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An Innovative Evidence-Based Laboratory Medicine (EBLM) Test to Assist Doctors in the Assessment of the Main Non-Malignant, Highly Prevalent, Morbid, Cancer-Precursor, and Deadly Diseases

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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**. That is because nowadays 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 as the most morbid and mortal diseases worldwide[2]. Although many of them 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 many highly morbid and mortal diseases linked to MetS —such as cardiovascular disease (CVD), heart failure (HF), type 2 diabetes mellitus (DM2), chronic liver disease (CLD), and chronic kidney disease (CKD)—, has become a serious global concern[5–8].

Healthcare Reactive Model

- Yet, **current healthcare system is based on being reactive to treat a patient when gets sick**[9,10], 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.**[11]
- Besides, **reactive health increases the lead time**[11] —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**[11–13]. 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**[13–15], but also as the best way to **reduce healthcare-related costs**[13–15]. The **preventive model is defined as the routine care that the patient receives to maintain its health**[13–15] and for this reason, **it is key to diagnosing medical conditions before they become a problem**.

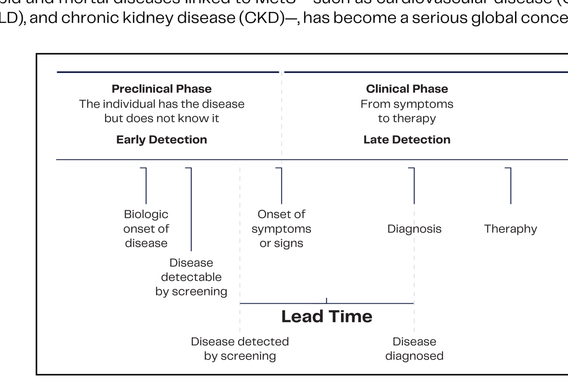

Figure 1. Lead time is the duration of time between the detection of the disease via screening tests and the time of its usual diagnosis after symptoms or signs appear and a patient goes to the doctor. It plays a critical role in the detection of several non-malignant, highly prevalent, morbid, cancer-precursor, 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**[11,12,16].
- About **half of U.S. adults say it is difficult to afford healthcare costs**[11,12,16], and one in four say they or a family member in their household had problems paying for healthcare in the past 12 months[11,12] —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**[11,12,17,18] —one in four adults say that in the past 12 months they have skipped or postponed getting healthcare they needed because of the cost[11,12,17,18]—.
- Notably **six in ten uninsured adults (61%) say they went without needed care because of the cost**[11].
- 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**[11], 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**[19], **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**[20]. At the same time, we are seeing a **consistent rise in chronic illnesses**[19], **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**[21]—. With an ageing population and these growing numbers, it is clear this model is not sustainable[15].

OBJECTIVES

- To **define a minimum blood and/or urine panel capable of confirming —and/or detecting—, the main non-malignant, highly prevalent, morbid, cancer-precursor, and deadly diseases**. 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—, test** could be used as a **non-invasive test to assist doctors in the basic assessment —as well as screening—, of several non-malignant, highly prevalent, morbid, cancer-precursor, and deadly diseases**. Concretely, the main diseases that this test can target are related with overweight, obesity, and metabolic syndrome (MetS) —e.g., cardiovascular disease (CVD), insulin resistance (IR), prediabetes, diabetes, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), liver fibrosis (LF) and cirrhosis, and chronic kidney disease (CKD), as their prevalences in the U.S. population are concerning (**Figure 2**)—. 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**[22], 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**[23]:
  - 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: triglycerides/HDL-c index, 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, atherogenic coefficient (AC), lipoprotein combine index (LCI), 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) and the triglycerides and glucose (TyG) index. Both 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, 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, NAFLD liver fat score (LFS), 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 simple clinical variables as well as laboratory determinations, such as complete blood count (CBC), albumin, ferritin, total protein, 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, glucose, and glycated hemoglobin (HbA1c).
  - Renal scores, such as creatinine clearance and estimated glomerular filtration rate (eGFR). Both 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—, since several previous correlation studies alerted about potentially moderate differences in the performance between different reagent vendors —mainly in the normality limits—[24,25].
- To **collect data for future mid and/or long-term studies related to health economics outcome research (HEOR)**[26] **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)[27]. 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 basic assessment —as well as screening—, of several non-malignant, highly prevalent, morbid, cancer-precursor, and deadly diseases**, 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 185,882 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 all the body systems and functions related with metabolic syndrome (MetS), as well as some other ones that are causes or consequences of it—. 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**). Besides, some inflammatory ratios (**Table 9**) were also performed —many studies have suggested their use as a novel tool in the assessment of many diseases—. We selected the ones that were Evidence-Based Laboratory Medicine (EBLM). In this way, performed atherogenic indices and cardiovascular scores were: triglycerides/HDL-c index[34], atherogenic index of plasma (AIP)[35–37], Castelli risk index I[38,39], Castelli risk index I + bilirubin[39], Castelli risk index II[39], Castelli risk index II + bilirubin[39], cholesterol/bilirubin ratio[39], atherogenic coefficient (AC)[34,39], lipoprotein combine index (LCI)[39], Framingham risk score[40], SCORE[41], and vascular age[42]. Besides, pancreatic endocrine indices performed were: adult treatment panel III (ATP-III)[43,44] —metabolic syndrome— and triglycerides and glucose (TyG) index[45] —insulin resistance—. Moreover, hepatic and biliary tract indices performed were: fatty liver index (FLI)[46,47], hepatic steatosis index (HSI)[47,48], K-NALFD score[49], NAFLD liver fat score (LFS)[47], and ALD NAFLD index (ANI)[50] for the assessment of non-alcoholic fatty liver disease (NAFLD); activity NASH (acNASH)[51] and Gholam score[52] for the assessment of non-alcoholic steatohepatitis (NASH); AST-to-platelet ratio index (APRI)[53,54], BMI-age-ALT-triglycerides (BAAT) score[54], BMI-AST/ALT ratio-diabetes (BARD) score[54,55], FIB 4 score[54,56], and Forns fibrosis index (FFI)[57], for the assessment of liver fibrosis and cirrhosis. R Factor[58], and chronic liver disease (CLivD) score[59] were also performed for further risk-assessment. Furthermore, inflammatory ratios performed were: RDW-to-LYM[60], RDW-to-NEU[60], RDW-to-MON[60], RDW-to-RBC[60], RDW-to-PLT[60], Hb-to-RDW[61], LYM-to-MON[62], MON-to-LYM[60,63], MON-to-NEU[60], MPV-to-LYM[64], MPV-to-NEU[60], MPV-to-MON[60], MPV-to-PLT[60], NEU-to-LYM[60,65], Derived NEU-to-LYM[60,66], NEU-to-LYM+PLT[67], NEU-to-MON[60,68], PDW-to-LYM[69], PDW-to-NEU[60], PDW-to-MON[60], PLT-to-WBC[70,71], PLT-to-LYM[63,72], PLT-to-NEU[73], PLT-to-MON[60,74], ALP-to-RBC[60], ALP-to-RDW[60], ALP-to-PLT[60,75], ALP-to-PDW[60], LDH-to-RBC[60], LDH-to-LYM[60,76], LDH-to-PLT[60,76], NEU-to-HDL-c[77], MON-to-HDL-c[77,78], PLT-to-HDL-c[78,79], and prognostic nutritional index (PNI)[80]. Finally, renal indices performed were: creatinine clearance[81], and eGFR[82]. On the other hand, all patient data was computed with two machine learning (ML) algorithms, such as Evidence-Based Laboratory Medicine Algorithm (EBLMA)[27,28] and Artificial Intelligence Recursive Algorithm (AIRA)[27,29] —both developed by Blueberry Diagnostics (Barcelona, Spain) in 2020 to help in COVID-19 diagnosis[30–33]—, to improve both sensitivity and specificity. EBLMA includes several functions —sub-algorithms— to detect the following conditions: iron transport and storage function diseases; cardiovascular disease (CVD) and atherosclerotic cardiovascular disease (ASCVD); pancreatic endocrine diseases —insulin resistance (IR), prediabetes, type 2 diabetes mellitus (DM2)—; hepatic function diseases —non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), liver fibrosis and cirrhosis—; 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 heterogeneous, 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[27] —with 90 laboratory determinations included—, from which this other study was developed —by using only 41 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 1–9**). Patient's blood samples were obtained from October 2021 to June 2023. Blood samples were obtained by peripheral venipuncture in all participants. All analytics were performed in Laboratorio Echevarne. After centrifugation of the blood samples, all the analytes were quantified. Complete blood count (CBC) was determined by Yumizen analyzers (Horiba, Kyoto, Japan). All the serum hepatic enzymes, sterols and fatty acids, as well as the remaining serum analytes were measured by Atellica analyzers (Siemens, Munich, Germany). 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 10**). Then, a global weighted score related to all findings was calculated. This score —called Health Score—, is a scoring system developed during the RCT to aid in patient management, according to the guidelines of the following organizations: the American Society of Hematology (ASH), the American Heart Association (AHA), the American Association of Clinical Endocrinology (AACE), the American Diabetes Association (ADA), the American Association for the Study of Liver Diseases (AASLD), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and the National Kidney Foundation (NKF). The Health Score scale is as follows: "E" for findings that require urgent attention from a healthcare professional; "D" for findings that should be checked by a healthcare professional; "C" for findings recommended to be checked by a healthcare professional; "B" for findings but, due to its nature, no action is recommended —avoid overdiagnosis—; and "A" for no findings. The Health Score weighs differently all the body systems and functions, according to the severity of each finding and the related body system or function. Besides, the Health Score takes in consideration five different predictive risk algorithms, including: the Framingham risk score (FRS) —10-year risk of developing a coronary heart disease (CHD)—; the Systematic Coronary Risk Evaluation (SCORE) —10-year risk of death due to coronary or noncoronary cardiovascular disease—; the Diabetes Risk Calculator (DRC) —7.5-year risk of developing type 2 diabetes mellitus (DM2)—; the Chronic Liver Disease (CLivD) score —14-year risk of developing chronic liver disease (CLD)—, as well as the Kidney Failure Risk Equation (KFRE) —2-year and 5-year risks for kidney failure (KF)—. 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.

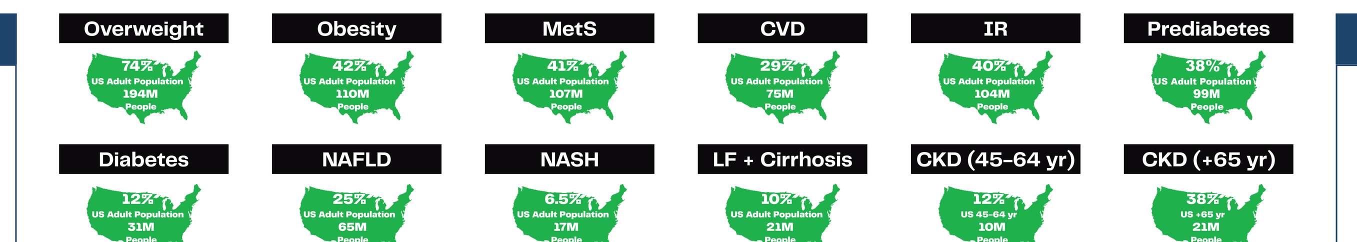

Figure 2. Prevalences of the main non-malignant, highly prevalent, morbid, cancer-precursor, and deadly diseases in the U.S. Data is shown as percentage over adult population and total number of adults affected (in millions).

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.

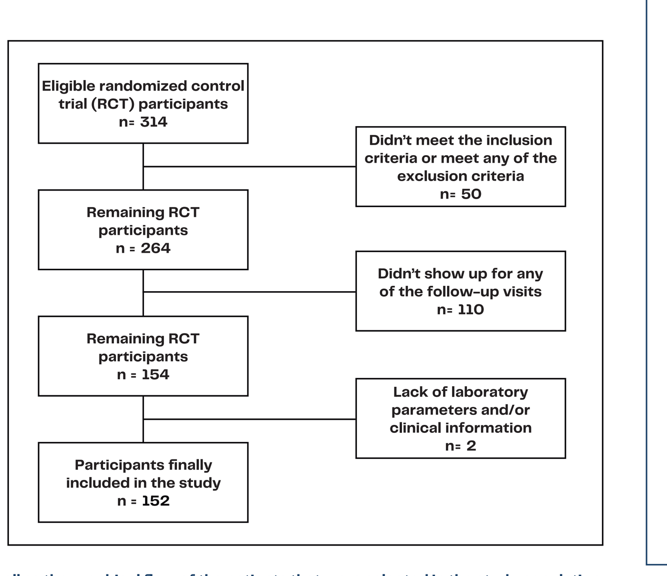

Figure 3. Inclusion and exclusion criteria for the selection of the study population, as well as the graphical flow of the patients that were selected in the study population.

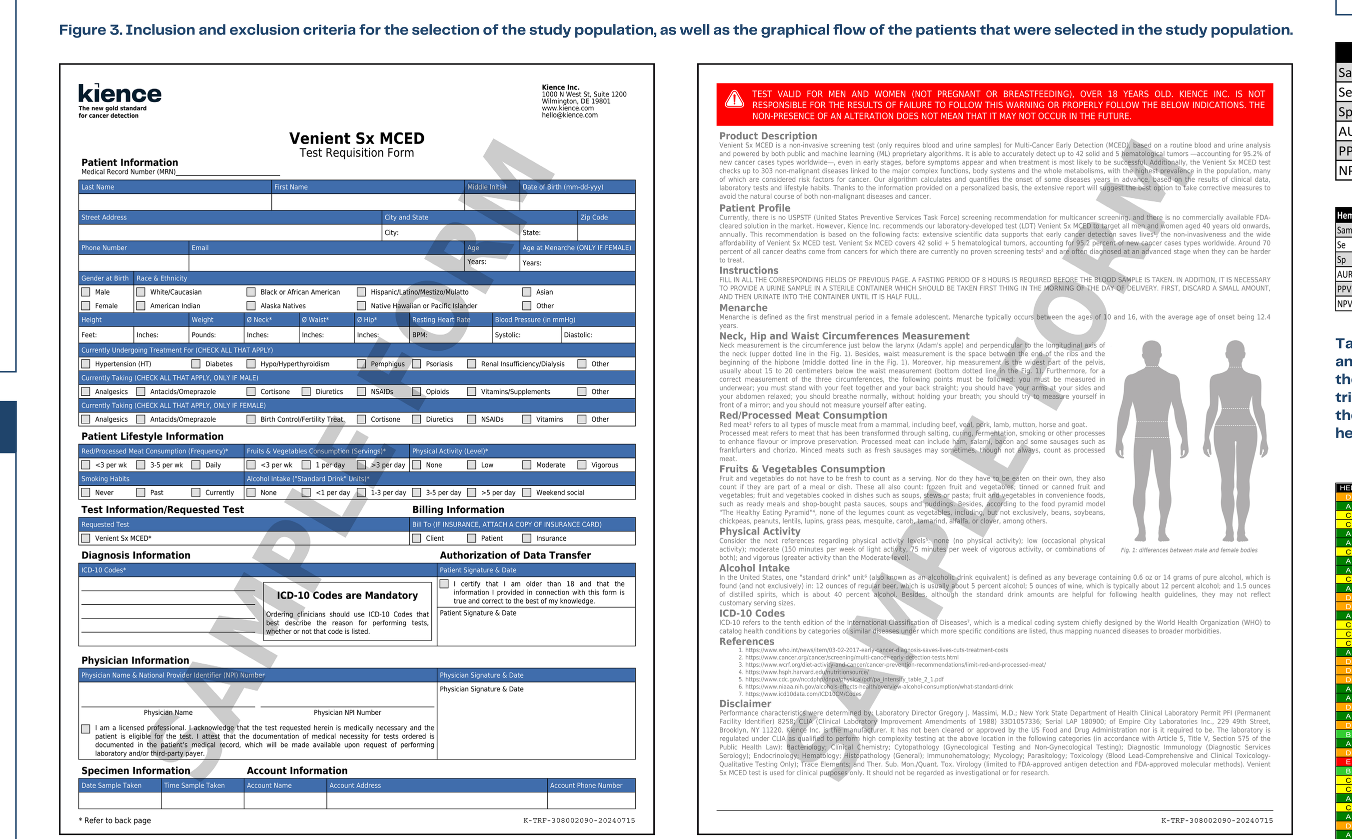

Figure 4. Test requisition form (TRF) for the RCT to be performed in the U.S. (Empire City Laboratories Inc., Brooklyn, NY, U.S.). This new RCT will be based in a sample size (n) of 1,000 patients —paying special attention to the proportion of different ethnicities of the population of the U.S.—.

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 - 0,32)	0,11 (0,04 - 0,82)
Urine Creatinine (g/L)	1,38 (0,35 - 3,42)	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). For instance, all tumor markers (TM) —as well as some other analytes—, were not considered for this study, because its main focus is to select only those that can be helpful to detect as many non-malignant, highly prevalent, morbid, cancer-precursor, and deadly diseases as possible (thus, excluding cancer). Besides, 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)
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)
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)
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)

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 Index I	3,48 (1,56 - 8,16)	4,1 (1,56 - 8,16)	2,86 (1,56 - 4,59)
Castelli Risk Index I + Bilirubin	1,58 (0,58 - 2,91)	1,68 (0,75 - 2,91)	1,47 (0,58 - 2,31)
Castelli Risk Index II	2,13 (0,37 - 6,14)	2,62 (0,37 - 6,14)	1,64 (0,37 - 3,08)
Castelli Risk Index 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)

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)
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)
Gholam Score	8,11 (6,74 - 11,39)	8,33 (7,11 - 11,39)	7,89 (6,74 - 10,53)
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)
Forns Fibrosis Index (FFI)	4,22 (1,22 - 7,09)	4,42 (1,22 - 7,09)	4,02 (1,69 - 6,54)
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.

Parameter	Total	Male	Female
RDW-to-LYM Ratio (RDWLR)	9,4 (4,98 - 28,18)	4,98 (4,98 - 28,18)	9,63 (5,27 - 20,48)
RDW-to-NEU Ratio (RDWNR)	5,11 (1,75 - 13)	1,87 (1,87 - 12,27)	5,33 (1,75 - 13)
RDW-to-MON Ratio (RDWMR)	37,91 (16,61 - 99,97)	16,61 (16,61 - 77,68)	41,65 (0,01 - 99,97)
RDW-to-RBC Ratio (RDWRBCR)	3,18 (2,39 - 5,05)	2,39 (2,39 - 5,05)	3,33 (2,62 - 4,78)
RDW-to-PLT Ratio (RDWPR)	0,06 (0,04 - 0,11)	0,04 (0,04 - 0,11)	0,06 (0,04 - 0,1)
Hb-to-RDW Ratio (RDWR)	9,82 (3,24 - 12,75)	3,24 (3,24 - 12,75)	9,3 (4,7 - 11,53)
LYM-to-MON Ratio (LMR)	4,23 (1,59 - 11,05)	1,59 (1,59 - 8,66)	4,5 (1,86 - 11,05)
MON-to-LYM Ratio (MLR)	0,27 (0,09 - 0,63)	0,12 (0,12 - 0,63)	0,25 (0,09 - 0,54)
MON-to-NEU Ratio (MNR)	0,14 (0,06 - 0,28)	0,07 (0,07 - 0,25)	0,13 (0,06 - 0,28)
MPV-to-LYM Ratio (MPVLR)	6,21 (3,4 - 13,15)	3,4 (3,4 - 13,15)	6,36 (3,4 - 10,86)
MPV-to-NEU Ratio (MPVNR)	3,39 (1,14 - 9,38)	1,19 (1,19 - 9,38)	3,51 (1,14 - 7,26)
MPV-to-MON Ratio (MPVMR)	25,08 (11,07 - 53,31)	11,18 (11,18 - 52,7)	27,34 (11,07 - 53,31)
MPV-to-PLT Ratio (MPVPR)	0,43 (0,19 - 0,86)	0,25 (0,25 - 0,77)	0,43 (0,19 - 0,86)
NEU-to-LYM Ratio (NLR)	2,04 (0,56 - 6,26)	0,56 (0,56 - 6,26)	2,05 (0,88 - 5,01)
Derived NEU-to-LYM Ratio (dNLR)	1,45 (0,48 - 3,61)	0,48 (0,48 - 3,61)	1,48 (0,68 - 3,29)
NEU-to-LYM+PLT Ratio (N/LPR)	0,92 (0,23 - 4,29)	0,23 (0,23 - 4,29)	0,91 (0,35 - 2,65)
NEU-to-MON Ratio (NMR)	7,84 (3,63 - 17,8)	3,99 (3,99 - 13,5)	8,31 (3,63 - 17,8)
PDW-to-LYM Ratio (PDWLR)	10,82 (5,8 - 26,14)	5,8 (5,8 - 24,33)	11,04 (5,8 - 26,14)
PDW-to-NEU Ratio (PDWNR)	5,88 (1,98 - 17,51)	2,03 (2,03 - 16,87)	6,07 (1,98 - 17,51)
PDW-to-MON Ratio (PDWMR)	43,37 (19,08 - 105,04)	19,08 (19,08 - 82,09)	47,08 (19,08 - 105,04)
PLT-to-WBC Ratio (PWR)	45,63 (15,94 - 98,98)	22,33 (22,33 - 84,25)	48,13 (15,94 - 98,98)
PLT-to-LYM Ratio (PLR)	152,14 (63,25 - 413)	63,25 (63,25 - 413)	157,21 (68,28 - 299,93)
PLT-to-NEU Ratio (PNR)	82,39 (21,81 - 223,75)	29,09 (29,09 - 223,75)	86,91 (21,81 - 203,85)
PLT-to-MON Ratio (PMR)	612,55 (232,6 - 1657,75)	245,54 (245,54 - 1244,32)	675,99 (232,6 - 1657,75)
ALP-to-RBC Ratio (ALPRBCR)	14,47 (7,2 - 66,31)	7,2 (7,2 - 66,31)	15,17 (7,35 - 66,31)
ALP-to-RDW Ratio (ALPRDWR)	4,61 (2,34 - 23,56)	2,62 (2,62 - 23,56)	4,63 (2,34 - 23,56)
ALP-to-PLT (ALPPR)	0,29 (0,13 - 1,86)	0,13 (0,13 - 1,86)	0,29 (0,14 - 1,86)
ALP-to-PDW Ratio (ALPPDWR)	4,01 (1,49 - 11,78)	1,76 (1,76 - 11,78)	4,08 (1,49 - 11,78)
LDH-to-RBC Ratio (LDHRBCR)	36,11 (24,12 - 60,98)	24,12 (24,12 - 60,98)	36,69 (25,61 - 55,66)
LDH-to-LYM Ratio (LDHLR)	106 (46,36 - 235,4)	55,82 (55,82 - 235,4)	104,86 (46,36 - 194,62)
LDH-to-PLT Ratio (LDHPR)	0,73 (0,37 - 1,84)	0,46 (0,46 - 1,84)	0,69 (0,37 - 1,25)
NEU-to-HDL-c Ratio (NHR)	2,35 (0,56 - 8,8)	0,75 (0,75 - 6,23)	1,99 (0,56 - 8,8)
MON-to-HDL-c Ratio (MHR)	7,93 (1,63 - 23,89)	3,69 (3,69 - 23,89)	6,28 (1,63 - 23,43)
PLT-to-HDL-c Ratio (PHR)	164,15 (69,27 - 407,24)	74,29 (74,29 - 290,65)	142,52 (69,27 - 407,24)
Prognostic Nutritional Index (PNI)	454,56 (390,01 - 520,01)	390,01 (390,01 - 520,01)	453,96 (400,01 - 500,01)

Table 9. Inflammatory ratios —hematological and mixed—, 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.

RESULTS

This new approach to a routine blood test **has detected all non-malignant, highly prevalent, morbid, cancer-precursor, and deadly diseases in the randomized controlled trial (RCT) validation set**, as can be seen in **Tables 10 and 16**.

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[83]. Since H. pylori infection is more frequent in people with lower income[84] 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 this way, only one patient (0.66%) obtained a **Health Score** "B". Besides, 151 patients (99.34%) resulted with a Health Score C or lower (that is, "C", "D" or "E"), which means that **almost all of them had at least one body function or system mild, moderate, severe or very severely altered**. In such manner, the number of patients with altered results, according to each function that was evaluated, were: hematologic system (n = 23; 15.13%); cardiovascular system (n = 74; 48.68%) —22 of them (14.47%) with a moderate-high 10-year risk of developing a coronary heart disease (CHD)—; pancreatic endocrine function and glucose metabolism (n = 37; 24.34%) —25 of them (16.45%) with MetS, 23 of them (15.13%) with moderate-high likelihood for insulin resistance, and 34 of them (22.37%) with a moderate-high 7.5-year risk for developing type 2 diabetes mellitus (DM2)—; liver and bile-pancreatic exocrine function (n = 82; 53.95%) —58 of them (38.16%) with non-alcoholic fatty liver disease (NAFLD), 18 of them (11.84%) with non-alcoholic steatohepatitis (NASH) and 7 of them (4.61%) with a moderate 15-year risk for developing chronic liver disease (CLD)—; renal function (n = 24; 15.79%); and uric acid metabolism (n = 2; 1.32%).

In **Table 10**, the results are displayed for the following groups: the training set #1 was tested for all 90 laboratory determinations, and the training set #2 was tested for the 41 laboratory determinations that were finally included in this RCT. The same happens with both validations sets: validation set #1 was also tested for all 90 laboratory determinations and validation set #2, was also tested for the same 41 final laboratory determinations. The sample size (n) of the training set #1 was 195,677 patients, but the reduction of 49 analytes for the training set #2 resulted in a reduction of some body functions and systems that were tested and for this reason, some patients were excluded for the #training set #2 that had an n of 185,882 patients.

In training set #1, the sensitivity (Se) and specificity (Sp) obtained were 99.98% and 98.64%, respectively. The estimated area under the receiver operating characteristic (AUROC) curve was 93.77%, and the positive predictive value (PPV) and the negative predictive value (NPV) were 98.66% and 99.97%, respectively (**Table 10**). On the other hand, the Se and Sp obtained in the training set #2 with the finally selected 41 laboratory determinations were 96.79% and 95.16%, respectively. Besides, the AUROC was 92.05%. Finally, the PPV and NPV were 95.16% and 95.82%, respectively (**Table 10**).

Besides, **in both validation sets it can be seen that false positives (FP) and false negatives (FN) were totally eliminated, because in both cases 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 in both cases), and it is also very biased, because all patients were 40 years old and older, white/Caucasian ethnicity, and with moderate-to-high income.

Moreover, **the performances obtained from the different sections included in this test were also improved in the validation set**. For example, for the hematological system, in the training set the Se, Sp, AUROC, PPV, and NPV were 99.79% and 95.61%, 95.18%, 95.79%, and 99.78%, respectively, with a sample size (n) of 2,160; but **all these parameters increased to 100.00%** in the validation set (**Table 10**). The same happened with the cardiovascular system, the pancreatic endocrine function, the hepatic function, and the renal function (**Tables 11–15**), where in all cases, all their accuracy parameters increased to 100.00%. Thus, all these results demonstrate the well performance of the test to detect several non-malignant, highly prevalent, morbid, cancer-precursor, and deadly diseases, even though considering to potential sources of bias in the study population, that had already been described.

Scenarios	Training Set 1	Training Set 2	Validation Set 1	Validation Set 2
Sample Size (n)	195,677	185,882	152	152
Se	99.98	96.79	100.00	100.00
Sp	98.64	95.16	100.00	100.00
AUROC	93.77	92.05	100.00	100.00
PPV	98.66	95.16	100.00	100.00
NPV	99.97	95.82	100.00	100.00

Table 10. Overall sensitivity (Se), specificity (Sp), AUROC, positive predictive value (PPV) and negative predictive value (NPV) results obtained in the randomized controlled trial (RCT) —validation set #2—. Sets labeled #1 correspond to results obtained with all 90 laboratory determinations included. Sets labeled #2 correspond to algorithm performance by using only the finally selected 41 laboratory determinations. 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—.

Hematologic System	Training Set	Validation Set
Sample Size (n)	2,160	152
Se	99.79	100.00
Sp	95.61	100.00
AUROC	95.18	100.00
PPV	95.79	100.00
NPV	99.78	100.00

Table 11. Se, Sp, AUROC, PPV and NPV results obtained in the randomized controlled trial (RCT) validation set for the algorithm related to the hematological system.

CVD System	Training Set	Validation Set
Sample Size (n)	42,834	152
Se	94.57	100.00
Sp	97.85	100.00
AUROC	92.15	100.00
PPV	97.78	100.00
NPV	94.74	100.00

Table 12. Se, Sp, AUROC, PPV and NPV results obtained in the randomized controlled trial (RCT) validation set for the algorithm related to the cardiovascular system.

Panc. Endo. Function	Training Set	Validation Set
Sample Size (n)	4,620	152
Se	98.54	100.00
Sp	95.52	100.00
AUROC	90.34	100.00
PPV	95.65	100.00
NPV	98.49	100.00

Table 13. Se, Sp, AUROC, PPV and NPV results obtained in the randomized controlled trial (RCT) validation set for the algorithm related to the pancreatic endocrine function.

Hepatic Function	Training Set	Validation Set
Sample Size (n)	98,658	152
Se	96.79	100.00
Sp	95.16	100.00
AUROC	92.26	100.00
PPV	95.24	100.00
NPV	96.74	100.00

Table 14. Se, Sp, AUROC, PPV and NPV results obtained in the randomized controlled trial (RCT) validation set for the algorithm related to the liver and bile-pancreatic exocrine function.

Renal Function	Training Set	Validation Set
Sample Size (n)	37,610	152
Se	94.26	100.00
Sp	91.65	100.00
AUROC	92.42	100.00
PPV	91.86	100.00
NPV	94.11	100.00

Table 15. Se, Sp, AUROC, PPV and NPV results obtained in the randomized controlled trial (RCT) validation set for the algorithm related to the renal function.

Table 16. 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; ANT: anthropometric indicators; BMI: body mass index; WHR: waist-to-hip ratio; HTW: hypertriglicemic waist; BP: blood pressure; AI: atherogenic indices; AC: atherogenic coefficient; AIP: atherogenic index of plasma; CRI-I: Castelli risk index I; CRI-II: Castelli risk index II; TC/TB: cholesterol-to-bilirubin ratio; THI: triglycerides-to-HDL cholesterol index; END: endocrinologic system; 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; THY: thyroid function and hypothalamic-pituitary axis; PTH: parathyroid function; VitD: vitamin D function; VitB12: vitamin B12 function; GAS: gastrointestinal tract; HEP: liver and bile-pancreatic exocrine function; FLI: fatty liver index; LFS: liver fat score; HSI: hepatic steatosis index; K-NAFLD: Korea NAFLD score; BAAT: BMI-age-ALT-triglycerides score; BARD: BMI-AST/ALT ratio-diabetes 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; GHOLAM: Gholam score; HAIR: hypertension-ALT-insulin resistance; NASH risk: non-alcoholic steatohepatitis risk; APRI: AST-to-platelet ratio index; FIB 4: fibrosis 4 score; FIB: fibrometer; FFI: Forns fibrosis index; NFS: NAFLD fibrosis score; SAFE: steatosis-associated fibrosis estimator; Fibrosis risk; CLivD: chronic liver disease score; REN: renal function; URI: urinalysis; HS: Health Score.

CONCLUSIONS

- This **innovative non-invasive blood-based biomarker algorithm holds promise in providing timely and accurate assistance to doctors in the basic assessment —as well as screening—, of non-malignant, highly prevalent, morbid, cancer-precursor, and deadly diseases —even in early stages—, before symptoms and signs appear and when treatment is most likely to be successful**[85–88]. It is particularly targeted to individuals aged 40 years and above. In this way, **the test enables the detection of the most prevalent diseases linked to main body functions, systems, and metabolisms, such as the hematologic system, cardiovascular system, pancreatic endocrine function, hepatic 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 cancer causes and/or are considered cancer risk factors**[89]. 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 hematological system, 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 chronic and severe 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 2.50 (USD 2.79) for the combination of Sysmex systems for hematology and Roche Diagnostics systems for biochemistry**.
- 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**[90]. Also, **by focusing on preventive care, this panel reduces the overall cost burden on healthcare systems, shifting resources away from expensive, late-stage treatments**[90]. 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**[90].
- 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)[91] and the Sustainable Development Goals (SDG)[92], particularly those **focused on reducing premature mortality from non-communicable diseases (NCDs)**[93].
- On the other hand, the case study also underlines the need to encourage healthcare professionals to explore how Evidence-Based Laboratory Medicine (EBLM)[94,95] 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**[96–98]. As a result, **diagnostic efficiency improves without incurring additional costs for patients, insurers, or healthcare providers**[96,99].
- 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**[96, 99–101], 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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