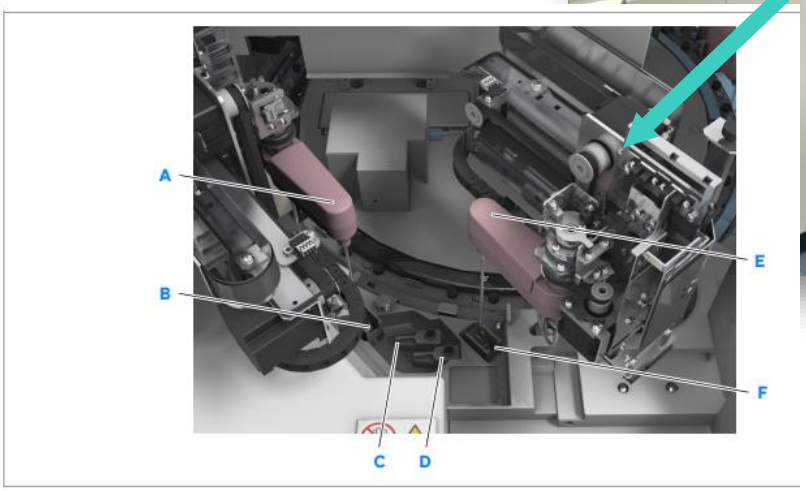


Figure 26: computer screen showing the green start button to take the samples to the Cobas c702 module.

Once the sample has reached the Cobas c702 module, the sample pipetters (A and E in figure 27) aspirate the material from the blood tubes and place it into reaction cells located in the reaction disk area. The sample probes are then rinsed with deionized water every time a sample has been dispensed. Sample cleaners 1 and 2 are used for special washes.

Figure 26: Cobas c702 module



A Sample pipetter B
B Rinse station
C Sample Cleaner 1
D Sample Cleaner 2
E Sample pipetter A
F Rinse station

Figure 27 Rear view of the sampling area of the **c** 702 module (safety cover removed) (Roche Diagnostics, 2017)

The reaction disk has 406 reaction cells. Here meet both the sample material and the reagent. This solution is then mixed in the cell using the ultrasonic mixer. The solution is incubated in the incubation bath to keep the reaction mixture at the temperature needed for testing. The photometer lamp emits light which travels through a glass window and into the incubation bath. Inside the bath, the light passes through the reaction mixture and cell before it exits through another glass window and enters the photometer. The photometer measures the absorbance of the reaction mixture 38 times for each reaction cell in just 10 minutes. By analysing these measurements and comparing them to a calibration curve, the instrument can accurately determine the concentration of the analyte being tested. When the measuring is finished, the reaction cell rinse units clean and dry the reaction cells using CellCln1, CellCln2 and deionized water. Afterwards, three cell blank measurements are tested to check the optical performance of the reaction cell. If these results deviate significantly from the results performed earlier, the reaction cell is then disabled.

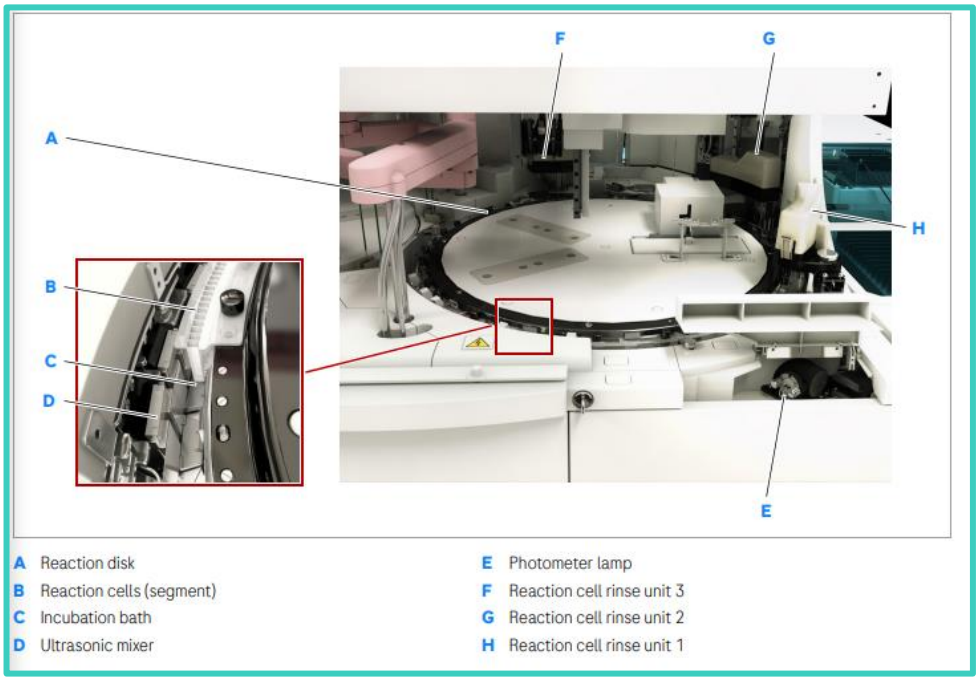


Figure 28: rear view of the reaction disk and photometer lamp of the c702 module (Roche Diagnostics, 2017).

The calculation is automatically sent from the analyser to infinity for validation. The sample is sent back into the front of the BRF module.

Figure 29: red rack in the BRF module after the test has finalized.

2.3 Post examination process

2.3.1 Result Interpretation

Results should only be validated once the requirements in the Departmental Internal Quality Control Policy have been met and there are no error flags associated with the result. Assuming the patient was not fasting, the test

was within the analytical range. Consequently, the result was released from infinity to Lab centre for the A&E consultant doctors to review the result.

Analyte	Reference interval or therapeutic range when fasting	Patient sample result	Specimen tube	Turn-around time	Sample volume
Glucose	3.3-6.1 mmol/L fasting	8.1 mmol/L	Grey	1 hour	2 mL

Table 4: a table showing the characteristics of the results, turnaround time and sample volume.

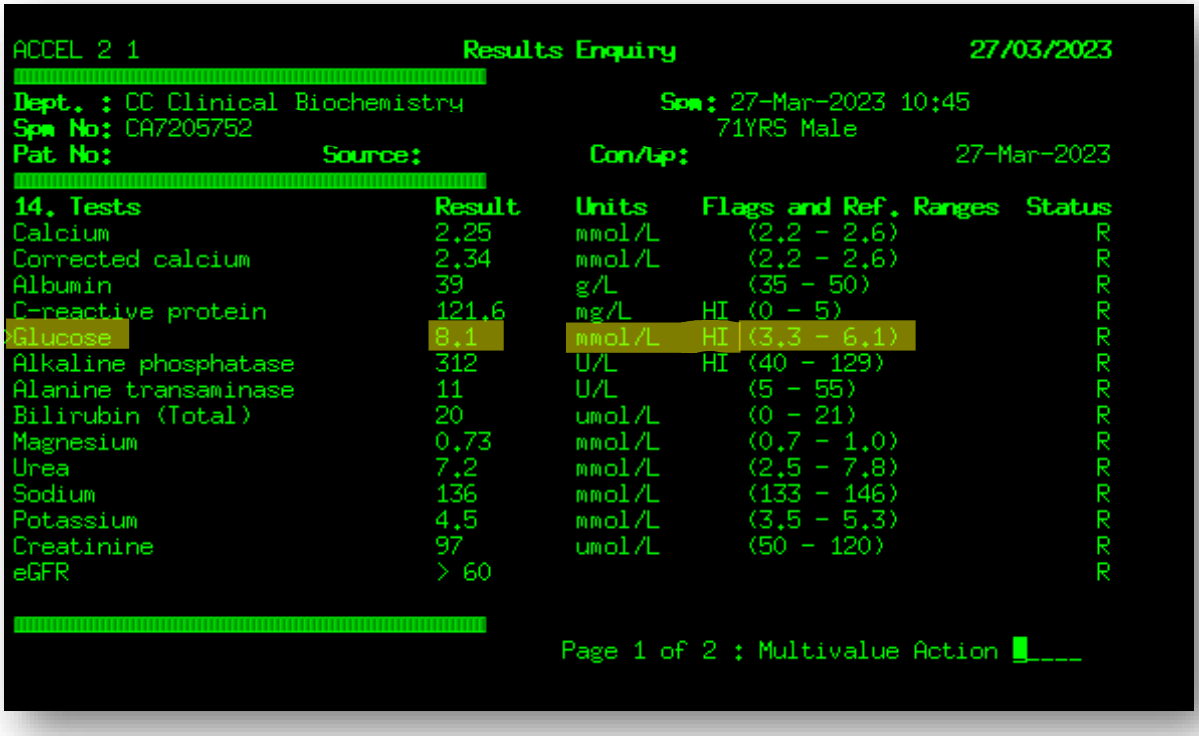


Figure 30: result enquiry of the glucose sample. Highlighted in yellow is the result of the UV test.

2.3.2 Possible Sources of Errors

During the analysis process of the glucose sample, no issues were raised. However, there are several problems that may happen during the analysis such as:

1. A sample without the minimum data set criteria would be rejected and the test could not be performed.
2. Barcode quality can be a problem for the analyser. This can be fixed by printing another barcode with the same sample number.
3. A low-quality sample including an insufficient sample or bubbles present in the sample will always raise a flag in infinity and the analyser will alarm. A member

Figure 31: barcode printer.

of staff should always check for bubbles if the sample is front loaded. On the other hand, if a sample is insufficient, it will be stored for 7 days in the fridge and discarded after that time. The service users would need to send another sample with enough blood to perform the test.

4. It may happen that the sample result fell outside the analytical range marked in the analyser as a limit.
    a. When the sample result is lower than 2.5, it is repeated automatically by the analyser.
    b. When the sample result is over 41.6, the analyser does on board automatic dilution and repeats the test again.

The reagents usually present interferences with other substances or abnormal blood events contained in the blood sample like drugs or haemolysis. Nevertheless, icterus, lipemia, haemolysis and different drugs were negligible in the reagent used for testing the sample, as it does not significantly interference with anything other than gammopathy particularly type IgM in very rare cases.

3. Sample storage & disposal

3.1 Sample storage

After the analytical line is finished testing, the sample was taken from the core unit to the Input Buffer Module (IPB) by a BMS. The sample then make its way to the AOB module. The AOB (Add on / Output Buffer Module) module can retrieve samples for repeat, rerun, add-on and reflex processing. One AOB can storage up to 400 glucose samples and the data is cleared every morning when the Data Cleanup is performed. This information is kept in the onboard software. These samples are only stored there for one day as the racks are emptied every day.

Figure 32: Core unit

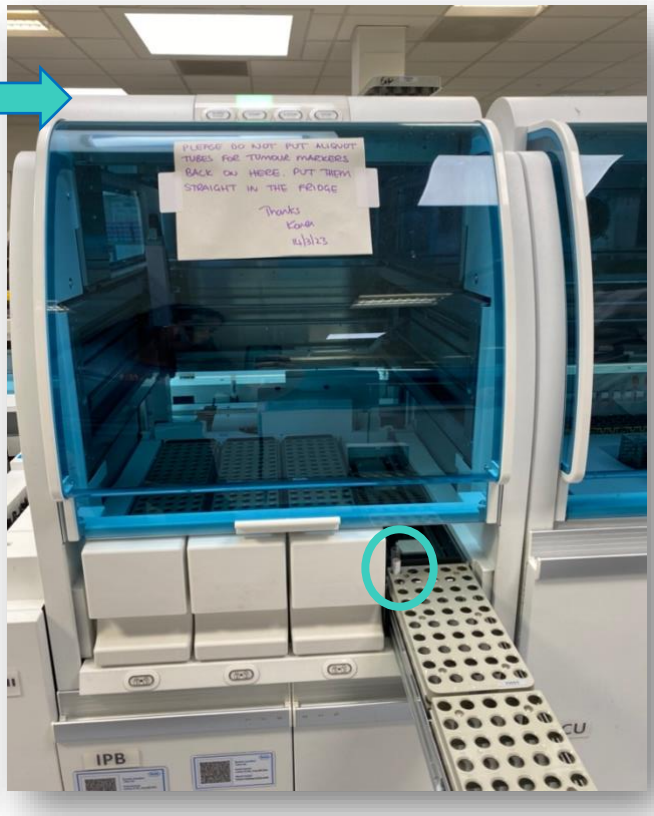


Figure 33: IPB module with the glucose sample

Figure 34: AOB module

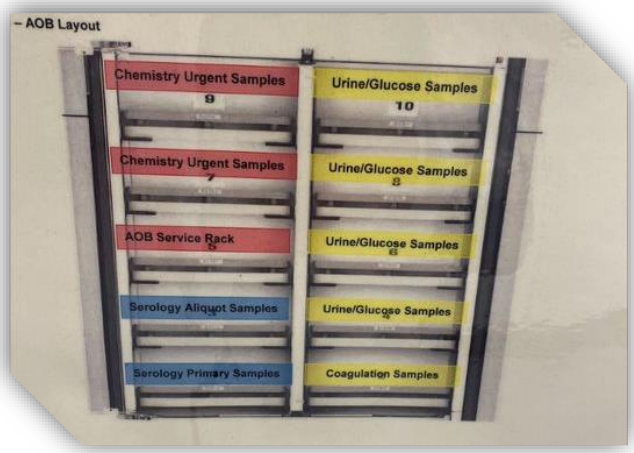


Figure 35: AOB layout.

3.2 Sample disposal

The pre-analytics maintenance of the AOB module includes pressing global stop on the CU to put all modules in stop. The AOB module is then emptied, and the samples are stored in a metal rack at room temperature. After 2 days, they are sealed labelled with the site name and description of waste then placed in the 770L yellow waste bins in the waste storage area.

Figure 36: AOB module during pre-analytics maintenance

Figure 37: trolley used to transport the samples to the metal rack.

Figure 38: metal rack where samples are storage.

Figure 39: sample container in the 770L bin

Figure 40: 770L yellow waste bin

4. References

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