510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:

k182384

B. Purpose for Submission:

New device

C. Measurand:

Albumin and creatinine in urine

D. Type of Test:

Semi-quantitative urinalysis

E. Applicant:

Healthy.io, Ltd.

F. Proprietary and Established Names:

ACR | LAB Urine Analysis Test System

G. Regulatory Information:

1. Regulation section:

Name	Regulation	Product Code	Device Class
Creatinine test system	21 CFR 862.1225	JFY	II
Urinary protein or albumin (nonquantitative) test system	21 CFR 862.1645	JIR	I
Automated urinalysis system	21 CFR 862.2900	KQO	I

2. Panel:

Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indication(s) for use below.

2. Indication(s) for use:

   The ACR | LAB Urine Analysis Test System is comprised of a smartphone application, a proprietary Color-Board, and ACR Reagent Strips. It is intended for the semi-quantitative detection of albumin and creatinine in urine, as well as the presentation of their ratio. The ACR | LAB Urine Analysis Test System is intended for in-vitro diagnostic use by a healthcare professional in a point of care setting. These results may be used in conjunction with clinical evaluation as an aid in the diagnosis for kidney function.

3. Special conditions for use statement(s):

   For prescription use only.

   For in vitro diagnostic use only.

   Samples should be screened for blood prior to testing.

4. Special instrument requirements:

   A dedicated iPhone 7 (iOS 12.0) should be used for testing.

I. Device Description:

The device is provided as a kit that comprises a canister of 100 ACON Mission Urinalysis Reagent Strips (Microalbumin/Creatinine) (ACON Laboratories Inc., k150330), 10 individually-wrapped Color-Boards, and a User Manual. The ACR | LAB Urine Analysis Test System also consists of a smartphone application for use on a dedicated iPhone 7 (iOS 12.0), and an image recognition algorithm running on a back-end, cloud-based server.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Mission U120 Ultra Urine Analyzer and Mission Urinalysis Reagent Strips (Microalbumin/Creatinine)

2. Predicate 510(k) number(s):

   k142391

3. Comparison with predicate:

Similarities		
Item	Subject Device k182384 ACR | LAB Urine Analysis Test System	Predicate Device k142391 Mission U120 Ultra Urine Analyzer and Mission Urinalysis Reagent Strips (Microalbumin/Creatinine)
Intended Use	For the semi quantitative measurement of albumin and creatinine to assist diagnosis for kidney function.	Same
Sample Type	Human urine	Same
Measurement Principle	Reflectance photometry	Same

Differences		
Item	Subject Device k182384 ACR | LAB Urine Analysis Test System	Predicate Device k142391 Mission U120 Ultra Urine Analyzer and Mission Urinalysis Reagent Strips (Microalbumin/Creatinine)
Reader	iPhone 7 (iOS 12.0)	Mission U120 Ultra Urine Analyzer
Data Transfer	Internet connection between the dedicated smartphone, back-end server, and patient's electronic medical records	USB port and standard RS232C port

K. Standard/Guidance Document Referenced (if applicable):

- IEC 62304:2006, Medical device software - Software life cycle processes
- CLSI EP5-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition
- CLSI EP6-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
- CLSI EP7-A2, Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition
- CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition

L. Test Principle:

The albumin test is based on affinity binding of albumin to a sulfonephthalein dye at a constant pH. The development of pale green to aqua blue indicates the presence of albumin. The creatinine test is based on the peroxidase-like activity of a copper creatinine complex that catalyzes the reaction of diisopropylbenzene dihydroperoxide and 3,3',5,5'-tetramethylbenzidine. The resulting color ranges from orange through green to blue.

The ACR | LAB Urine Analysis Test System scans and analyzes the test strip using a mobile device running the smartphone application.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Repeatability testing was conducted at 3 sites using one iPhone 7 (iOS 12.0) smartphone at each site. Each site had one operator performing the tests using 3 spiked urine samples, 3 strip lots, and 7 test strips per lot for a total of 63 results per level across sites (21 per site). The results are summarized by site in the tables below.

Albumin

Level (mg/L)	N	Within Run % Agreement (Exact Match) Site 1	Within Run % Agreement (Exact Match) Site 2	Within Run % Agreement (Exact Match) Site 3	% Agreement (± 1 Color Block)
10	63	100% (21/21)	100% (21/21)	100% (21/21)	100% (63/63)
30	63	100% (21/21)	100% (21/21)	100% (21/21)	100% (63/63)
150	63	100% (21/21)	100% (21/21)	100% (21/21)	100% (63/63)

Creatinine

Level (mg/dL)	N	Within Run % Agreement (Exact Match) Site 1	Within Run % Agreement (Exact Match) Site 2	Within Run % Agreement (Exact Match) Site 3	% Agreement (± 1 Color Block)
10	63	100% (21/21)	100% (21/21)	100% (21/21)	100% (63/63)
50	63	100% (21/21)	100% (21/21)	100% (21/21)	100% (63/63)
300	63	100% (21/21)	100% (21/21)	100% (21/21)	100% (63/63)

Reproducibility testing was conducted at 3 sites using five iPhone 7 (iOS 12.0) smartphones at each site. Each site had one operator performing the tests using 3 spiked urine samples, 3 strip lots, and 2 runs per day in singlicate over 20 days for a total of 360 results per level across sites (120 per site). The results are summarized by site in the tables below.

Albumin

Level (mg/L)	N	% Agreement (Exact Match)	% Agreement (± 1 Color Block)
10	360	100% (360/360)	100% (360/360)
30	360	100% (360/360)	100% (360/360)
150	360	99.7% (359/360)	100% (360/360)

Creatinine

Level (mg/dL)	N	% Agreement (Exact Match)	% Agreement (± 1 Color Block)
10	360	100% (360/360)	100% (360/360)
50	360	98.9% (356/360)	100% (360/360)
300	360	100% (360/360)	100% (360/360)

b. Linearity/assay reportable range:

The reportable range for each analyte was evaluated by measuring five levels of creatinine (10, 50, 100, 200, and 300 mg/dL) and four levels of albumin (10, 30, 80, and 150 mg/L). The study was performed by 3 operators using 3 lots of test strips in replicates of 10 per lot for a total of 90 measurements per sample. Each operator used one iPhone 7 (iOS 12.0).

Albumin

Block Cut-off (mg/L)	Concentrations Tested (mg/L)	% Exact Match	% ± 1 Color Block
10	6-14	100	100
30	18-50	100	100
80	60-108	98.89	100
150	> 122	100	100

Creatinine

Block Cut-off (mg/dL)	Concentrations Tested (mg/dL)	% Exact Match	% ± 1 Color Block
10	6-26	100	100
50	34-70	97.78	100
100	80-140	98.89	100
200	160-240	98.89	100
300	> 260	100	100

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Traceability:
The device is traceable to a commercially available method.

d. *Detection limit:*

A limit of detection study was conducted to determine the cut-off points for every color block for both albumin and creatinine. Urine samples spiked with albumin (6 mg/L to 210 mg/L) or creatinine (6 mg/dL to 420 mg/dL) were each tested using 3 test strip lots and 6 replicates per lot using one iPhone 7 (iOS 12.0) smartphone. The cut-off for each color block is defined as the lowest concentration at which over 55% of the test results were positive. The results of the study are shown below.

Albumin

Color Block (mg/L)	Cut-off Concentration (mg/L)	(% positive)
10	6	100
30	18	66.7
80	60	55.56
150	122	66.7

Creatinine

Color Block (mg/dL)	Cut-off Concentration (mg/dL)	(% positive)
10	6	100
50	34	83.33
100	80	66.67
200	160	55.56
300	260	66.67

e. *Analytical specificity:*

Interference
Urine samples spiked with albumin (10 mg/L, 30 mg/L, 150 mg/L) or creatinine (10

mg/dL, 50 mg/dL, 300 mg/dL) were spiked with each potentially interfering substance at low and high concentrations or not spiked (control). Each sample was tested with 1 lot of test strips with 8 replicates using one iPhone 7 (iOS 12.0) smartphone. Interference was defined as a change in output of one or more color blocks between spiked and control samples. When interference was observed, further testing was conducted to identify the lowest concentration at which interference was observed.

The interferents and the highest concentrations tested are listed in the table below:

Substance	Highest Concentration Tested (mg/dL)	Substance	Highest Concentration Tested (mg/dL)
Lithium acetoacetate	250	Sodium chloride	5500
Ammonium chloride	100	Oxalic acid	70
Ascorbic acid	200	Sodium acetate	2.25
Uric acid	150	Riboflavin	10
Unconjugated bilirubin	170	Sodium bicarbonate	1500
Calcium chloride	275	Sodium nitrate	10
Creatine	10	Sodium nitrite	10
Creatinine	600	Sodium phosphate	500
Fructose	100	Theophylline	100
Galactose	80	Urea	400
Glycine	450	Blood	0.05%
Glucose	5000	Leucocytes	2500
Lactose	10	Human IgG	25
Hemolysate	10	Citric acid	75
Potassium chloride	1500		
Glycine	450		

The following table shows the substances that interfered with the proposed device. Results are expressed as the lowest concentration of the interfering substance that exhibited interference and the resulting change in output of the color block. The lowest concentration causing interference will be included in the ACR | LAB Urine Analysis Test System user manual.

Albumin

Interferent	Lowest Concentration Interference was Observed	Analyte Level	Affect on Results
Hemoglobin	2.13 mg/dL	10 mg/L	Falsely elevated by one color block
		30 mg/L	
Blood	0.033%	10 mg/L	Falsely elevated by one color block
		30 mg/L	
Sodium phosphate	218.75 mg/dL	10 mg/L	Falsely elevated by one color block
		30 mg/L	
Sodium chloride	1787.5 mg/dL	30 mg/L	Falsely decreased by one color block
Unconjugated bilirubin	6.38 mg/dL	10 mg/L	Falsely elevated by one color block
		30 mg/L	Falsely decreased by one color block
Pastassium chloride	656.25 mg/dL	30 mg/L	Falsely decreased by one color block
Riboflavin	6.625 mg/dL	30 mg/L	Falsely decreased by one color block
Human IgG	8.13 mg/dL	10 mg/L	Falsely elevated by one color block
		30 mg/L	
pH	10	30 mg/L	Falsely elevated by one color block

Creatinine

Interferent	Lowest Concentration Interference was Observed	Analyte Level	Affect on Results
Hemoglobin	2.13 mg/dL	10 mg/dL	Falsely elevated by one color block
		50 mg/dL	
Blood	0.033%	10 mg/dL	Falsely elevated by one color block
		50 mg/dL	
Sodium phosphate	162.5 mg/dL	50 mg/dL	Falsely decreased by one color block
		300 mg/dL	
Unconjugated bilirubin	93.5 mg/dL	10 mg/dL	Falsely elevated by one color block
		50 mg/dL	

Interferent	Lowest Concentration Interference was Observed	Analyte Level	Affect on Results
Pastassium chloride	825 mg/dL	50 mg/dL	Falsely elevated by one color block
Sodium chloride	1787.5 mg/dL	10 mg/dL	Falsely elevated by one color block
		50 mg/dL	
Sodium bicarbonate	159.38 mg/dL	50 mg/dL	Falsely decreased by one color block
		300 mg/dL	
Calcium chloride	120.31 mg/dL	50 mg/dL	Falsely elevated by one color block
Ascrobic acid	42.5 mg/dL	50 mg/dL	Falsely decreased by one color block
		300 mg/dL	

All urine samples evaluated by this device should be tested for blood using a urinalysis device that tests for blood. If testing indicates the presence of blood equal to or greater than 80 erythrocytes/microliter (≥2+), the sample should not be tested with this assay.

Urine samples with visible levels of color interferents (e.g., riboflavin, ascorbic acid) should not be tested with the device.

Specific gravity (SG)
Urine samples spiked with albumin (10 mg/L, 30 mg/L, 150 mg/L) or creatinine (10 mg/dL, 50 mg/dL, 300 mg/dL) were adjusted to specific gravities of 1.000, 1.005, 1.015, 1.020, 1.025, 1.030, 1.035, and 1.040. No interference from SG was detected on abumin or creatinine measurements in the examined range.

pH
Urine samples spiked with albumin (10 mg/L, 30 mg/L, 150 mg/L) or creatinine (10 mg/dL, 50 mg/dL, 300 mg/dL) were adjusted to pH 4.0, 5.0, 6.0, 8.0, and 9.0. pH of 10 showed interference at the 30 mg/L albumin block, and generated falsely increased results of +1 block. None of the other pH levels had an interfering effect at any other concentration of albumin or creatinine.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

375 male and female subjects, aged 18 – 80 years and older undergoing routine physical examinations, or with diseases such as Type 1 or Type 2 diabetes, hypertension, heart disease, kidney disease, and subjects with other ailments that represent the target population for this device were enrolled for testing at three sites. 60 spiked samples were used to supplement some analyte concentrations. All subjects provided a urine sample, which was measured with the device by one operator, and on the predicate device by a second technician. Results were consistent across the three test sites; results are summarized in the tables below.

Candidate	Predicate				
Albumin (mg/L)	10	30	80	150	Total count
10	229 (92.0%)	3 (3.7%)	0	0	232
30	20 (8.0%)	65 (80.2%)	4 (10.0%)	0	89
80	0	13 (16%)	35 (87.5%)	5 (7.8%)	53
150	0	0	1 (2.5%)	59 (92.2%)	60
Total count	249	81	40	64	434
% Exact Match	92.0%	80.2%	87.5%	92.2%	
% ± 1 color block	100%	100%	100%	100%	

Candidate	Predicate					
Creatinine (mg/dL)	10	50	100	200	300	Total count
10	124 (86.1%)	0	0	0	0	124
50	20 (13.9%)	82 (82.0%)	5 (5.4%)	0	0	107
100	0	18 (18.0%)	77 (82.8%)	5 (8.5%)	0	100
200	0	0	11 (11.8%)	48 (81.4%)	3 (7.8%)	62
300	0	0	0	6 (10.2%)	35 (92.2%)	41
Total count	144	100	93	59	38	440
% Exact Match	86.1%	82.0%	82.8%	81.4%	92.2%	
% ± 1 color block	100%	100%	100%	100%	100%	

Candidate	Predicate			
Albumin:Creatinine ratio (ACR)	Normal	Abnormal	High-Abnormal	Total count
Normal	264 92.0%	2 2.1%	0	266
Abnormal	23 8%	87 92.6%	1 1.9%	111
High-Abnormal	0	5 5.3%	52 98.1%	57
Total count	287	94	53	434
% exact agreement	92.0%	92.6%	98.1%	92.86

b. Matrix comparison:

Not applicable. This device is for testing with human urine only.

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable.

b. Clinical specificity:

Not applicable.

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

The following statements regarding expected values are provided in the ACR | LAB Urine Analysis Test System user manual:

Albumin: Normally, albumin is present in urine at concentrations < 20 mg/L[1]. Results of 20-200 mg/L may indicate microalbuminuria. It is associated with early-stage kidney disease when a small amount of Albumin, also called Microalbumin, is consistently present in urine. Clinical albuminuria is indicated by results of > 200 mg/L. These levels can be predictive of albumin excretion rates of 30-300 mg/24 hours and > 300 mg/24 hours, respectively[2-3]. Exercise, acute illness and fever, and urinary tract infections may temporarily elevate urinary albumin excretions.

Creatinine: Creatinine concentrations of 10-300 mg/dL are normally present in urine.

Albumin-to-Creatinine Ratio (microalbumin/Creatinine): Albumin is normally present in urine at concentrations of < 30 mg/g. Microalbuminuria is indicated at a ratio result of 30 - 300 mg/g (moderately increased) and clinical albuminuria at a ratio of > 300 mg/g (severely increased)[4].

1. Burtis C.A.; and Ashwood ER.: Tietz Textbook of Clinical Chemistry 3rd ed. Philadelphia: Saunders; 1999; pp. 483-484.
2. Mangili, R. et al.: Prevalence of Hypertension and Microalbuminuria in Adult Type 1 (Insulin-Dependent) Diabetic patients Without Renal Failure in Italy-Validation of Screening Techniques to Detect Microalbuminuria. Acta Diabetol. 29: 156-166; 1992.
3. American Diabetes Association, Clinical Practice Recommendations, Diabetes Care, Vol. 31, Suppl. 1, January 2008.
4. Position Statement: Diabetic Nephropathy. Diabetes Care 20: S24-S27; 1997.

N. Instrument Name:

iPhone 7 (iOS 12.0)

O. System Descriptions:

1. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes ___X____ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes ___X____ or No _____

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes ___X___ or No _____

3. Specimen Identification:

   Operators manually enter the patient identification number into the device.

4. Specimen Sampling and Handling:

   The test is performed by dipping the urinalysis reagent strip into a urine sample collected into a cup.

5. Calibration:

   No calibration is required.

6. Quality Control:

   The app has internal controls designed to account for environmental conditions that impact the accuracy of the test. The sponsor recommends testing commercially available positive and negative quality controls per the laboratory policies, in accordance with local, state, and federal regulations.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

1. Carryover study: Test strips were held in both the "up" (with the creatinine on top) and

"down" (with the albumin on top) positions for 0 (control), 15, 30, 60, 90, and 120 seconds after being dipped in solutions. The "up" experiment used a high-positive creatinine solution (300 mg/dL) and a negative albumin solution. The "down" experiment used a high-positive albumin solution (150 mg/L) with a negative creatinine solution. The experiment consisted of 240 measurements (6 timings x 2 test strips lots x 5 replicates x 2 operating systems x 2 configurations ("up" / "down") = 240 results). Though none of these configurations demonstrated any impact, labeling directs the user to place the test strips on the Color-Board after dipping it in the urine to prevent run-off from flowing from one patch into another.

2. Dipping study: Test strips were dipped in samples containing negative, low positive, and high positive concentrations (measured as 10, 30, and 150 mg/L albumin, respectively and 10, 50, and 300 mg/dL creatinine, respectively). Samples were measured for four different time durations to test the impact of various dipping times on the ACR | LAB's ability to perform accurate measurements: 1 second (control), 2 seconds, 5 seconds, and 10 seconds. Wetting time was held constant at 0 seconds and assay time was held constant at 60 seconds. The experiment consisted of 80 measurements (4 timings x 2 test strip lots x 5 replicates x 2 operating systems = 80 results). For creatinine, none of the various dipping times impacted the accuracy of the device. For albumin, at times 5- and 10-seconds there was an increase in false positive results. The user manual and in-app instructions direct the professional user to dip the ACR Reagent Strip for 1-second, and state that increasing the dipping time longer than 5 seconds can cause falsely increased results for albumin.

3. Wetting (“Blotting”) study: This experiment tested different "blotting" times, i.e. the tester dipped the test strips and then waited a specific amount of time before blotting the test strips and scanning it with the ACR | LAB device. Samples containing negative, low positive, and high positive concentrations (measured as 10, 30, and 150 mg/L albumin, respectively and 10, 50, and 300 mg/dL creatinine, respectively) were measured. There were six different waiting times: 0 seconds (control), 5 seconds, 10 seconds, 20 seconds, 40 seconds, and 60 seconds. Dipping time was held constant at 1 second and assay time was held constant at 60 seconds. The experiment consisted of 60 measurements per sample (6 timings x 2 test strip lots x 5 replicates x 1 iPhone). For creatinine, none of the various dipping times impacted the accuracy of the device. For albumin, waiting 60-seconds to blot the strip resulted in false positive results. The labeling and the in-app instructions direct the user to wipe the strip on the edge of the urine cup and then immediately absorb it on a paper towel for 1 second to remove any excess urine after dipping. The labeling also includes a warning that waiting longer than 60 seconds before blotting the strip can cause falsely increased results for albumin.

4. Assay time study: This experiment tested how different assay times impact the ACR | LAB's ability to measure accurate results. Test strips were dipped and then immediately blotted, per the device's instructions. The user then waited a predetermined amount of time before scanning the test strips: 60 seconds (control), 80 seconds, 100 seconds, and 120 seconds. Dipping time was held constant at 1 second and wetting time was held constant at 0 seconds. Samples containing negative, low positive, and high positive

concentrations (measured as 10, 30, and 150 mg/L albumin, respectively and 10, 50, and 300 mg/dL creatinine, respectively) were measured. . The experiment consisted of 40 measurements per sample (4 timings x 2 test strip lots x 5 replicates x 1 iPhone). None of the assay time durations had any impact on the ACR | LAB's ability to accurately measure albumin or creatinine. Labeling and in-app instructions direct the user to wait for 60 seconds and then scan the test strip and Color-Board.

5. Illumination study: The accuracy of the subject device was tested under ten simulated lighting conditions (fluorescent 6000K, fluorescent 2700K, compact fluorescent lamp 6000K, compact fluorescent lamp 6500K, compact fluorescent lamp 2700K, LED 6000K, LED 6500K, incandescent, halogen, CW LED). Two operators used one iPhone 7 (iOS 12.0) to test 2 spiked urine samples (10 mg/L or 150 mg/L albumin and 10 mg/dL or 300 mg/dL creatinine) with 2 strip lots and 3 replicates per lot or 5 printed test strip configurations (with creatinine at 10, 50, 100, 200, and 300 mg/dL and albumin at 10, 30, 80, and 150 mg/L) at 4 replicates per lot. All results were reported as an exact match with expected results.

6. Boundary study: The accuracy of the subject device was tested under 5 boundary conditions (i.e., different distances, angles, and extreme lighting conditions). One iPhone 7 (iOS 12.0) was used to test 2 spiked urine samples (10 mg/L or 150 mg/L albumin and 10 mg/dL or 300 mg/dL creatinine) with 2 strip lots and 3 replicates per lot or 5 printed test strip configurations (with creatinine at 10, 50, 100, 200, and 300 mg/dL and albumin at 10, 30, 80, and 150 mg/L) at 5 replicates per lot. All results were reported as an exact match with expected results.

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable.

R. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.