# Laboratory Procedure Manual

| | |
|---|---|
| *Analyte:* | **Glucose** |
| *Matrix:* | **Plasma** |
| *Method:* | **Roche/Hitachi Cobas C Chemistry Analyzer – C311** |
| *Revised Date:* | ***July 5 ,2023*** |
| *As performed by:* | **Diabetes Diagnostic Laboratory**<br>**University of Missouri**<br>**1 Hospital Dr. Columbia, MO 65212** |
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**Important Information for Users**

The University of Missouri, Diabetes Diagnostic Laboratory periodically refines these laboratory methods. It is the responsibility of the user to contact the person listed on the title page of each write-up before using the analytical method to find out whether any changes have been made and what revisions, if any, have been incorporated.

**Public Release Data Set Information**

This document details the Lab Protocol for testing the items listed in the following table:

| File Name | Variable Name | SAS Label (and SI units) |
|-----------|---------------|--------------------------|
| GLU_L | LBXGLU | Fasting glucose (mg/dL) |
| | LBDGLUSI | Fasting glucose (mmol/L) |

1. **SUMMARY OF TEST PRINCIPLE AND CLINICAL RELEVANCE**

   Glucose is the major carbohydrate present in the peripheral blood. Oxidation of glucose is the major source of cellular energy in the body. Glucose derived from dietary sources is converted to glycogen for storage in the liver or to fatty acids for storage in the adipose tissue. The concentration of glucose in the blood is controlled within narrow limits by many hormones, the most important of which are produced by the pancreas. The most frequent cause of hyperglycemia is diabetes mellitus resulting from a deficiency in insulin secretion or action. A number of secondary factors also contribute to elevated blood glucose levels. These include pancreatitis, thyroid dysfunction, renal failure and liver disease.

   Hypoglycemia is less frequently observed. A variety of conditions may cause low blood glucose levels such as insulinoma, hypopituitarism, neoplasms, or insulin-induced hypoglycemia. Glucose measurement in urine is used as a diabetes screening procedure and to aid in the evaluation of glycosuria, to detect renal tubular defects, and in the management of diabetes mellitus. Glucose measurement in cerebrospinal fluid is used for evaluation of meningitis, neoplastic involvement of meninges and other neurological disorders.

   Test Principle – UV In vitro test for the quantitative determination of glucose in human plasma using the Roche/Hitachi cobas c system (c311).
   Hexokinase catalyzes the phosphorylation of glucose to glucose-6-phosphate using adenosine triphosphate (ATP) to form glucose-6-phosphate (G-6-P) and adenosine triphosphate (ADP). Glucose-6-phosphate dehydrogenase oxidizes glucose-6-phosphate in the presence of NADP to gluconate-6 phosphate. No other carbohydrate is oxidized. The rate of NADPH formation during the reaction is directly proportional to the glucose concentration and is measured photometrically at 340 nm.

**2. SAFETY PRECAUTIONS**

All specimens, control materials, and calibrator materials are considered potentially infectious. All staff are required to use personal protective equipment including gloves, lab coats, and eye protection when handling bodily fluids (substances). Staff not following proper PPE measures will receive a verbal warning. If a second offence occurs, this staff member will be written up. If this occurrence continues, the lab director and manager will schedule a meeting with the staff member to discuss and prevent additional occurrences. All technical staff are required to read and follow assigned Lab Safety Procedures. Safety Data Sheets (SDSs) and the Chemical Inventory Lists are located at the bench for each reagents used in the lab. All lab staff is required to complete mandatory on-line safety trainings provided by MU Environmental Health & Safety (EHS) department.

Disposal of all waste material should be in accordance with local guidelines. All Sharps must be placed in rigid puncture proof containers. Each container should be labeled with the biological hazard system. These containers should be kept in an upright position. Training provided by EHS on Biohazard Containers should be performed by each testing personnel at least annually.

**3. COMPUTERIZATION; DATA SYSTEM MANAGEMENT**

Data are maintained on a secured Microsoft Access / Microsoft SQL server client-server system in a 128-bit authenticated Windows domain environment.

A. Laboratory services are requested through the Westat system operations via an email notification containing a unique manifest list of the samples and sample analysis type (e.g. FGL), which confirms that specimens have been shipped to DDL.

B. Each Manifest Form should include and be verified against each sample received:

1) Patient Sample ID #
2) Test Name

3) Date Collected

4) Shipment ID #

5) Shipment Date

6) Lab Name

7) Lab ID

8) Survey Year

C. Once specimens are received and verified the corresponding file is imported electronically into the SQL server database via secure transfer.

D. After analysis the results, date analyzed and tech initials are imported from the instrument into the SQL server database via secure transfer.

E. Data check sheets are printed out and checked against the instrument printouts by the supervisor.

F. After results are cleared by the supervisor a results file in the specified format is exported and uploaded to Westat via secure transfer.

4. **SPECIMEN COLLECTION, STORAGE, AND HANDLING PROCEDURES; CRITERIA FOR SPECIMEN REJECTION**

A. Specimen Collection – Collect blood by venipuncture from fasting individuals using a NaF evacuated tube system; separate plasma from red cells. The patient status should be recorded when the specimen is drawn. Only the specimens listed below were tested and validated;
Plasma: sodium fluoride (NaF)

B. Sample and Reagent Volumes – sodium fluoride (NaF) plasma (grey top tubes).

**Application for plasma using c 311 test definition**

| | | |
|---|---|---|
| Assay type | 2-Point End | |
| Reaction time/Assay points | 10/6-32 | |
| Wavelength (sub/main) | 700/340 nm | |
| Reagent direction | Increase | |
| Units | mg/dL | |
| Reagent pipetting | | Diluent ($H_2O$) |
| R1 | 28 µL | 141 µL |
| R2 | 10 µL | 20 µL |

| Sample volumes | Sample | Sample Dilution Samples | Diluent (NaCl) |
|---|---|---|---|
| Normal | 2 µL | – | – |
| Decreased | 10 µL | 15 µL | 135 µL |
| Increased | 2 µL | – | – |

C. Sample Minimums – min volume required for analysis directly from collection tube is 200 µL.

D. Storage

Stability in fluoride plasma;     3 days at 15-25 °C

Stability in plasma;     3 months at -20 °C

13 years at -70 °C

E. Specimen Handling – Specimen are received under frozen conditions on dry ice. Each specimen must arrived in the laboratory labeled with two unique accession identifiers generated by NHANES. Each Manifest Form should include be verified against each samples received. Once checked all samples should be storage at -70°C until analysis. Refer to the NHANES study handling and reporting procedure for additional details.  Specimens should be thawed at room temperature prior to analysis and after analysis samples should be returned to -70 °C for long-term storage.

F. Specimen Rejection

1) Unlabeled specimens.
2) Quantity not sufficient samples.
3) Incorrect lab name.
4) Incorrect test name.
5) Wrong lab ID.
6) Urine samples

7) The below must be followed for unacceptable specimens;

    a.   Document all details on the sample manifest form and the Pre-analytical Problem Resolution Log.

    b.   Immediately contact NHANES for a corrective action on handling the issue.

## 5. Procedures for Microscopic Examinations; Criteria for Rejection of Inadequately Prepared Slides

Not applicable for this procedure

## 6. EQUIPMENT AND INSTRUMENTATION, MATERIALS, REAGENT PREPARATION, CALIBRATORS (STANDARDS), AND CONTROLS

A. Instrumentation

For cobas c 311 analyzers: GLUC3. Refer to Operator's Manual for Startup, Operation, and Shut down procedures.

B. Materials

| REF | CONTENT |
|---|---|
| 04404483 | Glucose HK (GLUC3) |
| Shelf life at 2-8 °C | See expiration date on Cobas c pack label. |
| On-board in use and refrigerated on the analyzer | 8 weeks |

C. Reagent Preparation
  Provided ready for use
  1) Buffers
      a. R1- MES buffer: 5.0 mmol/L, pH 6.0; $Mg^{2+}$: 24 mmol/L; ATP: $\geq$ 4.5 mmol/L; NADP: $\geq$ 7.0 mmol/L; preservative
      **b. R2 - HEPES buffer: 200 mmol/L, pH 8.0; $Mg^{2+}$: 4 mmol/L; HK (yeast): $\geq$ 300 µkat/L; G-6-PDH (E. coli): $\geq$ 300 µkat/L; preservative**
  2) NaOHD –SMS-SmpCln1+2 –SCCS
  3) Cell Wash Solution I/NaOH-D Detergent I
  4) Cell Wash Solution II/Acid Wash Detergent II
  5) Diluent NaCL 9%

D. Calibrators (Standards) – Calibrators are handled and prepared following manufacturer's instructions.

E. Controls

1) Lyphochek Assayed Chemistry Controls Levels 1 and 2 are purchased from Bio-rad Laboratories and are handled and processed following manufacturer's instructions.

2) In-house controls (in-house low ([IHL] and in-house high [IHH]) once thawed are ready for use – Controls are prepared by collecting 450 mL (one unit) of whole blood from two diabetic (IHH) and two non-diabetic (IHL) subjects. The blood is collected in blood bags without an anticoagulant. The serum is allowed to clot for 1 hour and then separated from the red blood cells by centrifugation in a refrigerated centrifuge (4oC) for 25 min at 1500 g. The serum is then removed from the red blood cells, aliquoted in 0.5-mL portions and stored at -70 °C or colder in Nalgene cryogenic vials.

**7. CALIBRATION AND CALIBRATION VERIFICATION PROCEDURES**
The concentration and activities of the calibrator components are lot-specific. The calibrator values were determined using the method stated in the values sheets.

Calibrators:  S1: diH20
  S2: C.f.a.s
Calibration Mode:  Linear 2-point calibration
Traceability: This method has been standardized against ID/MS.

Calibration Procedure: To calibrate the c311 for glucose

1. Calibrators:  S1: diH20

  S2: C.f.a.s

2. Calibration Mode: Linear 2-point calibration

3. Choose the "Calibration" tab

4. Select the glucose test

5. Select "2 point" under the method window

6. Insert calibrators and controls into the correct vial positions. These positions can be found in the Calibration load list report and QC load list report

7. Select "Save"

8. Select the "Start" button

**Calibration Verification**

The LN2 calibration verification survey is purchased through CAP. Specimens are assayed per survey instructions. Results are submitted to CAP and evaluated according to a goal for Total Error of 12%. The LN2 Calibration Verification/Linearity survey does not span the AMR for glucose. Therefore to verify the lower end of the AMR a serial dilution using the lowest LN2 sample is performed using three twofold dilutions (e.g. 1/2, 1/4, 1/8). Aliquots are assayed in duplicate measurements and the results regressed in EP evaluator against a Total Error of 12% (per CAP goal for TE).

8. **PROCEDURE OPERATING INSTRUCTIONS; CALCULATIONS; INTERPRETATION OF RESULTS**

1) Before turning on the analyzer, perform the maintenance checks as outlined on the cobas c311 analyzer Maintenance Log under the "Check" and "Hands-on" sections.

2) All healthcare personnel shall routinely use appropriate barrier precautions to prevent skin and mucous membrane exposure when contact with blood or other body fluids of any patient is anticipated. All products or objects that come in contact with human or animal body fluids should be handled, before and after cleaning, as if capable of transmitting infectious diseases. Wear appropriate Personal Protective Equipment (PPE), including facial protection, gloves, and protective clothing. Dispose of all biological samples and diluted specimens in a biohazard waste container at the end of analysis. Dispose of all liquid hazardous waste in properly labeled hazardous waste container.

3) Turn on the power to the analyzer and control unit. The Analytical Unit *must* be turned on before the control unit.

4) Log-in to the control unit using name: adm and password: adm

5) The system will perform the "Power On Pipe" automatically.

6) Ensure all "Push-button" maintenance functions were performed by checking the utility screen.

7) Perform any maintenance functions that have expired

8) Put machine into maintenance mode by flipping switch on the analyzer. Perform any necessary maintenance outlined in the Maintenance Log that has not already been done.

9) Return machine to operation mode.

10) Go to "System Overview" screen. Ensure that temperature of the incubator is within 37 °C ± 0.1 °C by clicking "AU" button and observing the core temperature.

11) Check the "Work Flow Guide" area at the top of the screen. If any of the first five buttons is highlighted, perform that action (Daily Maintenance, Sample Data Clear, Regent Preparing, Calibration and QC Select, Parameter Download). These actions should be automatically completed by the analyzer.

12) Calibrate if necessary following the calibration procedures.

13) Enter controls to run as samples

    a. Go to Utility menu

    b. Click on sample information

    c. Type in control name

    d. Hit enter

    e. Select "Gluc" test button

    f. Select "Save" test button

    g. Enter "Barcode Read Error" mode

    h. Enter name of control and position on machine

    i. Repeat for all 8 controls (beginning and end)

14) Enter samples and tests to run

    a.    Go to Utility menu

    b.    Click on sample information

    c.    Scan barcode for sample

    d.    Hit enter

    e.    Select "Gluc" test button

    f.    Select "Save" test button

    g.    Repeat for all samples

15) To run samples, choose "Start" button at lower right of the screen

16) Hit "Start" when prompted

17) To manually shut down the instrument, choose the "Deactivate system" option.

18) Preliminaries:

    a.    All reagents, controls, and calibrators should be at room temperature prior to testing.

    b.    All sample aliquots should be thoroughly mixed prior to analysis. Please remove all bubbles.

19) Sample preparation: Using printed labels, label the appropriate sample vials with the corresponding sample identification, and place the whole, uncapped original tubes into the sample vials.

20) After run is completed, print hard copy of the results and proceed to reporting results.

21) Discard the used cuvette segments, reagent, and sample cups in the appropriate waste container.

22) Turn off the instrument.

Calculations:

Roche cobas c systems automatically calculate the analyte concentration of each sample. Conversion factors: mmol/L x 18.02 = mg/dL

Reporting results:

1) All replicate values of QC data plus all pertinent assay information (date of analysis, reagent lot number, technician ID, samples ID etc.) are recorded in the Microsoft Access Glucose Daily Diary Log database located on the network drive. The calibrator value is also recorded. Enter the data under the form "Diary Sheet Entry Form". The Microsoft Access program will automatically calculate the daily mean and range for each control and determine if a run is accepted or rejected. The current above or below the mean trend is also calculated.

2) Any comments associated with the specimen are entered in the comment field. If a result is below the assay detection limit, or a sample is missing, or if the sample volume is less than 200 µL, or the sample is otherwise unacceptable, the result field is left blank or a –1 is entered, and an appropriate comment is entered in the assay comment field.

3) After analysis the results, date analyzed, and tech initials are imported from the instrument into the SQL server database via secure transfer.

4) Data check sheets are printed out and checked against the instrument printouts by the supervisor or delegate (signed by a supervisor or delegate).

5) After results are cleared by the supervisor or delegate a result file in the specified format is exported and uploaded to Westat via secure transfer.

## 9.    REPORTABLE RANGE OF RESULTS

A.    Analytic Range – 2 – 728 mg/dL
B.    Limit of Detection (LOD) – 2 mg/dL
C.    Linearity Limits – 2 – 728 mg/dL
D.    Reportable/Non-reportable values:
Results < 2 mg/dL are reported as < 2 mg/dL. Results > 728 mg/dL should be two-fold diluted with NaCL 9% (validation studies have also demonstrated acceptable performance using distilled water; approved on 5/7/2015) and reanalyzed. This is the maximum dilution for glucose. The final result should be multiplied by 2 to account for the dilution.

## 10.  QUALITY CONTROL (QC) PROCEDURES

1) QC is used to ensure that a test system is performing accurately. QC aliquots are tested in the same manner as patient specimens and by the same personnel performing patient testing. QC is used to monitor the analytic performance of the testing being performed at DDL and to certify that all results reported by the lab are accurate.

2) At least twenty runs (in duplicate measurements beginning and at the end of each analytical run) are used to establish target control values and tolerance limits (ranges). Defined acceptability limits specific for each assay are approved by the Lab Co-Director prior to implementation.

3) Controls are tested with every run. Control results must fall within the specified ranges prior to the release of results. Control results are reviewed daily by the bench tech and lab supervisor/delegee (prior to the release of results) and examined weekly by the Lab Supervisor or delegee (for trends).

4) If a QC trend of > ± 6 is observed it is the tech's responsibility to immediately perform a corrective action to avoid a rejected run. Examples include performing a re-calibration, retrieving new controls of the same lot, reconstitution of new quality controls, or performing analytical precision studies to access integrity of the QC in use against the acceptable limits. All corrective actions should be documented on the QC Corrective Action log.

5) QC chart plots are plotted for the daily means and ranges of the replicates (the difference between the highest and the lowest value of a single control within a run) for each control and compares them to the established target ranges. These are approved (monthly) by the Lab Director or delegee.

6) If control results are outside of the acceptable limits, patient results should not be reported. Patient samples should be return to optimal storage conditions until all QC issues are resolved. QC Corrective actions could include repeating of QC (of the same lot), performing a recalibration procedure or changing out the appropriate reagents.

7) QC results must be acceptable prior to releasing patient results. If QC results are still unacceptable after performing corrective actions immediately, call the appropriate technical hotline for additional troubleshooting advice and alert the supervisor or delegate immediately.

8) All Corrective Action/Preventive Action (CAPA) events concerning out of range controls, calibrators, or rejected runs that occur at the time of testing, must be documented (in the daily diary sheet for that particular assay) and immediately in the communicated (verbally and by email) to the Lab Director or Supervisor.

9) For the glucose assay two types of quality control (QC) systems are used in this analytical method: 1) "sample QC" and 2) "batch QC." For sample QC, 2% of specimens are randomly selected and analyzed either within-assay or between-assay for quality assurance purposes. If the difference between duplicates is greater than 10%, the specimen is reanalyzed. Batch QC specimens are placed in the calibration rack at the end of each sample rack the entire run.

Controls are assayed at the beginning and end of each analytical run. If the stock of these controls becomes low, another batch is ordered or prepared in time to analyze it concurrently with the current QC materials. The new controls are used only after their means and the ranges have been established by performing 20 characterization runs. Daily means and ranges of the controls are calculated from 20 interassay determinations. The bias ranges of the daily means are set at ±1 SD or 67% confidence interval (CI); the warning limits (WL) are set at ±2 SD or the 95% CI and the control limits (CL) are set at ±3 SD or 99% CI. For the daily ranges, the bias limit is the mean + 1 SD with warning and control limits set at the mean +2 SD and the mean + 3 SD, respectively.

10) After each assay run, all controls are recorded on the Daily Diary Log Sheet.

    a. The QC guideline for this glucose assay declares a system as "out-of-control" if any of the following events occur:

- The mean from a single run for a single control falls outside 99% confidence limits (3sd).
- The means from a single run for both controls fall outside 95% confidence limits (2sd).
- The means from eight successive runs for a single control fall either all above or all below the mean line. Runs for which the mean falls within 1sd of the established mean are not counted in this trend.
- The range from a single run for a single control falls above 99% confidence limits.
- The ranges from a single run for both controls fall above 95% confidence limits.
- The ranges from eight successive runs for a single control fall above the mean line.

11) The Diabetes Diagnostic Laboratory participates in an external QC program conducted by the College of American Pathologists (CAP). Two levels of survey materials are analyzed 3 times a year for glucose in a routine run, and results are submitted to CAP for inter-laboratory comparison.

## 11. REMEDIAL ACTION IF CALIBRATION OR QC SYSTEMS FAIL TO MEET ACCEPTABLE CRITERIA

1. When QC results fail to meet the acceptable criteria, check the sample cup containing the QC specimen for bubbles and reanalyze the QC specimen.
2. If QC is still unacceptable perform a recalibration of the assay and reanalyze the QC. QC must be considered acceptable prior to releasing patient results.
3. If steps above do not result in correction of the "out-of-control" values for QC materials, troubleshoot the instruments and reagents until the system is back "in control". Refer to the above QC procedure section for additional details.

4. Samples should be placed under optimal conditions during instrument and reagents troubleshooting.

5. All corrective actions should be documented.

6. QC must be considered acceptable prior to releasing patient results.

## 12. LIMITATIONS OF METHOD; INTERFERING SUBSTANCES AND CONDITIONS

Criterion: Recovery within ± 10 % of initial value at a glucose concentration of 70.3 mg/dL.

Icterus: No significant interference up to an I index of 60 conjugated and unconjugated bilirubin concentration (approximate conjugated and unconjugated bilirubin concentration: 60 mg/dL).

Hemolysis: No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 1000 mg/dL.

Lipemia (Intralipid): No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Drugs: No interference was found at therapeutic concentrations using common drug panels.

In very rare cases gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

## 13. REFERENCES RANGES (NORMAL VALUES)

Adults: 74-109 mg/dL

Per American Diabetes Association.

Fasting glucose: 100 – 125 mg/dL   Prediabetes
Fasting glucose: ≥ 126 mg/dL         Diabetes

**14.    CRITICAL CALL RESULTS ("PANIC VALUES")**

Critical Value:  < 40mg/dL or > 400mg/dL

*Critical results must be repeated and verified.*

**15.    SPECIMEN STORAGE AND HANDLING DURING TESTING**

Specimens are stored at -70°C until analyzed.  On the day of analysis, thaw the specimens.  Mix thoroughly.  Upon completion of analysis, refreeze at -70°C.

**16.    ALTERNATIVE METHODS FOR PERFORMING TEST OR STORING SPECIMENS IF TEST SYSTEM FAILS**

If the instrument is unable is perform the test, the specimens are stored at -70°C until testing is available. NHANES should be notified if the platform will be down for an extended period of time.

**17.    TEST RESULT REPORTING SYSTEM; PROTOCOL FOR REPORTING CRITICAL CALLS**

NHANES data files with results are exported from the NHANES database in the specified format and uploaded to Westat via secure transfer weekly.

**18.    TRANSFER OF REFERRAL OF SPECIMENS; PROCEDURES FOR SPECIMEN ACCOUNTABILITY AND TRACKING**

All shipments are recorded on the NHANES Shipping Log upon receipt.  Actions taken during the course of analysis, result reporting, and specimen retention are also recorded on the log.  Specimens are stored frozen at -70°C or colder after analysis; specimen locations are recorded according to sequential DDL accession number and box number.  After one year specimens may be discarded.

**19.    SUMMARY STATISTICS AND QC STATISTICS**

Please see following page

## August 2021-August 2023 Summary Statistics and QC Chart
## LBXGLU (Fasting Glucose (mg/dL))

| Lot | N | Start Date | End Date | MEAN | Standard Deviation | Coefficient of Variation |
|---|---|---|---|---|---|---|
| LBCFGH5_IHH8 | 118 | 06OCT21 | 24AUG23 | 322.9 | 3.4 | 1.1 |
| LBCFGH8_BR264 | 40 | 06OCT21 | 26JUL22 | 282.4 | 3.3 | 1.2 |
| LBCFGH8_BR897 | 78 | 18AUG22 | 24AUG23 | 275.6 | 3.2 | 1.2 |
| LBCFGL5_IHL8 | 69 | 06OCT21 | 15DEC22 | 93.1 | 1.1 | 1.2 |
| LBCFGL8_BR264 | 40 | 06OCT21 | 26JUL22 | 82.5 | 0.9 | 1.1 |
| LBCFGL8_BR897 | 12 | 18AUG22 | 07FEB23 | 84.3 | 0.6 | 0.7 |
| LBCFGL9_BR264 | 40 | 06OCT21 | 26JUL22 | 82.5 | 0.9 | 1.1 |
| LBCFGL9_BR897 | 78 | 18AUG22 | 24AUG23 | 83.6 | 1.1 | 1.3 |
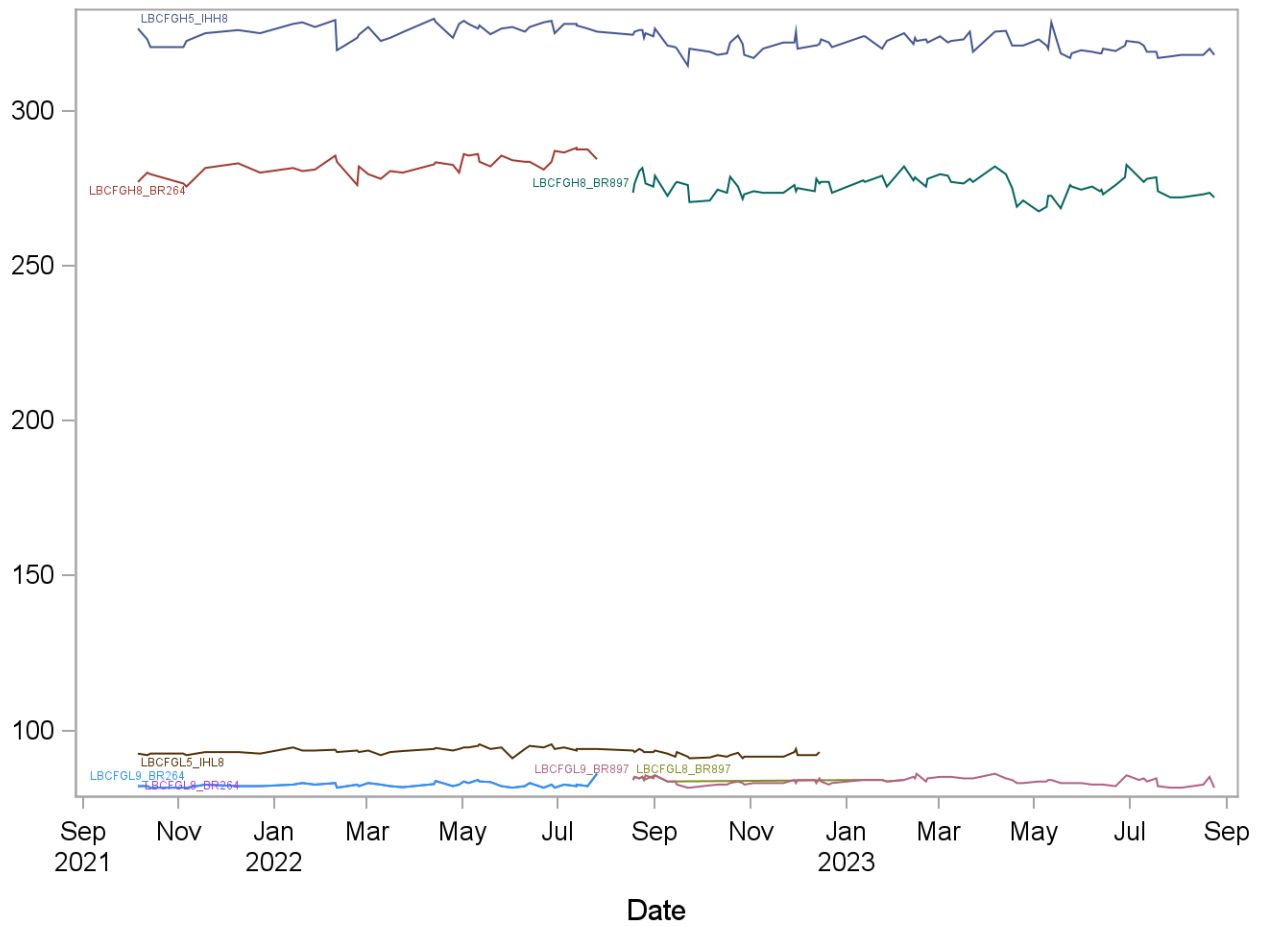
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