POSTER P0164

An Innovative Evidence-Based Laboratory Medicine (EBLM) Test to Assist Doctors in the Assessment of Hepatic and Bile-Pancreatic Exocrine Function

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BACKGROUND

Introduction

- According to the National Center for Health Statistics (NCHS)[1], **there are many diseases whose prevalence is highly concerning**. Some of these are related to the liver and bile-pancreatic exocrine function —such as hepatocellular and cholestatic diseases (intrahepatic, extrahepatic, and mixed origin)—, and the number of cases of these diseases is extremely high and it is predicted to continue increasing in the next years. For this reason, they are frequently listed among the most morbid diseases worldwide[2]. Although they are not life-threatening, they **can predispose patients to develop more severe conditions if they are not detected nor treated at an early stage**[2].
- Overweight and obesity, along with metabolic syndrome (MetS) are the main risk factors for these diseases[3].
- There are **2 billion people worldwide with overweight or obesity** —including 124 million children—, and these figures are expected to continue to increase[4]. As a consequence, the global prevalence of liver and bile-pancreatic exocrine diseases —such as non-alcoholic fatty liver disease (NAFLD), as well as its progression to non-alcoholic steatohepatitis (NASH), liver fibrosis (LF), and cirrhosis—, has become a serious global concern[2,5].

Healthcare Reactive Model

- Yet, **current healthcare system is based on being reactive to treat a patient when gets sick**[6,7], that is, when first symptons or signs appear. However, many diseases are asymptomatic —clinically silent, subclinical or paucisymptomatic—, or have absence or lack of symptoms and signs until the disease is more advanced.
- According to some estimates, **reactive health accounts for more than 75% of healthcare spending in the U.S.**[8]
- Besides, **reactive health increases the lead time**[8] —the time between the early detection of a disease by screening tests and the time of usual diagnosis after the onset of symptoms or signs and the patient's visit to a doctor—. The lead time in detecting these diseases is crucial, because **the sooner they are detected, the better the outcome will be for the patient**[8-10]. Nonetheless, many of these diseases have few or no symptoms in the early stages and the patient is not aware of them until they are in an advanced stage (**Figure 1**). So, it is mandatory to detect them even in the very early stages, before symptoms appear and when treatment is most likely to be successful.
- In response to the reactive model, the **preventive model has been proposed as the solution for a longer and healthier life**[10-12], but also as the best way to **reduce healthcare-related costs**[10-12]. The **preventive model is defined as the routine care that the patient receives to maintain its health**[10-12] and for this reason, **it is key to diagnosing medical conditions before they become a problem**.

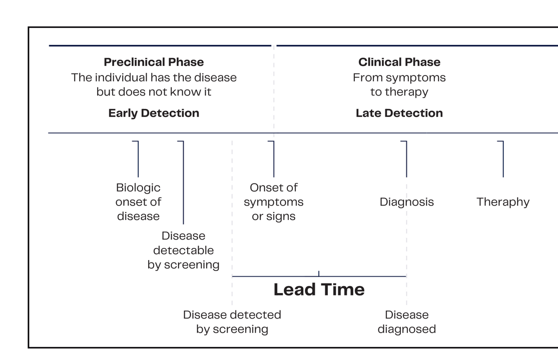


Figure 1. Lead time is the duration of time between the detection of the disease via screening tests and the time of its usual diagnosis after symptoms or signs appear and a patient goes to the doctor. It plays a critical role in the detection of several non-malignant, highly prevalent, morbid, cancer-precursor, and deadly diseases, because the shorter the lead time, the earlier the detection of the disease, the faster the next steps can be defined, potentially the better the prognosis, and the lower treatment-related costs.

Healthcare Costs

- The **high cost of healthcare is a burden on U.S. families**[8,9,13]. About **half of U.S. adults say it is difficult to afford healthcare costs**[8,9,13], and one in four say they or a family member in their household had problems paying for healthcare in the past 12 months[8,9] —younger adults, those with lower incomes, adults in fair or poor health, and the uninsured are particularly likely to report problems affording healthcare in the last year—.
- The **cost of healthcare can lead some to put off needed care**[8,9,14,15] —one in four adults say that in the past 12 months they have skipped or postponed getting healthcare they needed because of the cost[8,9,14,15]—.
- Notably **six in ten uninsured adults (61%) say they went without needed care because of the cost**[8].
- Healthcare debt is a burden for a large share of Americans —**about four in ten adults (41%) report having debt due to medical or dental bills including debts owed to credit cards, collections agencies, family and friends, banks, and other lenders to pay for their healthcare costs**[8], with disproportionate shares of Black and Hispanic adults, women, parents, those with low incomes, and uninsured adults saying they have healthcare debt—.

Chronic, Morbid and Cancer-Precursor Diseases, and Aging

- The World Health Organization (WHO) estimates that **chronic illnesses account for half of the global disease burden**[16], **a figure that will only rise as the world's population ages**. Chronic diseases pose a unique challenge as they require proactive, planned and integrated care because they are continuous and often caused by specific and preventable health risks.
- On the other hand, **long waiting lists exacerbated by the pandemic and new cases being treated further and further down the line**[17]. At the same time, we are seeing a **consistent rise in chronic illnesses**[16], **such as cardiovascular disease, diabetes and cancer**. Moreover, the risk of these chronic diseases actually increases with age as **nearly 95% of adults 60 and older have at least one —while nearly 80% have two or more**[18]—. With an ageing population and these growing numbers, it is clear this model is not sustainable[12].

OBJECTIVES

- To **define a minimum blood and/or urine —if needed—, panel capable of confirming —and/or detecting—, a wide range of liver —hepatocellular diseases—, and bile-pancreatic exocrine diseases —cholestatic diseases (extrahepatic, intrahepatic, or mixed origin)—**, that can result or not in hyperbilirubinemia. **Hepatocellular diseases** include: non-alcoholic fatty liver disease (NAFLD), as well as their subsequent complications, such as non-alcoholic steatohepatitis (NASH), liver fibrosis and cirrhosis and hepatocellular carcinoma (HCC); other not NAFLD-associated hepatitis —viral, alcoholic, or autoimmune—; genetic-related diseases —Budd Chiari syndrome (BCS); or Wilson's disease (WD)—; acute biliary obstruction (ABO); and rhabdomyolysis. On the other hand, **cholestatic extrahepatic diseases** include: biliary diseases —e.g., choledocholithiasis, choledochal cyst (CC)—; and pancreatic diseases —e.g., acute or chronic pancreatitis, pancreatic pseudocyst—. In the same way, **cholestatic intrahepatic diseases** include: obstructive diseases —e.g., primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), veno-occlusive disease (VOD)—; infectious diseases —e.g., sepsis, viral hepatitis—; and toxic diseases —e.g., drug-induced liver injury (DILI), alcoholic hepatitis—. In this process the price should be a very important variable since this panel should be the cheapest one to **enable universal and quality access to healthcare**.
- To **validate whether this new approach to a Evidence-Based Laboratory Medicine (EBLM) routine blood and/or urine —if needed—, could be used as a non-invasive test to assist doctors in the assessment —as well as screening— of a wide range of liver and bile-pancreatic exocrine diseases**, including: **hepatocellular diseases**, such as NAFLD, NASH, liver fibrosis, cirrhosis and HCC —as their prevalences in the U.S. population are concerning (**Figure 2**)—, other not NAFLD-associated hepatitis (viral, alcoholic, autoimmune), BCS, WD, ABO and rhabdomyolysis; **cholestatic extrahepatic diseases**, such as choledocholithiasis, CC, acute pancreatitis, chronic pancreatitis, and pancreatic pseudocyst; and **cholestatic intrahepatic diseases**, such as PBC, PSC, VOD, sepsis, viral hepatitis, DILI, and alcoholic hepatitis. If achieved, use these results to help the medical community to understand how EBLM and new technologies —mainly machine learning (ML) algorithms (also known as AI-powered diagnostic tools), based in large and quality datasets—, can help healthcare professionals to **improve diagnosis accuracy, reduce medical errors and misdiagnoses, as well as avoiding invasive —and/or unnecessary—, procedures**.
- To fine-tune the final details of our algorithm as a preliminary step to the upcoming multicenter and international clinical trial of 26,000 patients that will be performed from March 2025 to December 2026 (we are still in the process of recruiting hospitals and medical centers).
- To **validate the performance, accuracy and usefulness of several advanced EBLM indices, ratios, scores and/or coefficients** —all of them analyzed individually and by **different types of groupings in serial and in parallel**[19], to optimize overall specificity (Sp) and sensitivity (Se), respectively—, as tools based on machine learning (ML) algorithms for **clinical decision support system (CDSS)**, to **improve healthcare delivery by enhancing medical decisions with targeted clinical knowledge, patient information, and other health information**[20]:
  - Anthropometric indices, ratios and/or products: body mass index (BMI), waist-to-hip ratio (WHR), Deurenberg body fat (%), Palafolls body fat (%), Hodgdon Beckett body fat (%), body fat mass, lean body mass, ideal body fat Jackson Pollard, body fat to lose to ideal, body density, waist-to-height ratio (WHtR), lipid accumulation product (LAP), body adiposity index (BAI), visceral adiposity index (VAI), body shape index (BSI), and conicity index (CI). All these indices, ratios and products were calculated from a few simple clinical variables, such as age, height, weight, neck circumference, waist circumference, and hip circumference.
  - Atherogenic indices, ratios and/or coefficients and cardiovascular scores: atherogenic coefficient (AC), atherogenic index of plasma (AIP), Castelli risk index I, Castelli risk index I + bilirubin, Castelli risk index II, Castelli risk index II + bilirubin, cholesterol/bilirubin ratio, lipoprotein combine index (LCI), triglycerides/HDL-c index, Framingham risk score, SCORE, and vascular age. All these indices and ratios were calculated from a few simple clinical variables as well as laboratory determinations, such as gender, age, smoking habits, systolic pressure, diastolic pressure, total cholesterol, HDL-c, LDL-c, triglycerides, bilirubin, and glucose.
  - Pancreatic endocrine panels and/or indices, such as the National Cholesterol Education Program-Adult Treatment Panel III (ATP-III), the triglycerides and glucose (TyG) index, homeostatic model assessment for insulin resistance (HOMA-IR), HOMA-Beta, HOMA-S, HOMA-2, and quantitative insulin sensitivity check index (QUICKI). All these panels and indices were calculated from a few simple clinical variables as well as laboratory determinations, such as gender, waist circumference, systolic pressure, diastolic pressure, insulin, HDL-c, triglycerides, and glucose.
  - Hepatic and biliary tract indices and/or ratios, such as fatty liver index (FLI), hepatic steatosis index (HSI), K-NAFLD, ALD NAFLD index (ANI), activity NASH (acNASH), Gholam score, AST-to-platelet ratio index (APRI), BMI-age-ALT-triglycerides (BAAT), BMI-AST/ALT ratio-diabetes (BARD), FIB 4 score, Forns fibrosis index (FFI), R factor, and chronic liver disease (CLivD) score. All these indices and ratios were calculated from a few clinical variables as well as laboratory determinations, such as complete blood count (CBC), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), total cholesterol, HDL-c, LDL-c, triglycerides, insulin, total bilirubin, direct bilirubin, creatinine, and glucose.
  - Renal scores, such as creatinine clearance, and estimated glomerular filtration rate (eGFR). These scores were calculated from a few clinical variables as well as laboratory determinations, such as gender, age, ethnicity, weight, and serum creatinine.
- To **validate the performance and accuracy of the algorithm when used with vendors other than those with which the original algorithms were developed** —Sysmex (Kobe, Japan) for hematology and Roche Diagnostics (Rotkreuz, Switzerland) for biochemistry and immunoassay—, since several previous correlation studies alerted about potentially moderate differences in the performance between different reagent vendors —mainly in the normality limits—[21,22].
- To **collect data for future mid and/or long-term studies related to health economics outcome research (HEOR)**[23] **to analyze the cost effectiveness of machine learning (ML) algorithms as a CDSS**.

METHODS

This study was developed as a part of a previous one that has been presented at the European Society for Medical Oncology (ESMO) Congress 2024 for Multi-Cancer Early Detection (MCED)[24]. From this previous study —with 90 routine laboratory determinations included (**Table 3**)—, new studies were conducted, such as the one described here.

In this way, on the one hand, to develop the original algorithm for **an innovative evidence-based laboratory medicine (EBLM) test to assist doctors in the assessment of the hepatic and bile-pancreatic exocrine function**, several approximations were performed until find the best cost-effectiveness ratio (CER) —correlation of the net difference in the costs of two interventions to the net difference in their effectiveness—. First, the statistical evaluation of the algorithm was performed following the next steps: 1. The initial sample —training set of 99,631 patients— was divided in the training and validation sets (80% of the total patients for the training set and the remaining 20% for the validation set), to determine an initial accuracy. 2. All the data was preprocessed by converting those numeric variables that are categoric. 3. The next step consisted in visualizing the categoric dependent variables and all the different qualitative variables, to verify if the distribution was balanced or not, and if necessary, a corrective method was applied to adjust the unbalance of the classes, by modifying the original size of the whole training data. 4. The absent cases were detected, and an imputation treatment was implemented, either with the median or not, or with the most frequent values. 5. All the training and validation sets were analyzed, to detect variables with a variance of zero or close, because their variability will be similar or very low and they will bring noise. 6. The atypical values (outliers) that can affect the distribution of the variables were detected in the quantitative variables of the training set, to apply corrective measures and, if very atypical values were found, the imputation of atypical values was studied, determining firstly the cut-off value that indicates the abnormality of the variable, and the median was used as a replacement value for those observations that were above the cut-off. 7. The initial binary logistic regression (logit) was estimated by the general linear model (GLM) algorithm, with the argument *family = binomial (link = "logit")*, because the dependent variable is binary categoric, and the threshold to classify the attribute depended on what we wanted to predict (a priori the cut-off point was 0.5, because it is the standard cut-off to classify as healthy and sick). 8. The logit model achieved was evaluated through the following methods: assessment of the influential values and possibly atypical from the residues of the logit model; multicollinearity analysis —to evaluate the presence and the magnitude of strong linear relationships between predictive variables (independent variables) in the model—; goodness of fit —to determine if the model is valid and adequate for its use in decision making or in making predictions—; calculation of the importance of the predictive variables in the model, considering their weight through the decreasing of the mean average precision and the Gini decreasing average; as well as the final validation for the model with the validation set of the 20%, to determine the sensitivity, specificity, area under the receiver operating characteristic (AUROC) curve, positive predictive value (PPV), and negative predictive value (NPV). 9. The cut-off point was optimized, to finally adjust the binary logistic regression model. 10. The final evaluation of the binary logistic regression model was performed with the optimal cut-off point. Second, several combinations —up to 1 x 10^{90}—, were performed to find most significant groupings of laboratory determinations —mainly for the liver and bile-pancreatic exocrine function, but also for all other body functions and systems involved and/or related with them, this is, both causes and/or consequences—. Third, several calculations were performed, mainly those related with atherogenic indices (**Table 5**), pancreatic endocrine indices (**Table 6**), hepatic and biliary tract indices (**Table 7**), and renal indices (**Table 8**). We selected the ones that were Evidence-Based Laboratory Medicine (EBLM). In this way, performed atherogenic indices and cardiovascular scores were: atherogenic coefficient (AC)[25,26], atherogenic index of plasma (AIP)[25,27,28], Castelli risk index I (CRI-I)[29,30], CRI-I + bilirubin[30], Castelli risk index II(CRI-II)[30], CRI-II + bilirubin[30], cholesterol/ bilirubin ratio[30], lipoprotein combine index (LCI)[25], triglycerides/HDL-c index[31], Framingham risk score[32], Systematic Coronary Risk Evaluation (SCORE) model[33], and vascular age[34]. Besides, pancreatic endocrine indices performed were: adult treatment panel III (ATP-III)[35,36] —metabolic syndrome—, triglycerides and glucose (TyG) index[37], homeostatic model assessment for insulin resistance (HOMA-IR)[38,39], HOMA-Beta[38,39], HOMA-S[38,39], HOMA-2[40], and quantitative insulin sensitivity check index (QUICKI)[39] —insulin resistance—. Moreover, hepatic and biliary tract indices performed were: fatty liver index (FLI)[41,42], hepatic steatosis index (HSI)[42,43], K-NALFD score[44], liver fat score (LFS)[42], NAFLD logit score (NLS)[45], NAFLD Ridge score (NRS)[45], and ALD NAFLD index (ANI)[46] for the assessment of non-alcoholic fatty liver disease (NAFLD); activity NASH (acNASH)[47], ferritin-AST&ALT-platelets (FAT) score[48], Gholam score[49], and hypertension-ALT-insulin resistance (HAIR) score[50] for the assessment of non-alcoholic steatohepatitis (NASH); AST-to-platelet ratio index (APRI)[51,52], BMI-age-ALT-triglycerides (BAAT) score[52], BMI-AST/ALT ratio-diabetes (BARD) score[52,53], FIB 4 score[52,54], Fibrometer[55], Forns fibrosis index (FFI)[56], NAFLD Fibrosis Score (NFS)[53,57], and Steatosis-Associated Fibrosis Estimator (SAFE)[58], for the assessment of liver fibrosis and cirrhosis. R Factor[59], and chronic liver disease (CLivD) score[60] were also performed for further risk-assessment. Finally, renal indices performed were: creatinine clearance[61], and eGFR[62].

On the other hand, all patient data was computed with two machine learning (ML) algorithms, such as Evidence-Based Laboratory Medicine Algorithm (EBLMA)[24,63] and Artificial Intelligence Recursive Algorithm (AIRA)[24,64] —both developed by Blueberry Diagnostics (Barcelona, Spain) in 2020 to help in COVID-19 diagnosis[65-68]—, to improve both sensitivity and specificity. EBLMA includes several functions —sub-algorithms— to detect the following conditions: iron transport and storage function diseases; hemostasis alterations —coagulopathies and bleeding disorders (BD)—; cardiovascular disease (CVD) and atherosclerotic cardiovascular disease (ASCVD); pancreatic endocrine diseases —insulin resistance (IR), prediabetes, type 2 diabetes mellitus (DM2)—; hepatic function diseases —hepatocellular and cholestatic (both extrahepatic, intrahepatic or mixed origin)—; and renal function diseases —chronic kidney disease (CKD)—. Besides, AIRA is an algorithm that computes in a recursive way all the values from 0 to 100% for both sensitivity and specificity to find the optimal cutoff values for low, moderate (moderate-low and moderate-high), and high-risk results. Then, parallel approximations to optimize sensitivity (Se) were conducted. Afterwards, serial approximations to enhance specificity (Sp) were also performed. Finally, Cost Effectiveness Ratio Effect Boosting Recursive Optimizer (CEREBRO) —developed by Kience (Wilmington, DE, U.S.)—, adjusts resulting predictive values —the *p*-value— with the cost-effectiveness ratio (CER) —correlation of the net difference in the costs of two interventions to the net difference in their effectiveness—.

The training set was very heterogenous, as it included results analyzed by different suppliers for the same laboratory determinations —Sysmex, Horiba, Roche Diagnostics, Siemens Healthineers, or Beckmann Coulter, among others—, with their own systems and reference values. So, the variability and the potential biases of the results obtained by this way may be too high, thus affecting the quality of the results. In this way, to avoid these potential biases that can alter the results — and consequently, the accuracy of the algorithm—, the present study was designed with one single laboratory —Laboratorio Echevarne (Sant Cugat del Vallès, Barcelona, Spain)—, and consisted in a randomized controlled trial (RCT) with a target sample size (n) of 300.

All patients included in the RCT were recruited through three medical centers in Barcelona (Spain). Patients had to accept and sign the informed consent, the ethics committee approval, and the test requisition form (TRF) —an example of the new TRF designed for the upcoming RCT that will be performed in the U.S. with Empire City Laboratories (Brooklyn, NY, US) is shown (**Figure 4**)—. This TRF corresponds to the MCED trial[24] —with 90 laboratory determinations included—, from which this other study was developed —by using only 46 routine laboratory determinations (complete blood count included) of the total analyzed—. In the case of the present study, although target sample size was 300 patients, we decided to enroll 314 patients to allow some backup. However, according to the inclusion and exclusion criteria (**Figure 3**), 50 patients were initially excluded from the study, because they had ongoing clinically diagnosed pathologies, symptoms or signs, so the sample size dropped to 264 patients. From this new study population, 110 patients were excluded because they didn't show up at the clinical facility for any of the follow-up visits —this is a critical point to improve for the upcoming RCT, since the cost of each patient is very high and for this RCT almost a third of the patients already tested were lost—, so the new n consisted of 154 patients. From this new n, 2 patients were excluded, because some of their laboratory parameters and/or clinical information were wrong or incorrect. Thus, a final n of 152 patients was achieved. In this final n, both genders (male and female) were equally represented and the mean age of the participants was 53.34 years, being 54.64 (40 – 82) in the male population and 52.03 (41 – 77) in the female population (**Tables 1-8**). Patient's blood samples were obtained from October 2021 to June 2023. Blood samples were obtained by peripheral venipuncture in all participants. Complete blood count (CBC) was determined by Yumizen analyzers (Horiba, Kyoto, Japan). Coagulation analysis was determined by Stago analyzers (Paris, France). Serum proteins, hepatic enzymes, sterols and fatty acids, hormones, as well as the remaining serum analytes were measured by Atellica analyzers (Siemens, Munich, Germany). Glycated hemoglobin (HbA1c) was measured by Biorad analyzers (Hercules, CA, U.S.). Some of these analytes were tested with different analyzers from other providers during the study, because the laboratory changed them during these years, but that's not a big problem for us becuase is in accordance with one of our main objectives (to test the algorithm efficiency with different providers to see how it works with all of them). The majority of the tests were performed within two days after samples were obtained. Therefore, it is important to note that the laboratory where the RCT was performed does not have Roche Diagnostics analyzers —as one of the main objectives of the RCT—, so false positives (FP) and false negatives (FN) could occur since most major studies were conducted in hospitals using these equipments. Thus, the present study could have an additional bias due to the difference between the analyzers used in the modeling process of the algorithm and the RCT.

In this way, although several previous correlation studies alerted about potentially moderate differences in the performance between different reagent vendors —as mentioned above—, the reason why the validation of the algorithm was done in a lab with no Roche Diagnostics analyzers was to validate also its robustness and overall performance against different analyzers from different vendors. Therefore, in the upcoming clinical trial of 26,000 patients, several parallel studies of 120 patients will be performed by analysing blood and/or urine samples with different vendors to achieve correlation coefficients and curves, in order to further evaluate their overall robustness.

Once all results were obtained, all those that exhibited abnormal values —outside their reference ranges— were reprocessed, to make sure that they were not obtained due to technical errors and were real and potentially pathological. When all laboratory determinations were finished per each patient, they were processed by the last version of the above-mentioned algorithm giving their final result as well as determining the final accuracy with a validation set of 152 patients (**Table 9**). In turn, all patients with suspicious findings were referred to the corresponding medical centers for confirmation and subsequent classification in each of the groups —case and control—, designed for the biostatistics upcoming phase. Patients attended follow-up visits in one year.

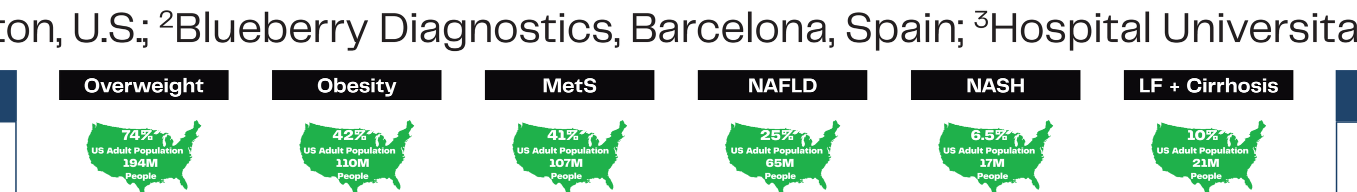


Figure 2. Prevalences of the main types of chronic liver disease (CLD) —non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), liver fibrosis (LF) and cirrhosis—, in the U.S., as well as their main risk factors —overweight, obesity, and metabolic syndrome (MetS)—.

Inclusion Criteria

- Men and women with not known currently clinically diagnosed pathologies, without symptoms or signs, white/caucasian ethnicity, aged 40, onwards; and
- Patients whose high anthropometric indicators and/or lifestyle habits may predispose them to non-malignant, highly prevalent, morbid, cancer-precursor, and deadly diseases (**Figure 2**).
  - Body mass index (BMI), waist-to-hip ratio (WHR), waist-to-height ratio (WtHR), hypertriglyceridemic waist (HW), visceral adiposity index (VAI) —which are indicative of overweight and obesity—; and/ or
  - High red/processed meat consumption, low fruits and vegetables intake, lack of physical activity, smoking habits, and/or alcohol intake.

Exclusion Criteria

- Patients who didn't meet the inclusion criteria or meet any of the following criteria:
  - Patients with any confirmed or found cancer during the whole study.
  - Patients that didn't show up at the clinical facility in any of the follow-up visits.
  - Patients lacking any of the laboratory parameters and/or clinical information.

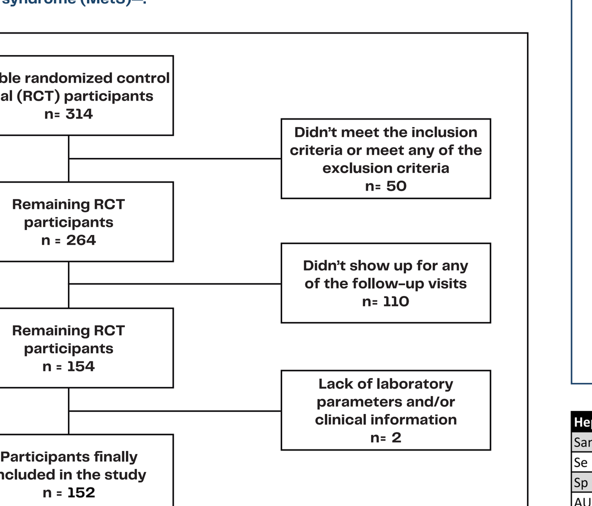
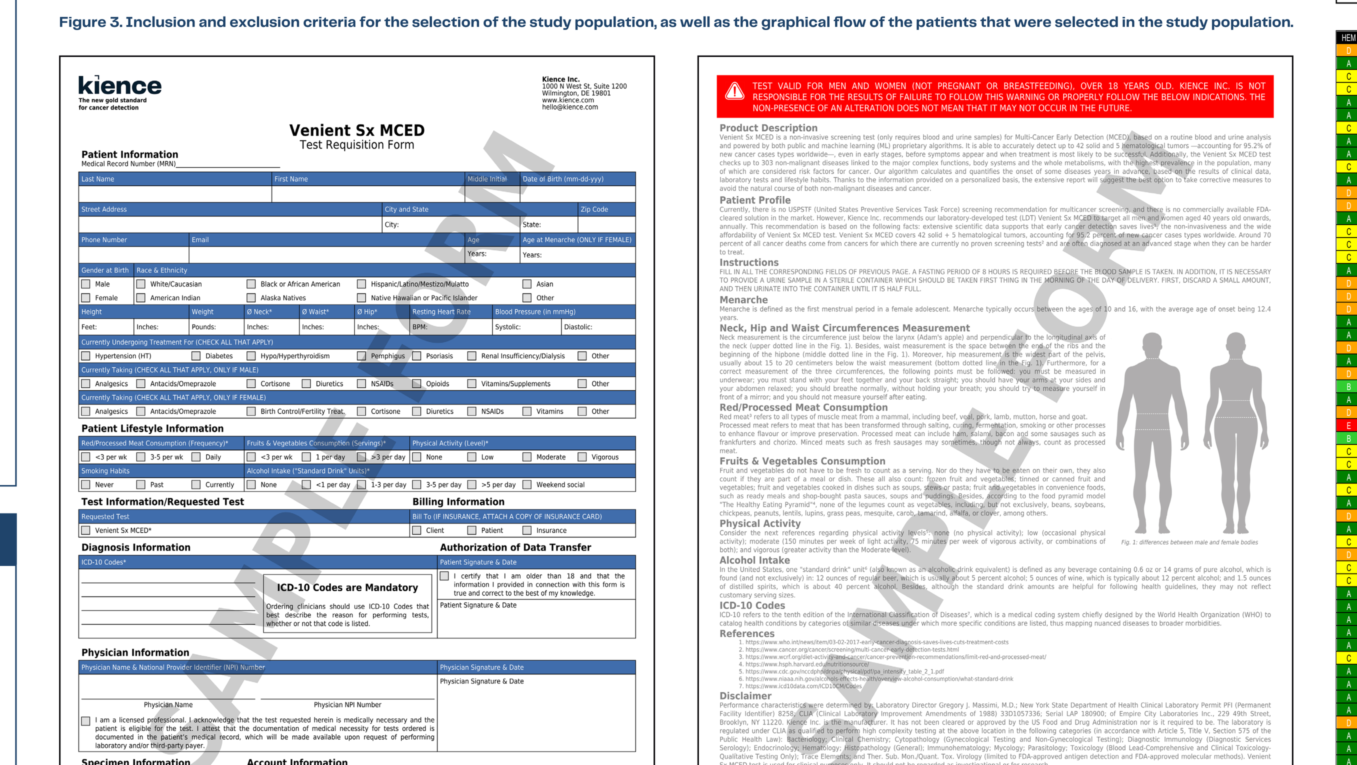


Figure 3. Inclusion and exclusion criteria for the selection of the study population, as well as the graphical flow of the patients that were selected in the study population.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Venient Sx MCED
Test Requisition Form

Patient Information
Medical Record Number (MRN)

Last Name	First Name	Middle Initial	Date of Birth (mm-dd-yyy)

Street Address | City and State | Zip Code
Phone Number | Email | Age | Age at Menarche (ONLY IF FEMALE)
Gender at Birth: Male; Female. Race & Ethnicity: White/Caucasian; American Indian; Black or African American; Alaska Natives; Hispanic/Latino/Mestizo/Mulatto; Native Hawaiian or Pacific Islander; Asian; Other
Height | Weight | Ø Neck* | Ø Waist* | Ø Hip* | Resting Heart Rate | Blood Pressure (in mmHg)
Feet: Inches: | Pounds: | Inches: | Inches: | Inches: | BPM: | Systolic: Diastolic:
Currently Undergoing Treatment For (CHECK ALL THAT APPLY): Hypertension (HT); Diabetes; Hypo/Hyperthyroidism; Pemphigus; Psoriasis; Renal Insufficiency/Dialysis; Other
Currently Taking (CHECK ALL THAT APPLY, ONLY IF MALE): Analgesics; Antacids/Omeprazole; Cortisone; Diuretics; NSAIDs; Opioids; Vitamins/Supplements; Other
Currently Taking (CHECK ALL THAT APPLY, ONLY IF FEMALE): Analgesics; Antacids/Omeprazole; Birth Control/Fertility Treat.; Cortisone; Diuretics; NSAIDs; Vitamins; Other

Patient Lifestyle Information
Red/Processed Meat Consumption (Frequency)*: <3 per wk; 3-5 per wk; Daily. Fruits & Vegetables Consumption (Servings)*: <3 per wk; 1 per day; >3 per day. Physical Activity (Level)*: None; Low; Moderate; Vigorous
Smoking Habits: Never; Past; Currently. Alcohol Intake ("Standard Drink" Units)*: None; <1 per day; 1-3 per day; 3-5 per day; >5 per day; Weekend social

Test Information/Requested Test
Requested Test: Venient Sx MCED*
Billing Information
Bill To (IF INSURANCE, ATTACH A COPY OF INSURANCE CARD): Client; Patient; Insurance

Diagnosis Information
ICD-10 Codes*
ICD-10 Codes are Mandatory
Ordering clinicians should use ICD-10 Codes that best describe the reason for performing tests, whether or not that code is listed.
Authorization of Data Transfer
Patient Signature & Date
I certify that I am older than 18 and that the information I provided in connection with this form is true and correct to the best of my knowledge.
Patient Signature & Date

Physician Information
Physician Name & National Provider Identifier (NPI) Number | Physician Signature & Date
Physician Name | Physician NPI Number
I am a licensed professional. I acknowledge that the test requested herein is medically necessary and the patient is eligible for the test. I attest that the documentation of medical necessity for tests ordered is documented in the patient's medical record, which will be made available upon request of performing laboratory and/or third-party payer.

Specimen Information | Account Information
Date Sample Taken | Time Sample Taken | Account Name | Account Address | Account Phone Number

* Refer to back page
K-TRF-308002090-20240715

TEST VALID FOR MEN AND WOMEN (NOT PREGNANT OR BREASTFEEDING), OVER 18 YEARS OLD. KIENCE INC. IS NOT RESPONSIBLE FOR THE RESULTS OF FAILURE TO FOLLOW THIS WARNING OR PROPERLY FOLLOW THE BELOW INDICATIONS. THE NON-PRESENCE OF AN ALTERATION DOES NOT MEAN THAT IT MAY NOT OCCUR IN THE FUTURE.
Product Description
Patient Profile
Instructions
Menarche
Neck, Hip and Waist Circumferences Measurement
Red/Processed Meat Consumption
Fruits & Vegetables Consumption
Physical Activity
Alcohol Intake
ICD-10 Codes
References
Disclaimer
Fig. 1: differences between male and female bodies
K-TRF-308002090-20240715

Figure 4. Test requisition form (TRF) for the RCT to be performed in the U.S. (Empire City Laboratories Inc., Brooklyn, NY, U.S.). This new RCT will be based in a sample size (n) of 1,000 patients —paying special attention to the proportion of different ethnicities of the population of the U.S.—.

Parameter	Total	Male	Female
Age (y.o.)	53,34 (40 - 82)	54,64 (40 - 82)	52,03 (41 - 77)
Height (cm)	170,14 (150 - 190)	176,77 (152 - 190)	163,51 (150 - 177)
Weight (kg)	71,66 (38,6 - 128)	83,32 (38,6 - 128)	59,99 (45 - 112)
Neck Circumference (cm)	36,5 (28 - 50)	40,2 (30 - 47)	32,79 (28 - 50)
Waist Circumference (cm)	86,57 (62,5 - 131)	96,71 (68,5 - 131)	76,43 (62,5 - 115)
Hip Circumference (cm)	97,79 (70 - 127)	100,66 (70 - 119)	94,91 (75 - 127)
Menarche (y.o.)	NA	NA	12,87 (9 - 17)
Systolic Pressure (mmHg)	116,93 (77 - 170)	122,45 (95 - 170)	111,42 (77 - 148)
Diastolic Pressure (mmHg)	73,56 (43 - 109)	77,03 (53 - 109)	70,09 (43 - 92)
Resting Heart Rate (BPM)	69,11 (42 - 110)	68,23 (42 - 110)	69,99 (55 - 99)

Table 1. Clinical data, displayed as the mean value of each parameter with the corresponding minimal (Min) and maximal (Max) value, for all patients and by gender: male and female.

Parameter	Total	Male	Female
Body Mass Index (BMI)	24,49 (15,94 - 36,6)	15,94 (16,71 - 36,6)	22,41 (-9,62 - 36,29)
Neck Circumference (cm)	36,56 (28 - 50)	30 (30 - 47)	32,92 (28 - 35,5)
Waist Circumference (cm)	86,64 (62,5 - 131)	68,5 (68,5 - 131)	76,58 (62,5 - 116)
Hip Circumference (cm)	97,61 (70 - 127)	70 (70 - 119)	94,56 (75 - 127)
Waist-to-Hip Ratio (WHR)	0,88 (0,7 - 1,17)	0,8 (0,8 - 1,12)	0,81 (0,7 - 1,17)
Deurenberg Body Fat (%)	30,79 (13,51 - 54,06)	13,51 (13,51 - 39,69)	33,31 (25 - 54,06)
Palafolls Body Fat (%)	32,26 (19,15 - 49,71)	19,15 (19,15 - 39,53)	35,19 (28,47 - 49,71)
Hodgdon Beckett Body Fat (%)	25,14 (8,49 - 54,01)	9,1 (9,1 - 38,7)	27,34 (8,49 - 54,01)
Body Fat Mass	18,68 (4,58 - 56,71)	5,34 (5,34 - 45,67)	17,53 (4,58 - 56,71)
Lean Body Mass	52,98 (33,26 - 82,5)	33,26 (33,26 - 82,5)	42,46 (34,59 - 64,28)
Ideal Body Fat Jackson Pollard	21,23 (15,3 - 26,3)	15,3 (15,3 - 20,9)	24,01 (20,9 - 26,3)
Body Fat To Lose To Ideal	3,76 (-9,62 - 30,25)	-8,58 (-8,58 - 24,51)	3,06 (-9,62 - 30,25)
Body Density	1,04 (0,98 - 1,08)	1,01 (1,01 - 1,08)	1,04 (0,98 - 1,08)
Waist-to-Height Ratio (WHtR)	0,51 (0,37 - 0,73)	0,41 (0,41 - 0,73)	0,47 (0,37 - 0,68)
Lipid Accumulation Product (LAP)	28,82 (2,75 - 202,98)	3,92 (3,92 - 202,98)	15,29 (2,75 - 77,48)
Body Adiposity Index (BAI)	26,09 (15,54 - 43,27)	18,27 (18,27 - 34,82)	27,3 (15,54 - 43,27)
Visceral Adiposity Index (VAI)	0,97 (0,2 - 7,58)	0,2 (0,2 - 7,58)	0,7 (0,25 - 2,95)
Body Shape Index (BSI)	0,08 (0,06 - 0,1)	0,07 (0,07 - 0,1)	0,08 (0,06 - 0,06)
Conicity Index (CI)	1,23 (0,94 - 1,53)	1,06 (1,06 - 1,53)	1,16 (0,94 - 1,48)

Table 2. Anthropometric indices and ratios, displayed as the mean value of each parameter with the corresponding minimal (Min) and maximal (Max) value, for all patients and by gender: male and female.

Parameter	Total	Male	Female
Red Blood Cell Count (*10^12/L)	4,53 (3,18 - 5,64)	4,76 (4,07 - 5,64)	4,3 (3,18 - 5,49)
Hemoglobin (g/dL)	13,82 (7,1 - 17,3)	14,6 (7,1 - 17,3)	13,04 (9,3 - 15,8)
Hematocrit (%)	41,14 (23,3 - 51)	43,36 (23,3 - 51)	38,93 (29,3 - 47,7)
HCT/Hb	2,99 (2,79 - 4,69)	2,98 (2,79 - 4,69)	2,99 (2,82 - 3,6)
ESR (mm)	5,63 (2 - 38)	4,96 (2 - 18)	6,3 (2 - 38)
MCV (fL)	91,13 (53,69 - 107,37)	91,34 (53,69 - 107,37)	90,92 (70,77 - 106,6)
MCH (pg)	30,71 (16,36 - 35,63)	30,9 (16,36 - 35,63)	30,52 (22,46 - 34,52)
MCHC (g/dL)	33,68 (30,47 - 36,22)	33,8 (30,47 - 36,22)	33,57 (31,74 - 35,44)
RDW (%)	14,25 (11,7 - 21,9)	14,37 (11,9 - 21,9)	14,12 (11,7 - 19,8)
Leukocytes Absolute (x10^9/L)	5,51 (2,93 - 9,33)	5,73 (2,96 - 9,28)	5,29 (2,93 - 9,33)
Neutrophils Absolute (x10^9/L)	3,22 (1,11 - 7,13)	3,33 (1,11 - 7,13)	3,12 (1,31 - 6,67)
Lymphocytes Absolute (x10^9/L)	1,67 (0,76 - 2,89)	1,73 (0,76 - 2,72)	1,61 (0,91 - 2,89)
Monocytes Absolute (x10^9/L)	0,42 (0,15 - 0,79)	0,46 (0,23 - 0,79)	0,39 (0,15 - 0,76)
Eosinophils Absolute (x10^9/L)	0,17 (0,02 - 1,01)	0,19 (0,02 - 0,59)	0,15 (0,03 - 1,01)
Basophils Absolute (x10^9/L)	0,03 (0 - 0,09)	0,03 (0 - 0,09)	0,02 (0 - 0,07)
Neutrophils Ratio (%)	57,38 (32,6 - 78,3)	57,17 (32,6 - 78,3)	57,6 (40,6 - 76,7)
Lymphocytes Ratio (%)	31,21 (12,5 - 58)	30,78 (12,5 - 58)	31,65 (15,3 - 48,2)
Monocytes Ratio (%)	7,79 (4 - 12,8)	8,1 (4,4 - 11,9)	7,48 (4 - 12,8)
Eosinophils Ratio (%)	3,07 (0,4 - 12,3)	3,37 (0,4 - 10,3)	2,76 (0,4 - 12,3)
Basophils Ratio (%)	0,55 (0,1 - 1,8)	0,59 (0,1 - 1,8)	0,52 (0,1 - 1,4)
Platelet Count (x10^9/L)	232,98 (136 - 372)	230,3 (136 - 332)	235,67 (143 - 372)
MPV (fL)	9,56 (6,8 - 14)	9,55 (8 - 14)	9,57 (6,8 - 12,8)
PDW (%)	16,65 (8,2 - 30,4)	16,68 (8,2 - 26,4)	16,62 (9,2 - 30,4)
PT (%)	92,61 (24 - 100)	90,96 (24 - 100)	94,26 (67 - 100)
aPTT (s)	31,11 (24,6 - 52,4)	31,2 (25,2 - 52,4)	31,03 (24,6 - 38,1)
Calcium (mg/L)	96,45 (85,6 - 114,3)	96,76 (86,3 - 106,8)	96,14 (85,6 - 114,3)
Chloride (mmol/L)	105,95 (98 - 110)	105,7 (98 - 110)	106,21 (103 - 110)
Magnesium (mg/dL)	1,99 (1,64 - 2,97)	2,02 (1,75 - 2,97)	1,95 (1,64 - 2,52)
Phosphorus (mg/dL)	3,49 (1,9 - 6,7)	3,36 (2,2 - 4,7)	3,61 (1,9 - 6,7)
Potassium (mmol/L)	4,24 (3,42 - 5,21)	4,3 (3,42 - 5,21)	4,18 (3,51 - 4,98)
Sodium (mmol/L)	140,09 (131,8 - 147)	140,23 (131,8 - 147)	139,96 (136,5 - 147)
Albumin (g/L)	45,44 (39 - 52)	45,54 (39 - 52)	45,34 (40 - 50)
Apolipoprotein A1 (mg/dL)	147,34 (93 - 230)	136,38 (93 - 230)	158,29 (109 - 220)
Apolipoprotein B (mg/dL)	89,03 (50 - 179)	96,22 (56 - 179)	81,83 (50 - 133)
CRP-hs (mg/L)	1,66 (0,15 - 17,47)	1,7 (0,15 - 12,54)	1,61 (0,15 - 17,47)
Ferritin (ng/mL)	83,91 (3,3 - 457,1)	117,98 (3,6 - 457,1)	49,85 (3,3 - 330,7)
Globulin (g/L)	25,79 (18 - 39)	25,51 (18 - 33,6)	26,08 (19 - 39)
Lipoprotein (a) (mg/dL)	32,6 (9,99 - 158,58)	39,61 (9,99 - 158,58)	25,59 (9,99 - 112,04)
Total Protein (g/L)	71,23 (59 - 83)	71,05 (59 - 78,3)	71,42 (64 - 83)
ALP (IU/L)	65,3 (30 - 311)	65,53 (39 - 311)	65,08 (30 - 311)
AST (IU/L)	23,03 (13 - 70)	25,32 (15 - 70)	20,75 (13 - 55)
ALT (IU/L)	22,39 (7 - 88)	26,24 (8 - 88)	18,54 (7 - 62)
GGT (IU/L)	23,2 (6,99 - 167)	26,5 (10 - 167)	19,89 (6,99 - 105)
LDH (IU/L)	162,63 (114 - 250)	168,54 (114 - 250)	156,72 (116 - 204)
Total Cholesterol (mg/dL)	194,02 (120 - 302)	196,54 (135 - 302)	191,5 (120 - 268)
Cholesterol HDL (mg/dL)	60,01 (31 - 95)	50,82 (31 - 95)	69,2 (42 - 95)
Cholesterol non-HDL (mg/dL)	134,01 (53 - 265)	145,72 (53 - 265)	122,3 (53 - 185)
Cholesterol LDL (mg/dL)	115,86 (35,4 - 223,49)	123,82 (35,4 - 223,49)	107,89 (35,4 - 173)
Cholesterol VLDL (mg/dL)	18,15 (6,6 - 74,44)	21,9 (6,8 - 74,44)	14,41 (6,6 - 32,66)
Triglycerides (mg/dL)	96,48 (33 - 603)	120,32 (34 - 603)	72,64 (33 - 209)
Vitamin B 12 (pg/mL)	415,97 (221 - 1092)	392,37 (221 - 1084)	439,58 (262 - 1092)
Vitamin D 25-OH (ng/mL)	28,71 (12,03 - 104,18)	26,93 (12,03 - 104,18)	30,49 (12,77 - 88,29)
Anti-CCP ab (U/mL)	0,73 (0,43 - 10,3)	0,78 (0,43 - 10,3)	0,68 (0,49 - 4,1)
H. pylori IgG Ab. (U/mL)	1,95 (0,32 - 8,01)	2,18 (0,32 - 8,01)	1,72 (0,39 - 8,01)
Rheumatoid Factor (UI/mL)	8,86 (3,99 - 210)	12,44 (3,99 - 210)	5,29 (3,99 - 12)
FSH (mIU/mL)	NA (0,29 - NA)	(-)	42,88 (0,29 - 175,54)
Insulin (µU/mL)	7,76 (1,37 - 37,05)	8,04 (1,37 - 26,73)	7,5 (3,01 - 37,05)
PTHi (pg/mL)	41,71 (10 - 140,6)	42,99 (14,4 - 85)	40,43 (10 - 140,6)
TSH (mIU/L)	2,59 (0,22 - 40,22)	2,29 (0,27 - 40,22)	2,88 (0,22 - 40,22)
T4 Free (ng/dL)	1,05 (0,63 - 1,7)	1,06 (0,63 - 1,56)	1,03 (0,63 - 1,7)
AFP (ng/mL)	2,89 (1,09 - 16,4)	3,1 (1,09 - 16,4)	2,68 (1,09 - 15,3)
Beta-hCG (mU/mL)	1127,26 (1,99 - 85483,2)	NA	1127,26 (1,99 - 85483,2)
CA 19,9 (U/mL)	8,42 (1,19 - 56,39)	39,76 (1,19 - 56,39)	9,84 (1,19 - 45,64)
CA 125 (U/mL)	13,96 (2,6 - 50,5)	NA	13,96 (2,6 - 50,5)
CEA (ng/mL)	1,49 (0,39 - 4,3)	1,59 (0,49 - 4,3)	1,39 (0,39 - 3,15)
Total PSA (ng/mL)	1,23 (0,07 - 12,86)	1,23 (0,07 - 12,86)	NA
Free PSA (ng/mL)	0,36 (0,01 - 1,39)	0,36 (0,01 - 1,39)	NA
Creatinine (mg/dL)	0,88 (0,56 - 1,78)	0,99 (0,62 - 1,78)	0,77 (0,56 - 1)
Glucose (mg/dL)	95,05 (74 - 142)	96,78 (75 - 142)	93,33 (74 - 125)
HbA1c (%)	5,28 (3,6 - 7,2)	5,34 (3,6 - 7,2)	5,22 (4,4 - 6,2)
Serum Iron (µg/dL)	92,16 (13 - 237)	95,05 (21 - 206)	89,28 (13 - 237)
Total Bilirubin (mg/dL)	0,72 (0,22 - 1,98)	0,76 (0,26 - 1,72)	0,68 (0,22 - 1,98)
Direct Bilirubin (mg/dL)	0,23 (0,09 - 0,65)	0,24 (0,09 - 0,58)	0,22 (0,09 - 0,65)
Indirect Bilirubin (mg/dL)	0,49 (-0,43 - 1,36)	0,53 (0,17 - 1,36)	0,46 (-0,43 - 1,35)
Urea (mg/dL)	35,31 (17 - 62)	36,96 (19 - 62)	33,66 (17 - 51)
BUN (mg/dL)	16,48 (7,93 - 28,93)	17,25 (8,87 - 28,93)	15,71 (7,93 - 23,8)
Uric Acid (mg/dL)	5,05 (2,1 - 10,3)	5,89 (2,7 - 10,3)	4,22 (2,1 - 7,7)
Urine Albumin (g/L)	0,11 (0,04 - 0,82)	0,11 (0,04 - 0,82)	0,11 (0,04 - 0,82)
Urine Creatinine (g/L)	1,38 (0,35 - 3,92)	1,56 (0,39 - 3,92)	1,2 (0,35 - 3,42)
Urine Density (g/L)	1020,22 (1007 - 1034)	1020,88 (1008 - 1032)	1019,55 (1007 - 1034)
Urine pH	5,76 (5 - 7,5)	5,82 (5 - 7,5)	5,7 (5 - 7,5)
Urine Leukocytes	0,31 (0 - 3)	0,04 (0 - 2)	0,58 (0 - 3)
Urine Nitrites	0,05 (0 - 1)	0,03 (0 - 1)	0,07 (0 - 1)
Urine Protein	0,03 (0 - 2)	0 (0 - 0)	0,07 (0 - 2)
Urine Glucose	0,01 (0 - 2)	0,03 (0 - 2)	0 (0 - 0)
Urine Ketones	0,07 (0 - 3)	0,07 (0 - 3)	0,08 (0 - 3)
Urine Urobilinogen	0,04 (0 - 2)	0,05 (0 - 2)	0,03 (0 - 2)
Urine Urobilin	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)
Urine Red Blood Cells	0,09 (0 - 2)	0,03 (0 - 2)	0,14 (0 - 2)
Urine Hemoglobin	0,09 (0 - 2)	0,03 (0 - 2)	0,14 (0 - 2)

Table 3. Raw laboratory data, displayed as the mean value of each parameter with the corresponding minimal (Min) and maximal (Max) value, for all patients and by gender: male and female. Urine leukocytes, urine nitrites, urine protein, urine glucose, urine ketones, urine urobilinogen, urine urobilin, urine red blood cells and urine hemoglobin are expressed as 0 for "no/none", 1 for "positive +", 2 for "positive ++" and 3 for "positive +++". The data for this study comes from the results obtained from a few of these laboratory determinations (see selected laboratory determinations in Table 4), since the main approach is to generate the cheapest and universally useful panel possible for as many of these diseases as possible.

Parameter	Total	Male	Female
Red Blood Cell Count (*10^12/L)	4,53 (3,18 - 5,64)	4,76 (4,07 - 5,64)	4,3 (3,18 - 5,49)
Hemoglobin (g/dL)	13,82 (7,1 - 17,3)	14,6 (7,1 - 17,3)	13,04 (9,3 - 15,8)
Hematocrit (%)	41,14 (23,3 - 51)	43,36 (23,3 - 51)	38,93 (29,3 - 47,7)
HCT/Hb	2,99 (2,79 - 4,69)	2,98 (2,79 - 4,69)	2,99 (2,82 - 3,6)
MCV (fL)	91,13 (53,69 - 107,37)	91,34 (53,69 - 107,37)	90,92 (70,77 - 106,6)
MCH (pg)	30,71 (16,36 - 35,63)	30,9 (16,36 - 35,63)	30,52 (22,46 - 34,52)
MCHC (g/dL)	33,68 (30,47 - 36,22)	33,8 (30,47 - 36,22)	33,57 (31,74 - 35,44)
RDW (%)	14,25 (11,7 - 21,9)	14,37 (11,9 - 21,9)	14,12 (11,7 - 19,8)
Leukocytes Absolute (x10^9/L)	5,51 (2,93 - 9,33)	5,73 (2,96 - 9,28)	5,29 (2,93 - 9,33)
Neutrophils Absolute (x10^9/L)	3,22 (1,11 - 7,13)	3,33 (1,11 - 7,13)	3,12 (1,31 - 6,67)
Lymphocytes Absolute (x10^9/L)	1,67 (0,76 - 2,89)	1,73 (0,76 - 2,72)	1,61 (0,91 - 2,89)
Monocytes Absolute (x10^9/L)	0,42 (0,15 - 0,79)	0,46 (0,23 - 0,79)	0,39 (0,15 - 0,76)
Eosinophils Absolute (x10^9/L)	0,17 (0,02 - 1,01)	0,19 (0,02 - 0,59)	0,15 (0,03 - 1,01)
Basophils Absolute (x10^9/L)	0,03 (0 - 0,09)	0,03 (0 - 0,09)	0,02 (0 - 0,07)
Neutrophils Ratio (%)	57,38 (32,6 - 78,3)	57,17 (32,6 - 78,3)	57,6 (40,6 - 76,7)
Lymphocytes Ratio (%)	31,21 (12,5 - 58)	30,78 (12,5 - 58)	31,65 (15,3 - 48,2)
Monocytes Ratio (%)	7,79 (4 - 12,8)	8,1 (4,4 - 11,9)	7,48 (4 - 12,8)
Eosinophils Ratio (%)	3,07 (0,4 - 12,3)	3,37 (0,4 - 10,3)	2,76 (0,4 - 12,3)
Basophils Ratio (%)	0,55 (0,1 - 1,8)	0,59 (0,1 - 1,8)	0,52 (0,1 - 1,4)
Platelet Count (x10^9/L)	232,98 (136 - 372)	230,3 (136 - 332)	235,67 (143 - 372)
MPV (fL)	9,56 (6,8 - 14)	9,55 (8 - 14)	9,57 (6,8 - 12,8)
PDW (%)	16,65 (8,2 - 30,4)	16,68 (8,2 - 26,4)	16,62 (9,2 - 30,4)
PT (%)	92,61 (24 - 100)	90,96 (24 - 100)	94,26 (67 - 100)
aPTT (s)	31,11 (24,6 - 52,4)	31,2 (25,2 - 52,4)	31,03 (24,6 - 38,1)
Albumin (g/L)	45,44 (39 - 52)	45,54 (39 - 52)	45,34 (40 - 50)
Ferritin (ng/mL)	83,91 (3,3 - 457,1)	117,98 (3,6 - 457,1)	49,85 (3,3 - 330,7)
Globulin (g/L)	25,79 (18 - 39)	25,51 (18 - 33,6)	26,08 (19 - 39)
Total Protein (g/L)	71,23 (59 - 83)	71,05 (59 - 78,3)	71,42 (64 - 83)
ALP (IU/L)	65,3 (30 - 311)	65,53 (39 - 311)	65,08 (30 - 311)
AST (IU/L)	23,03 (13 - 70)	25,32 (15 - 70)	20,75 (13 - 55)
ALT (IU/L)	22,39 (7 - 88)	26,24 (8 - 88)	18,54 (7 - 62)
GGT (IU/L)	23,2 (6,99 - 167)	26,5 (10 - 167)	19,89 (6,99 - 105)
LDH (IU/L)	162,63 (114 - 250)	168,54 (114 - 250)	156,72 (116 - 204)
Total Cholesterol (mg/dL)	194,02 (120 - 302)	196,54 (135 - 302)	191,5 (120 - 268)
Cholesterol HDL (mg/dL)	60,01 (31 - 95)	50,82 (31 - 95)	69,2 (42 - 95)
Cholesterol non-HDL (mg/dL)	134,01 (53 - 265)	145,72 (53 - 265)	122,3 (53 - 185)
Cholesterol LDL (mg/dL)	115,86 (35,4 - 223,49)	123,82 (35,4 - 223,49)	107,89 (35,4 - 173)
Cholesterol VLDL (mg/dL)	18,15 (6,6 - 74,44)	21,9 (6,8 - 74,44)	14,41 (6,6 - 32,66)
Triglycerides (mg/dL)	96,48 (33 - 603)	120,32 (34 - 603)	72,64 (33 - 209)
Insulin (µU/mL)	7,76 (1,37 - 37,05)	8,04 (1,37 - 26,73)	7,5 (3,01 - 37,05)
Creatinine (mg/dL)	0,88 (0,56 - 1,78)	0,99 (0,62 - 1,78)	0,77 (0,56 - 1)
Glucose (mg/dL)	95,05 (74 - 142)	96,78 (75 - 142)	93,33 (74 - 125)
HbA1c (%)	5,28 (3,6 - 7,2)	5,34 (3,6 - 7,2)	5,22 (4,4 - 6,2)
Total Bilirubin (mg/dL)	0,72 (0,22 - 1,98)	0,76 (0,26 - 1,72)	0,68 (0,22 - 1,98)
Direct Bilirubin (mg/dL)	0,23 (0,09 - 0,65)	0,24 (0,09 - 0,58)	0,22 (0,09 - 0,65)
Indirect Bilirubin (mg/dL)	0,49 (-0,43 - 1,36)	0,53 (0,17 - 1,36)	0,46 (-0,43 - 1,35)

Table 4. Selected laboratory data, displayed as the mean value of each parameter with the corresponding minimal (Min) and maximal (Max) value, for all patients and by gender: male and female.

Parameter	Total	Male	Female
Triglycerides/HDL-c index	1,91 (0,42 - 16,75)	2,7 (0,49 - 16,75)	1,13 (0,42 - 4,86)
Atherogenic index of plasma (AIP)	-0,2 (-0,73 - 0,86)	-0,05 (-0,67 - 0,86)	-0,36 (-0,73 - 0,33)
Castelli risk I	3,48 (1,56 - 8,16)	4,1 (1,56 - 8,16)	2,86 (1,56 - 4,59)
Castelli risk I + bilirubin	1,58 (0,58 - 2,91)	1,68 (0,75 - 2,91)	1,47 (0,58 - 2,31)
Castelli risk II	2,13 (0,37 - 6,14)	2,62 (0,37 - 6,14)	1,64 (0,37 - 3,08)
Castelli risk II + bilirubin	0,95 (0,23 - 2,14)	1,06 (0,23 - 2,14)	0,84 (0,23 - 1,47)
Cholesterol/bilirubin ratio	3,23 (0,83 - 8,81)	3,09 (1 - 8,81)	3,37 (0,83 - 8,73)
Atherogenic coefficient (AC)	2,48 (0,56 - 7,16)	3,1 (0,56 - 7,16)	1,86 (0,56 - 3,59)
Lipoprotein combine index (LCI)	4,49 (3,66 - 5,62)	4,68 (3,69 - 5,62)	4,3 (3,66 - 4,95)
Framingham Score	6,6 (0,7-37,36)	9,97 (2,12-37,36)	3,22 (0,7-23,87)
CVD Score	1,47 (0,02 - 12,6)	2,2 (0,13 - 12,6)	0,74 (0,02 - 6,32)
Vascular Age	53,68 (40 - 86)	55,91 (40 - 86)	51,46 (40 - 79)

Table 5. Atherogenic and cardiovascular indices, displayed as the mean value of each parameter with the corresponding minimal (Min) and maximal (Max) value, for all patients and by gender: male and female.

Parameter	Total	Male	Female
ATP-III	1,58 (1 - 5)	1,79 (1 - 5)	1,37 (1 - 4)
TyG Index	8,27 (7,29 - 10,3)	8,49 (7,32 - 10,3)	8,05 (7,29 - 9,17)
HOMA-IR	1,89 (0,28 - 9,97)	2 (0,28 - 6,53)	1,8 (0,63 - 9,97)
HOMA-Beta	89,26 (21,6 - 289,96)	87,72 (21,6 - 267,3)	90,67 (35,9 - 289,96)
HOMA-S	93,65 (10,03 - 357,14)	102,86 (15,31 - 357,14)	85,29 (10,03 - 158,73)
HOMA-2	4,47 (4,01 - 5,5)	4,61 (4,01 - 5,5)	4,35 (4,09 - 4,7)
QUICKI	0,37 (0,28 - 0,49)	0,37 (0,29 - 0,49)	0,37 (0,28 - 0,42)

Table 6. Pancreatic endocrine indices, displayed as the mean value of each parameter with the corresponding minimal (Min) and maximal (Max) value, for all patients and by gender: male and female.

Parameter	Total	Male	Female
Fatty Liver Index (FLI)	29,92 (1,18 - 96,3)	44,57 (2,9 - 96,3)	15,27 (1,18 - 88,52)
Hepatic Steatosis Index (HSI)	33,3 (21,45 - 49,46)	35,07 (21,45 - 49,46)	31,53 (22,87 - 48,97)
K-NAFLD	-2,05 (-6,05 - 6,06)	-0,8 (-5,63 - 6,06)	-3,3 (-6,05 - 3,02)
NAFLD Liver Fat Score (LFS)	-1,7 (-3,36 - 2,86)	-1,23 (-2,91 - 2,86)	-2,13 (-3,36 - 2,49)
NAFLD Logit Score (NLS)	0,16 (0 - 1)	0,29 (0 - 1)	0,03 (0 - 1)
NAFLD Ridge Score (NRS)	-7,19 (-16,79 - 25,06)	-3,88 (-15,16 - 25,06)	-10,49 (-16,79 - 2,46)
ALD NAFLD Index (ANI)	-2,65 (-16,73 - 11,19)	-0,37 (-15,32 - 11,19)	-4,93 (-16,73 - 5,23)
Total NAFLD Risk	0,91 (0 - 3,2)	1,34 (0 - 3,2)	0,49 (0 - 2,6)
Activity NASH (acNASH)	3,01 (1,58 - 10,24)	2,95 (1,58 - 10,24)	3,07 (1,82 - 6,48)
Ferritin-AST&ALT-Platelets (FAT) Score	0,16 (0 - 3)	0,25 (0 - 3)	0,07 (0 - 2)
Gholam Score	8,11 (6,74 - 11,39)	8,33 (7,11 - 11,39)	7,89 (6,74 - 10,53)
HT-ALT-Insulin Resistance (HAIR)	0,71 (0 - 3)	1,1 (0 - 3)	0,36 (0 - 2)
Total NASH Risk	0,43 (0 - 2,67)	0,54 (0 - 2,67)	0,32 (0 - 1,67)
AST-to-Platelet Ratio Index (APRI)	0,3 (0,13 - 1,01)	0,33 (0,14 - 1,01)	0,27 (0,13 - 0,62)
BMI-Age-ALT-Triglycerides (BAAT)	0,86 (0 - 3)	1,17 (0 - 3)	0,55 (0 - 2)
BMI-AST/ALT Ratio-Diabetes (BARD)	1,43 (0,52 - 3,93)	1,53 (0,52 - 3,93)	1,34 (0,56 - 2,46)
Chronic Liver Disease (CLivD) Score	68,32 (18 - 144)	75,43 (21 - 144)	61,2 (18 - 126)
FIB 4 Score	1,22 (0,47 - 4,01)	1,29 (0,47 - 4,01)	1,15 (0,48 - 2,62)
Fibrometer	20,34 (16,89 - 25,29)	21,14 (18,97 - 25,29)	19,53 (16,89 - 24,6)
Forns Fibrosis Index (FFI)	4,22 (1,22 - 7,09)	4,42 (1,22 - 7,09)	4,02 (1,69 - 6,54)
NAFLD Fibrosis Score (NFS)	-2,15 (-5,45 - 0,62)	-1,89 (-4,08 - 0,62)	-2,4 (-5,45 - 0,55)
Steatosis-Associated Fibrosis Estimator (SAFE)	-51,2 (-203,41 - 197,88)	-31,49 (-192,01 - 197,88)	-70,91 (-203,41 - 132,73)
Total Fibrosis Risk	0,38 (0,13 - 1,88)	0,44 (0,13 - 1,88)	0,32 (0,13 - 1,25)
R factor	0,92 (0,12 - 3,95)	1,18 (0,15 - 3,95)	0,66 (0,12 - 1,91)

Table 7. Hepatic and billiary tract indices, displayed as the mean value of each parameter with the corresponding minimal (Min) and maximal (Max) value, for all patients and by gender: male and female.

Parameter	Total	Male	Female
Creatinine Clearance	91,93 (50,1 - 183,93)	101,98 (53,47 - 183,93)	81,87 (50,1 - 168,4)
Estimated Glomerular Filtration Rate (eGFR)	87,45 (45,7 - 122,35)	86,65 (45,7 - 122,35)	88,24 (63,03 - 113,69)

Table 8. Renal scores, displayed as the mean value of each parameter with the corresponding minimal (Min) and maximal (Max) value, for all patients and by gender: male and female.

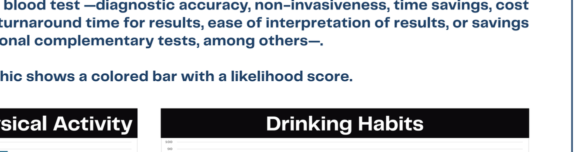

Figure 5. Sample graphic for hepatic function assessment —this is the graphic designed for NAFLD/MASLD, NASH, fibrosis and cirrhosis assessment—, shared with healthcare professionals to validate the usefulness of this new approach to a routine blood test —diagnostic accuracy, non-invasiveness, time savings, cost savings, turnaround time for results, ease of interpretation of results, or savings on additional complementary tests, among others—.

The graphic shows a colored bar with a likelihood score.

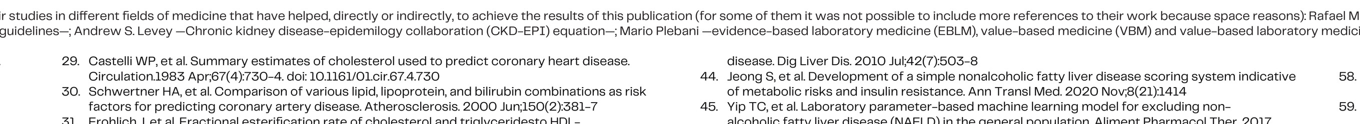

Figure 6. Lifestyle —red and processed meat consumption (displayed as frequency), fruits and vegetables consumption (displayed as serving), physical activity (displayed as level), smoking habit, and drinking habits (displayed as standard drink units)—, for all patients.

RESULTS

This new approach to a routine blood test **has detected all the cases of liver and bile-pancreatic exocrine diseases —hepatocellular diseases and cholestatic diseases (of extrahepatic, intrahepatic, and mixed origin)— as well as their possible causes and associated diseases —cardiovascular disease, pancreatic endocrine diseases, and kidney disease—, in the randomized controlled trial (RCT) validation set**, as can be seen in **Tables 9 and 10**.

Given that the prevalence of *Helicobacter pylori* infection in the raw laboratory data is very low (**Table 3**), it could be an indicative that the study population was biased. This is because the overall prevalence in Spain is much higher versus the one achieved in this study[69]. Since H. pylori infection is more frequent in people with lower income[70] this low prevalence in the validation group suggests that the study population is principally composed by middle-to-high class patients, with moderate-to-high income.

In **Table 9**, the results are displayed for the following groups: the training set was tested for all 46 laboratory determinations, but with different providers with their own reference limits and the validation set was tested for the same 46 laboratory determinations, but all of them were performed by the same providers. The sample size (n) of the training set was 99,631 patients, but this unification of the providers resulted in a reduction of the sample size, because only those patients tested in Laboratorio Echevarne were used in the validation set, and for this reason, the sample size dropped to 152 patients.

In training set, the sensitivity (Se) and specificity (Sp) obtained were 100.00% and 91.74%, respectively. The estimated area under the receiver operating characteristic (AUROC) curve was 92.45%, and the positive predictive value (PPV) and the negative predictive value (NPV) were 92.11% and 100.00%, respectively (**Table 9**).

Finally, in validation set it can be seen that false positives (FP) and false negatives (FN) were totally eliminated, because the Se and the Sp, as well as the PPV and the NPV, increased to 100.00%. But it must be considered that the sample size (n) is very low (152 patients), and it is also very biased, because all patients were 40 years old and older, white/Caucasian ethnicity, and with moderate-to-high income.

Hepatic and Bile-Pancreatic Exocrine Function	Training Set	Validation Set
Sample Size (n)	99,631	152
Se	100.00	100.00
Sp	91.74	100.00
AUROC	92.45	100.00
PPV	92.11	100.00
NPV	100.00	100.00

Table 9. Overall sensitivity (Se), specificity (Sp), AUROC, positive predictive value (PPV) and negative predictive value (NPV) results obtained in both the algorithm modeling —training set—, as well as in the randomized controlled trial (RCT) —validation set—. Overall accuracy of the training was calculated with the same 46 laboratory determinations included in the validation set, by performing several approximations until find the best cost-effectiveness ratio (CER) —correlation of the net difference in the costs of two interventions to the net difference in their effectiveness—.

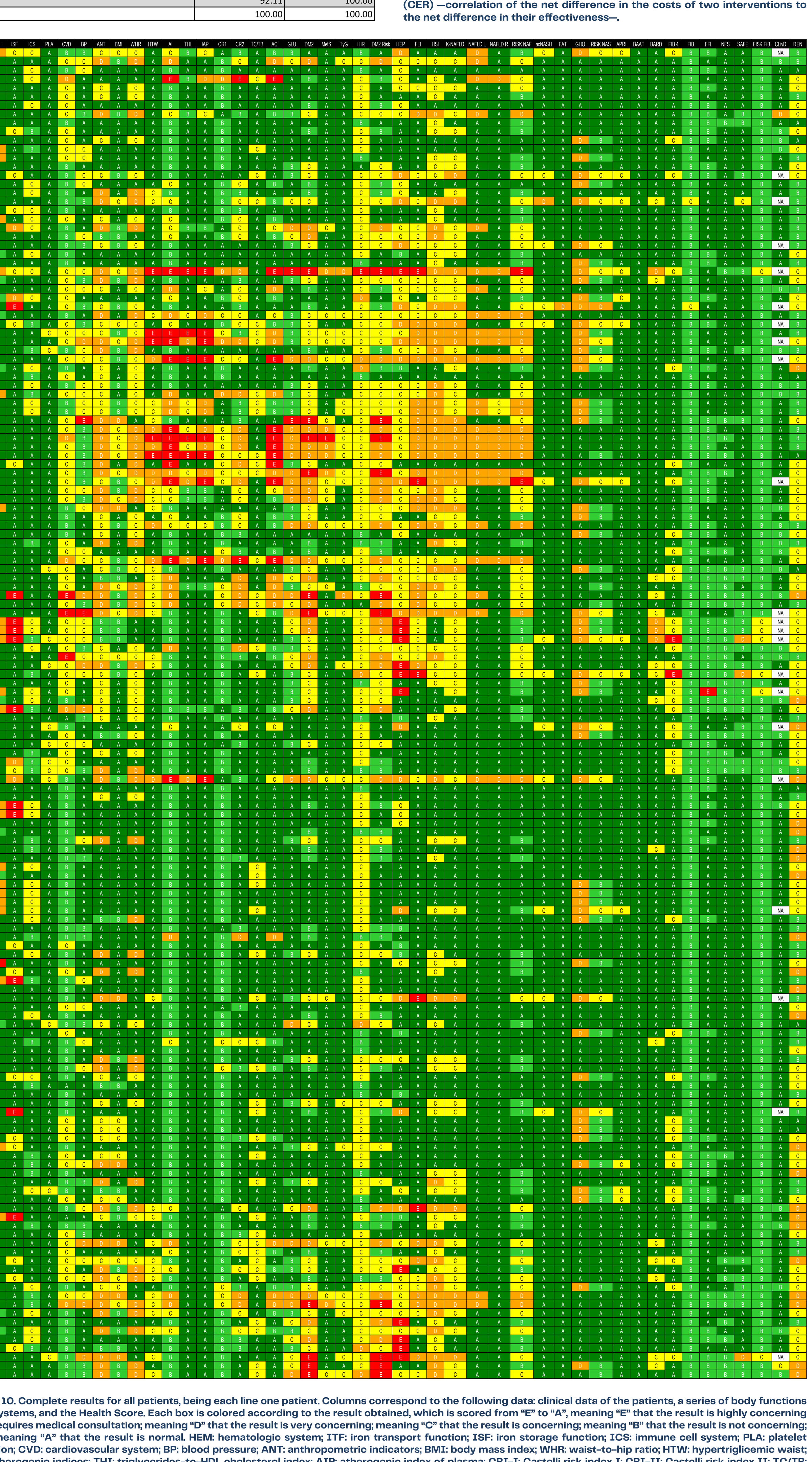

Table 10. Complete results for all patients, being each line one patient. Columns correspond to the following data: clinical data of the patients, a series of body functions and systems, and the Health Score. Each box is colored according to the result obtained, which is scored from "E" to "A", meaning "E" that the result is highly concerning and requires medical consultation; meaning "D" that the result is very concerning; meaning "C" that the result is concerning; meaning "B" that the result is not concerning; and meaning "A" that the result is normal. HEM: hematologic system; ITF: iron transport function; ISF: iron storage function; ICS: immune cell system; PLA: platelet function; CVD: cardiovascular system; BP: blood pressure; ANT: anthropometric indicators; BMI: body mass index; WHR: waist-to-hip ratio; HTW: hypertriglicemic waist; AI: atherogenic indices; THI: triglycerides-to-HDL cholesterol index; AIP: atherogenic index of plasma; CRI-I: Castelli risk index I; CRI-II: Castelli risk index II; TC/TB: cholesterol-to-bilirubin ratio; AC: atherogenic coefficient; GLU: glucose metabolism; DM2: type 2 diabetes mellitus; MetS: metabolic syndrome; TyG: triglycerides and glucose index; HIR: homeostatic model assessment for insulin resistance; DM2 Risk: type 2 diabetes mellitus risk; HEP: hepatic function; FLI: fatty liver index; HSI: hepatic steatosis index; K-NAFLD: K-NALFD score; NAFLD-L: NAFLD logit score; NAFLD-R: NAFLD ridge score; NAFLD Risk: non-alcoholic fatty liver disease risk; acNASH: NAFLD activity score; FAT: ferritin-AST/ALT-platelet score; GHO Gholam score; NASH risk: non-alcoholic steatohepatitis risk; APRI: AST-to-platelet ratio index; BAAT: BMI-age-ALT-triglycerides score; BARD: BMI-AST/ALT ratio-diabetes score; FIB 4: fibrosis 4 score; FIB: fibrometer; FFI: Forns fibrosis index; NFS: NAFLD fibrosis score; SAFE: steatosis-associated fibrosis estimator; FIB Risk: Fibrosis risk; CLivD: chronic liver disease score; REN: renal function.

CONCLUSIONS

- This **innovative non-invasive blood-based biomarker algorithm holds promise in providing timely and accurate assistance to doctors in the assessment —as well as screening—, of liver and bile-pancreatic exocrine diseases —even in early stages—, before symptoms and signs appear and when treatment is most likely to be successful**[71-75]. It is particularly targeted to individuals aged 40 years and above. In this way, **the test enables the detection of liver and bile-pancreatic exocrine diseases, as well as their possible causes and associated diseases, which are linked to the cardiovascular system, pancreatic endocrine function, and renal function**. It is specially **relevant for those diseases related to overweight, obesity, and metabolic syndrome (MetS), as they are closely linked to liver and bile-pancreatic exocrine diseases and/or are considered risk factors for them**[3]. Even though the Se and Sp achieved were of 100.00%, it must be considered that the laboratory where the test was performed was not equipped with Roche Diagnostics analyzers. Thus, the obtention of these high results may be due to a possible ease from our side in assessing the cardiovascular system, pancreatic endocrine function, hepatic function, and renal function with a small sample size (152 patients).
- This RCT shows the **achievement of a routine, affordable —accessible to low-income and underserved populations—, and high accurate blood test**. The **panel maximizes diagnostic yield while minimizing costs**. The selected analytes can **detect early signs of liver and bile-pancreatic exocrine diseases, without requiring expensive or invasive procedures**. Besides, by focusing on high-prevalence diseases and selecting analytes that are both low-cost and widely available, this panel is economically feasible on a large scale. **Automated laboratory systems for blood tests help reduce labor costs and increase throughput, further driving down overall costs**.
- Given the concerning problem about the healthcare costs in the U.S. —but also worldwide—, and its access for a considerable portion of its population, this algorithmic test can also be a solution for this, **costing only EUR 5.91 (USD 6.46) for the combination of Sysmex systems for hematology and Roche Diagnostics systems for biochemistry and immunoassay**.
- The **affordability of this panel could enable wider access to routine screening**. This ensures earlier detection and management of diseases before they progress into more severe, costly conditions, ultimately reducing the economic burden on both patients and healthcare systems.
- Implementing this minimum diagnostic panel as part of routine care has demonstrated significant economic benefits, both at the individual and societal levels, because **early detection leads to more cost-effective treatment strategies and prevents progression to more severe disease states, reducing hospital admissions and complex interventions**[76]. Also, **by focusing on preventive care, this panel reduces the overall cost burden on healthcare systems, shifting resources away from expensive, late-stage treatments**[76]. In this way, **early diagnosis and management of chronic diseases improve patient outcomes, leading to fewer sick days and enhancing workforce productivity, contributing to the overall economic growth of communities**[76].
- The establishment of a universally accessible, affordable diagnostic panel contributes to closing the healthcare gap in low and middle-income countries. By addressing the most common and preventable diseases at a fraction of the cost of traditional healthcare models, this initiative aligns with global health goals such as universal health coverage (UHC)[77] and the Sustainable Development Goals (SDG)[78], particularly those **focused on reducing premature mortality from liver and bile-pancreatic exocrine diseases**[79].
- On the other hand, this study also underlines the need to encourage healthcare professionals to explore how Evidence-Based Laboratory Medicine (EBLM)[80,81] and new technologies —mainly machine learning (ML) algorithms—, can help them to **improve diagnosis accuracy, reduce medical errors and misdiagnoses, as well as avoid invasive procedures, while reducing healthcare-related costs**.
- The **most critical aspect of achieving the goals of the RCT was the management of the follow-up visits**. This is because the no assistance to any of these visits implies losing a patient, as well as the cost of the performed analytics. Therefore, this is specially relevant in the upcoming RCT, where the total cost of the study will be of USD 18 M, being USD 3 M exclusively dedicated for analytics and USD 7 M for the contract research organization (CRO) —the two largest budget items related to patients.
- Moreover, the HEOR data collection framework is poised to deliver critical insights into the long-term cost benefits of ML-based Clinical Decision Support Systems (CDSS). **Initial findings show that ML in CDSS improves diagnostic accuracy, optimizes treatment, and enhances resource allocation, leading to cost savings by reducing misdiagnoses, unnecessary invasive and costly diagnostic tests, and hospitalizations**.
- Data will support future research on the cost savings and improved health outcomes from ML/CDSS, focusing on patient health, healthcare cost reductions, and reduced health disparities.
- Beyond the use of large-scale, sophisticated ML algorithms, simple calculations were also incorporated, providing valuable insights into patient health without adding significant costs. By **automating these calculations in the laboratory side, the burden on clinicians to manually compute these metrics is removed**[82-84]. As a result, **diagnostic efficiency improves without incurring additional costs for patients, insurers, or healthcare providers**[82,85]. In this way, all the calculations results for 80,000 patients were performed in just 6 seconds.
- These conclusions highlight the transformative role of ML algorithms, both large and small, in improving healthcare delivery and outcomes. By **reducing the cost burden through automation and improving decision-making at every stage of patient care**[82,85-87], these tools not only benefit healthcare systems and patients economically but also ensure that personalized, data-driven care becomes the standard.
- Finally, despite promising results have been achieved, **there is still a lot of information to be obtained from blood —and urine—**, and a lot of work to be done to understand it. In this way, **a multicenter, international clinical trial of 26,000 patients will be conducted from March 2025 until December 2026 to continue enhancing the algorithm's accuracy in the general population**.

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