METHOD AND SYSTEM FOR ESTIMATING RISK OF A MULTIPLE ORGAN PATHOLOGY

Field of the Invention

The present invention relates to a method and system for estimating the risk and/or predicting the occurrence of a pathology and/or clinical event.

In particular, the present invention provides means to assess the likelihood, risk, or possible occurrence of a pathology that impacts multiple organs and/or systems, referred to as a multi-organ pathology. Organs and systems affected may include, for example, a blood circulatory system and organs in it, liver, pancreas, kidneys, heart, and so forth. For example, systems may be endocrine or exocrine or respiratory or circulatory. Hypertension is a multi-organ disease state. The means to assess the likelihood, risk, or possible occurrence of the multi-pathology incorporates organ specific information and its relative role in and on the systemic risk.

In an embodiment the present invention provides a method in which a single measurement or a few specific measurements of the health/status on each one of several individual organs serves as a basis for foresight into a likelihood, risk or prediction of occurrence of a systemic pathology / clinical event, Each of the organs upon which the single measurement or few measurements are made may be part of a system, such as a blood circulatory system in which all the organs have a role to fulfill.

People for whom the invention is applicable may be healthy or feel healthy at the time of the measurement(s) but have a subclinical organ impairment that may be picked up by the measurement(s). The measurement(s) may be from an MRI scan that is performed on a person to collect data to formulate an image of organs in the system.

Background

The term ‘pathology’ is used here to mean a condition that may impact multiple organs, i.e. a multi-organ pathology, including where such a ‘pathology’ may also not manifest itself in specific organs but in a systemic way, such as hyperglycaemia, hypertension, metabolic dysfunction etc.

Likelihood, risk, or possible occurrence are referred to together as ‘risk’.

Many, and an increasing number of, pathologies impact on multiple organs, for example, Type-2 Diabetes (T2D), cardiovascular disease (CVD), Long Covid, sleep apneoa, and others. Pathologies that impact on multiple organs may be termed multi-organ pathologies.

This necessitates the measurement of organ 'state' (health, presence and extent of pathology) in each of the organs potentially impacted.

An individual person may have several organs affected by the pathology, and to differing extents.

Many methods and systems are known to assess and/or calculate risk of disease in a specific organ. Methods and systems have been disclosed that combine different measurements to assess a status of a target organ: for example, a combination of measurements of the brain to assess the 'brain age' and the susceptibility for disease. Methods are known where organ feature data is used to determine treatment and treatment related risk, including probability of toxicity for a specific organ.

Methods have been applied to classify asymptomatic patients into a risk category for a category of disease, for example, the risk of having or developing cancer and/or classifying a patient with an increased risk of having or developing cancer into an organ system-based malignancy class.

Methods are known that evaluate a generality: for example, a category of physiology such as an individual's phenotype / body composition and associated propensity for disease relative to stored population data/profiles. For example, values from MRI scans relating to fat / adipose tissue (the amount of visceral fat, subcutaneous fat, the volume of fat, the concentration of fat in tissue (of an organ and/or bone marrow) have been combined with the phenotype or phenotype variable (such as glycemic status, blood pressure, age or health state) characteristics to determine risk of a future disease.

Methods that rely on artificial intelligence (AI) entail the mining and analysis of extensive data, population, image features and synthetic data for diagnostic, prognostic and predictive information. For example, methods are known to rely on meta data and aggregate series level data (combinations of patient studies, clinical contextual information, statistical data) as an input to a classifier. Some incorporate

natural language processing.

Some methods disclose improved risk by analysing a whole organ from a lesion agnostic perspective. Imaging information may be derived from an MRI scan that is performed to collect data to formulate an image. The imaging information, clinical imaging metadata relating to the MRI scan or data collected and additional information relating to the pathology or potential tumour type and tumour vicinity may be combined.

Many disclosures that claim multi-organ solutions, are confounded by the complexity of segmentation.

Certain conditions or multi-organ pathologies, for example metabolic conditions or multi-organ pathologies, benefit from the simultaneous indication of multiple-organ or system state: for example. Assessment of the exocrine, respiratory and circulatory systems may be via constituent organ status. The state of the organ may be or be dependent upon the organ's status.

However, clinicians can be inundated with myriad data that is at best of very limited informative use. Furthermore, where clinicians are specialised, the lack of interpretive systemic relevance can render such data inappropriate and potentially misleading. For example, when observed in isolation neither qualitative measures (e.g. extent of mass spiculation) or quantitative measures (e.g. tumour dimension) reflect the complexity of morphology or behavior within systems of a multi-organ pathology. Where such measures are based on average values for example, average values over a region then a lack of relevance may be aggravated.

Products are commercially available that report measures of the states of a number of organs. Some of the products report measures of a number of quantitative measurements (over one hundred) from medical imaging across multiple organs $|U_i M_i|$. The range of organs individually includes the liver, kidneys, pancreas, heart, spleen, aorta and lungs; and collectively extends to measurement of inflammatory conditions such as 'Long Covid' which in many patients, impacts several organs including the brain. A number of "relevant parameters" may also be impacted in these conditions or pathologies including biomarkers such as enzymes in blood serum (alanine transaminase [ALT], alanine transferase [AST], Bilirubin etc). The relevant parameters may encode epidemiologically relevant information such as age, gender etc. and/or genomic information.

However, clinicians find it almost impossible to use this plethora of information. No solution exists where the status and respective role of accurate single organ measures informs systemic assessment in a useful, informative manner for the clinician. The present invention offers such a solution. It provides means to calculate the risk of a pathology and/or clinical event as it impacts multiple organs and/or systems, such as endocrine system, exocrine system, circulatory system, hepatobiliary system etc.

Summary of the Invention

According to an aspect of the disclosure, there is provided a method of estimating a risk of a multi-organ pathology in a person, comprising: collecting medical metrics from the person, the medical metrics comprising quantitative parameters of phenotype of the person, and one or more quantitative measures of each one of a plurality of organs of the person from at least one MRI scan performed to obtain MRI data of the organs, using the metrics to assess a state of each one of the organs, and selecting a plurality of the states and at least one of the quantitative parameters to estimate the risk of the multi-organ pathology in the person.

In some examples, the method may be used for estimating the risk and/or predicting the occurrence of a pathology and/or clinical event. A multi-organ pathology risk estimation system may execute the method of estimating a risk of a multi-organ pathology in a person. The system may comprise a computer, a data receiving device by which the computer receives the quantitative parameters and the quantitative measures of a plurality of organs of the person from at least one MRI scan, a display by which the computer shows a numerical or graphical visualization of the risk, and a computer program directly loadable into a memory of the computer for controlling the method when the program is run on the computer. An MRI scanner may be configured to acquire MRI scans of a plurality of organs in a person, wherein the MRI scanner is in electronic communication with a multi-organ pathology risk estimation system.

In some examples, the method and system provide means to assess the likelihood, risk, or possible occurrence of a condition or pathology that impacts multiple organs and/or systems, such as endocrine, exocrine, hepatobiliary, circulatory etc, that incorporates organ specific information and its relative role in and on the systemic risk.

In an example, the present disclosure provides a method to transform multiple specific measurements of the health/status of an individual organ or multiple organs affected

by a multi-organ pathology into a likelihood, risk or prediction of occurrence of a systemic pathology / clinical event. The measurements may be quantitative measurements from MRI medical imaging.

In some examples, the method of estimating the risk may include selecting the states of all the organs. The method may use all of the metrics to assess every state. The method may use a selection of the metrics that the multi-organ pathology directly affects to assess the state of each of the organs.

In some examples, the metrics may comprise a selection of the quantitative measures from each of the organs that the multi-organ directly affects. The method may include selecting the states particularly from other than those of the organs that the multi-organ pathology directly affects plus those that the multi-organ pathology directly affects. The list of organs may not be obvious from traditional clinical teachings ~ e.g. adding in a combination of liver and pancreas state or liver, kidneys, and pancreas state to improve prediction of cardiac outcomes – something that is not part of standard clinical thought. The multi-organ pathology may be cardiovascular or cardiac, organs other than those that the multi-organ pathology directly affects may include the kidneys, or the liver and the pancreas plus those the multi-organ pathology directly affects may include the heart. Here ‘or’ may be inclusive as in ‘and’.

In some examples, the method may include selecting the states of the organs that the multi-organ pathology directly affects according to levels of the quantitative parameters or quantitative measures of blood, liver, and biliary tree required for autoimmune liver disease.

In some examples, subsets of measurements may be defined, and their importance may be adjusted, or may be weighted relative to each other. The subsets may define risk scores to characterise the health of specific systems (circulatory, respiratory, exocrine, endocrine, etc.) or clinically relevant events ~e.g. hospitalisation, hepatic decompensation, etc. Therefore, the method may assess the state of each of the organs using a weighted sum of the metrics. The method may include assessing the respective state of each of the organs using a weighted sum of a plurality of the quantitative measures. The weights may be determined by linear or logistic regression.

In some examples, a logistic regression model may have a dependent variable dependent upon independent variables, wherein the dependent variable is for status

of the multi-organ pathology and the independent variables are respective to each one of the medical metrics. The method may include reducing the logistic regression model by removing from the logistic regression model at least one of the independent variables by a stepwise backwards selection process removing the independent variables one at a time sequentially to identify a parsimonious model based on Akaike Information Criterion optimization.

In some examples, the method may use a point in a space having a number of dimensions equal to how many there are of the quantitative measures of the each of the organs, wherein an n-cube that represents the states that are normal healthy is calculated, and clustering may be performed within the space to quantify the sensitivity of the risk to each of the quantitative measures of each of the individual organs.

In some examples, the method may use a Bayesian network in which the metrics for each of the organs are nodes, assigning a categorical value to each of the nodes, and propagating the categorical values through the Bayesian network to estimate the risk.

In some examples, at the time of the measurement(s), the person may have only subclinical organ impairment. In the future, the multi-organ pathology may progress in the person upon whom the measurement(s) are taken. In the future the person may require treatment for the multi-organ pathology or organs which currently have subclinical organ impairment.

In some examples, the method may provide a quantitative indication of risk of future occurrence of the multi-organ pathology developing in the person that may require treatment of the multi-organ pathology.

In some examples, the MRI data may be standardized or adjusted to that of a reference MRI scanner. For example, the data may be standardized to a reference main magnetic field level. Thus the measurement(s) or quantification of the risk may also be standardized.

In some examples, the method may turn all of the metrics except age into thresholded, categorical variables using clinically defined cutoffs.

In some examples, the method may include monitoring separate groups of healthy people in a population. Those of the healthy people who go on to be diagnosed with

disease or the multi-organ pathology are recorded and the group that they are in is recorded. Each group may be characterized by a specific combination of the metrics. This information may be used in the method of quantifying the risk of the disease or multi-organ technology being diagnosed or occurring according to specific combinations of the metrics or levels of the metrics in each combination.

In some examples, the information from the population and separate groups of healthy people within the population may quantify a risk that different subsets of healthy people will become unhealthy according to the metrics or levels of the metrics in each combination which characterize the group. It may be used to as guide to quantify the risk that the person upon whom the measurements are made and for who the metrics are determined will develop the multi-organ pathology or disease in the future.

In some examples, the method of estimating the risk may include identifying a relevant population pool of people who are initially healthy and monitoring over time the same medical metrics and the state of each of the same organs of each one of the people of the relevant population pool as are collected from the person; recording quantitative levels of the metrics and the state of each of the organs of the people in the relevant population pool over time; and correlating a rate of change in each of the metrics and the state of each of the organs of the people in the relevant population pool with a rate of occurrence of the multi-organ pathology in the people and using the correlation to adjust the estimate of the risk of the multi-organ pathology in the person. The risk estimate is thereby made robust because the pool of people accounts for variations in individual susceptibility to the multi-organ pathology.

In some examples, the method of estimating the risk may include identifying a relevant population pool of people in which an indication that the multi-organ pathology is present develops over time from an initial indication that the multi-organ pathology is not present, and identifying a control population pool without the indication that the multi-organ pathology is present, collecting the same medical metrics and assessing the same states for the people in the relevant population pool and for people in the control population as are collected from the person, and determining a difference between the states in the people in the relevant population compared to the control population, correlating each difference with a rate of occurrence of the multi-organ pathology in the relevant population pool over the time, and using the correlation to adjust the estimate of the risk of the multi-organ pathology in the person. The risk

estimate may be thereby made dependable because the control population provides a statistical baseline.

According to another aspect of the disclosure, there is provided a method of estimating the risk of a multi-organ pathology in a person wherein the risk is developing diabetic hyperglycaemia, comprising: collecting medical metrics from the person, the medical metrics comprising quantitative parameters of phenotype of the person including body mass index BMI, gender, and glycerated haemoglobin HbA1c, and one or more quantitative measures of each one of a plurality of organs of the person from at least one MRI scan performed to obtain MRI data of the organs including visceral adipose tissue VAT, subcutaneous adipose tissue SAT, skeletal muscle tissue SMI, liver fat, and liver iron corrected-T1 CT1, using the metrics to assess a state of each of the organs, and selecting a plurality of the states and at least one of the quantitative parameters to estimate the risk of the multi-organ pathology in the person, using a Bayesian network in which the metrics for each one of the organs are nodes, assigning a categorical value of either low or elevated to each of the nodes, and propagating the categorical values through the Bayesian network to estimate the risk as probability of a future occurrence of hyperglycemia wherein HbA1c exceeds 48 mmol/mol.

According to another aspect of the disclosure, there is a method of estimating the risk of a multi-organ pathology in a person wherein the risk is developing a cardiovascular disease or cardiac disease, comprising: collecting medical metrics from the person, the medical metrics comprising quantitative parameters of phenotype of the person, and one or more quantitative measures of each one of a plurality of organs of the person from at least one MRI scan performed to obtain MRI data of the organs, the quantitative measures including: iron-corrected T1 data of the liver indicative of fibro-inflammation, PDFF data of the liver indicative of liver fat, scanner-referenced T1 data of the pancreas indicative of fibro-inflammation, the quantitative parameters including: the person’s age, body mass index BMI, their type or value of blood and urine biochemistry including quantitative values of at least one circulating biomarker: aspartate aminotransferase (AST), alanine aminotransferase (ALT), glycerated haemoglobin (HbA1c), or C-reactive protein, using the metrics to assess a state of each one of the organs, and selecting a plurality the states and a plurality of the quantitative parameters to estimate the risk of the multi-organ pathology in the person.

In some examples, the method may include identifying a relevant population pool of

people who are initially healthy and monitoring over time the same medical metrics and the state of each of the same organs of each one of the people of the relevant population as are collected for the person, and correlating a rate of change in each of the metrics or the state of each of the organs in the people in the relevant population pool, or both the metrics and the states, with a rate of occurrence of the cardiovascular disease or cardiac disease in the people in the relevant population pool, and using the correlation to adjust the estimate of the risk of the multi-organ pathology in the person. Separate groups of initially healthy people in the relevant population may be compared and tracked over time. Each of the groups may comprise people who have metrics or states of each of their organs that are different from those of people in the other groups. By comparing the groups, their metrics, and their states, how different combinations of the metrics and states quantify risk to the multi-organ pathology, for example cardiovascular disease or cardiac disease, may be determined.

In some examples, the method may identify a relevant population pool of people in which an indication that the cardiovascular disease or cardiac disease is present develops over time from an initial indication that the cardiovascular disease or cardiac disease is not present. The method may identify a control population pool without the indication that the cardiovascular disease or cardiac disease is present. The method may collect the same medical metrics and assess the same states for the people in the relevant population pool and for people in the control population as are collected from the person, and determine a difference between the states in the people in the relevant population compared to the control population. The method may include correlating each difference with a rate of occurrence of the cardiovascular disease or cardiac disease in the population pool over the time that the cardiovascular disease or cardiac disease develops, and using the correlation to adjust the estimate of the risk of the multi-organ pathology in the person.

According to another aspect of the disclosure, there is provided a method of estimating the risk of a multi-organ pathology in a person wherein the risk is of developing diabetic macular oedema DMO, comprising: collecting medical metrics from the person, the medical metrics comprising quantitative parameters of phenotype of the person, and one or more quantitative measures of each one of a plurality of organs of the person from at least one MRI scan performed to obtain MRI data of the organs, the quantitative measures including: iron-corrected T1 data of the liver indicative of fibro-inflammation, PDFF data of the liver indicative of liver fat, scanner-referenced T1 data of the

pancreas indicative of fibro-inflammation, the quantitative parameters including a demographic, a feature of the person's medical history relevant to DMO, their type or value of blood and urine biochemistry, using the metrics to assess a state of each one of the organs, and selecting a plurality the states and a plurality of the quantitative parameters to estimate the risk of the multi-organ pathology in the person.

In another aspect of the disclosure, there is provided a computer implemented method of estimating a risk of a multi-organ pathology in a person, comprising: collecting medical metrics from the person, the medical metrics comprising quantitative parameters of phenotype of the person, and one or more quantitative measures of each one of a plurality of organs of the person from at least one MRI scan performed to obtain MRI data of the organs; using the metrics to assess a state of each one of the organs; and selecting a plurality of the states and at least one of the quantitative parameters to estimate the risk of the multi-organ pathology in the person.

In another aspect of the disclosure, there is provided a multi-organ pathology risk estimation system to execute a method of estimating a risk of a multi-organ pathology in a person according to the preceding aspect, the system comprising: a computer; a data receiving device by which the computer receives the quantitative parameters and the quantitative measures of a plurality of organs of the person from at least one MRI scan; a display by which the computer shows a numerical or graphical visualization of the risk; and a computer program directly loadable into a memory of the computer for controlling the method when the program is run on the computer.

The disclosure will now be described, by way of example only, with reference to the accompanying figures in which:

Brief Description of the Figures

Figure 1 shows a flowchart summarizing the main steps of the invention;

Figure 2 shows a schematic representation of combining the multiple quantitative measurements with relevant parameters to predict single organ and multi-organ pathologies;

Figure 3 shows estimation of diabetic hyperglycaemia using a Bayesian network; and

Figure 4 shows multi-organ risk of cardiovascular outcomes.

Detailed Description of the Invention

A flowchart is shown in Figure 1 of method (100) of estimating a risk of a multi-organ pathology in a person , comprising: collecting medical metrics from the person, the medical metrics comprising quantitative parameters (104) of phenotype of the person, and quantitative measures (102) of a plurality of organs of the person from at least one MRI scan performed to obtain MRI data of the organs, using the metrics to assess a state (106) of each of the organs, and selecting a plurality of the states (108) and at least one of the quantitative parameters to estimate the risk of the multi-organ pathology (110) in the person.

In an embodiment a number of quantitative measurements m_{ij} are made from medical imaging data, there is a set M (220) of the quantitative measurements:

$$M_i = \{m_{ij} | j = 1, \dots, J_i\}$$

of each of a set of organs (210).

$$\{O_i | i = 1, \dots, I\}$$

as well as a number of 'relevant parameters' (240)

$$C = \{c_l : l = 1, \dots, L\}.$$

As shown in Figure 2 there are quantitative measurements (221, 222, 223, 224) of each organ (211, 212, 213, 214). The quantitative measurements of one of the organs may be different than the quantitative measurements on another of the organs. Some organs may have quantitative measurements in common with other organs. Figure 2 also shows that there are additional relevant parameters (241, 242, 243, 244) which may not be organ specific.

The "relevant parameters" (240) C may be biomarkers such as the enzymes (ALT (327), AST (328), Bilirubin, ….) or they may encode epidemiologically relevant information such as age (332), gender (329) etc . They may also encode genomic information of the person in the medical imaging scans.

Each measurement or parameter may be continuous, for example glycerated haemoglobin (HbA1c) blood glucose level (336) or cT1 (331), or it may be categorical

(e.g. very low, low, normal, high, very high). It is often the case that clinicians use categorical measures.

An error bar may be associated with each measurement, which may or may not be made explicit (e.g. an iron corrected T1 determined from data collected from an MRI scan of a liver, cT1 = 850ms +/- 20ms).

A continuous measure typically has an associated distribution. Such a distribution may be summarised by parameters (e.g. mean and standard deviation in the case of a normally distributed parameter, or mode and left and right spread in the case of a non-normally distributed, asymmetric measure).

The quantitative measurement (e.g. cT1 = 900 ms) may either have a probability/likelihood estimate relative to the distribution or will be assigned a categorical value. For example, parameter, body mass index (BMI) = height (m) divided by weight^2 (kg^2) is continuously varying but is often categorised as below normal, normal, overweight, obese, and morbidly obese, where, for example obese means $30 \leq BMI < 40$.

An example of such a categorical distribution, which gives the probability of diabetic hyperglycaemia (DHG) given the BMI status (335) is as follows :

Obesity status	Probability of DHG (%)
Normal weight (<25kg/m^2)	23%
Overweigh (25-30 kg/m^2)	23%
Obese (30-40kg/m^2)	26%
Severe obesity (>40 kg/m^2)	31%

An estimation of diabetic hyperglycaemia (DHG) using a Bayesian network (300) is shown in Figure 3.

A similar set of categorical distributions may be established for the medical imaging metrics, C and M_i. The categories can be created by comparison to a normal range (e.g. normal [<upper limit of normal {ULN}], slightly elevated [1-2x ULN], significantly elevated [>2xULN]) or by previously established empirical thresholds (e.g. cT1<800 is "Normal", 800 ≤ cT1 ≤ 875 is "nonalcoholic steatohepatitis (NASH)", cT1 > 875 ms is "high-risk NASH"). The individual measurements, m_{ij}, are made of each individual organ O_i..

In an embodiment, the state of each organ $\mathrm{O_i}$ (211, 212, 213, 214) is determined via the totality of information that are the quantitative measurements (221, 222, 223, 224) of the respective organ together with the relevant parameters (241, 242, 243, 244) of the person,

$$\Omega_\mathrm{i} = \mathrm{M_i} \cup \mathrm{C}$$

from which the state of the organ is determined and a set of pathologies (250, 252, 252, 253) specific to a respective organ $\mathrm{O_i}$. The multi-organ pathology affects the state of a plurality of the organs, and the state (231, 232, 233,234) of each of the organ can affect or indicate the progress or risk of the multi-organ pathology (260, 261, 262, 263).

For example, with reference to the liver, a set of pathologies refer specifically to organ $\mathrm{O_i}$ include: steatosis, metabolic-associated steatohepatitis, cirrhosis, hepatocellular carcinoma, metastatic liver cancer, jaundice etc. For most of these pathologies no additional information is required about the organs other than $\mathrm{O_i}$.

The pathologies p_{ik} that impact only organ $\mathrm{O_i}$ are denoted by:

$$\{\mathrm{p_{ik}}|\mathrm{k} = 1, \dots, \mathrm{K}\},$$

and the risk of one of these pathologies by:

$$\mathrm{p}(\mathrm{p_{ik}}) = \mathrm{f_{ik}}(\Omega_\mathrm{i}),$$

Where not all of the parameters Ω_i are needed to determine $\mathrm{p}(\mathrm{p_{ik}})$, a subset of parameters is identified by:

$$\Omega_{\mathrm{ik}} \subseteq \Omega_\mathrm{i}$$

so that

$$\mathrm{p_{ik}} = \mathrm{f_{ik}}(\Omega_{\mathrm{i}}) = \mathrm{f_{ik}}(\Omega_{\mathrm{ik}}).$$

We refer to this herein as 'pathology projection' as it defines the reduction in the parameters and quantitative measurements needed to determine the risk to a predetermined level of accuracy.

$$\Omega_{\mathrm{i}} \rightarrow \Omega_{\mathrm{ik}}$$

The attention of a clinician is drawn to one or more measurements $\mathrm{m_{ij}}$ thus guiding the clinician's focus to the measurements that appear of concern.

The state of a specific organ within the set and/or subset Ω_{i} is required, expressed by:

$$\sigma_{\mathrm{ik}} \epsilon \Omega_{\mathrm{ik}} \text{ and } \mathrm{p_{ik}} = \mathrm{f_{ik}}(\sigma_{\mathrm{i}}) = \mathrm{f_{ik}}(\sigma_{\mathrm{ik}}).$$

For single-organ pathologies clinicians know which subset of the totality of parameters that are reported for an organ are relevant for a specific pathology $\mathrm{p_{ik}}$. Examples of 'single-organ' pathologies include: steatohepatitis, fatty pancreas disease, ischemic-type biliary lesions (post-liver transplantation), pancreatitis.

In an embodiment, the function $f_{ik}(\sigma_{ik})$ from which the risk of the pathology p_{ik} is calculated, comprises any machine learning (ML) technique: for example, where a sufficient number of cases of the pathology, and of "normal" cases (i.e. non-pathology) are available.

In an embodiment, the function $f_{ik}(\sigma_{ik})$ from which the risk of the pathology p_{ik} is calculated, may be a weighted sum of the parameters C and quantitative measurement Mi in Ω_{ik}. the weights may be learned by an appropriate ML technique.

In an embodiment, the function $f_{ik}(\sigma_{ik})$ from which the risk of the pathology p_{ik} is calculated, may be a weighted sum where the weights are not learned, but optimised in a conventional way (e.g. linear or logistic regression).

In an embodiment, the 'function', f_{ik}, describes a point in n dimensional space, where $n = |m_{ij}|$, or $|m_{ij}| + |C|$. . A distance (e.g. Euclidian, Gower) from an n-cube that represents 'normal' or 'healthy' states may then be calculated either in a specific dimension, d_i, or the totality of all dimensions, $\sum d_i$.

Additionally, clustering (e.g. k-means, portioning around medoids, …) can be performed within the n-dimensional space to characterise the pathology and highlight the key parameters C or quantitative measurements mij (i.e. those which have the most impact on likelihood of the pathology being present) to a clinician.

In a preferred embodiment, the 'function' f_{ik}may be best represented by a Bayesian network (300) in which the parameters and quantitative measurements in Ω_{ik} are the nodes (311, 312, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 337), each one of which has an associated probability or categorical value and these values/probabilities are propagated through the Bayesian network to estimate the risk/likelihood/possibility of pathology p_{ik}.

In an embodiment, a multi-organ pathology p_{γ_u}impacts more than one organ, but not necessarily all of the organs :

$$\gamma_u \subseteq \{O_i | i = 1, \dots, I\}$$

where the u[th] such pathology, p_{γ_u}, is associated with the set γ_u of organs. A function assesses the risk of the pathology from the states of the organs that are affected:

$$p(p_{\gamma_u}) = g_u(\sigma_{u_1}, \sigma_{u_2}, \dots, \sigma_{u_U})$$

where σ_{u_j} is the state of the j[th] organ relevant to this pathology.

In an embodiment, the list of organs may be derived from expert input (e.g. measurements of blood, liver, and biliary tree required for autoimmune liver disease).

In an embodiment, the list of organs is derived from data.

In an embodiment, the list of organs is not obvious from traditional clinical teachings (e.g. adding in liver state to improve prediction of cardiac outcomes – something not part of standard clinical thought).

The mechanisms to calculate a single organ apply.

In an embodiment, a risk of a multi-organ pathology p(p_{γ_u}) is calculated using any machine learning (ML) technique: for example, where a sufficient number of cases of the pathology, and of 'normal' cases (i.e. non-pathology) are available.

In an embodiment, a risk of a multi-organ pathology p(p_{γ_u}) is calculated using a weighted sum of the parameters C or measurement Mi in $\Omega_{ik}$and the weights may be learned by an appropriate ML technique.

In an embodiment, a risk of a multi-organ pathology p(p_{γ_u}) is calculated using a weighted sum where the weights are not learned but optimised in a conventional way (e.g. linear or logistic regression).

In an embodiment, a risk of a multi-organ pathology p(p_{γ_u}) is calculated using a point in n dimensional space, where $n = |m_{ij}|$. A distance (e.g. Euclidian, Gower) from an n-cube that represents 'normal' or 'healthy' states may then be calculated either in a specific dimension, d_i, or the totality of all dimensions, $\sum d_i$. Additionally, clustering (e.g. k-means, portioning around medoids, …) can be performed within the n-dimensional space to characterise the pathology and highlight the key measurements (i.e. those which have the most impact on likelihood of the pathology being present) to a clinician.

In a preferred embodiment, a risk of a multi-organ pathology p(p_{γ_u}) is represented by a Bayesian network (300) in which the parameters C and measurement Mi in Ω_{ik} are the nodes, each one of which has an associated probability or categorical value and these values/probabilities are propagated through the Bayesian network to estimate the risk/likelihood/possibility of pathology p_{ik}.

With reference to Figure 3, diabetic hyperglycaemia is estimated using a simplified Bayesian network (300) whereby MR-derived measures Mi of visceral adipose tissue (VAT) (333), subcutaneous adipose tissue (SAT) (330), skeletal muscle index (SMI) (334), liver fat (337) and liver iron corrected-T1 (cT1) (311) are combined with routinely collected parameters C, for example biomarkers such as body mass index (BMI) (335), sex (329) and glycerated haemoglobin (HbA1c) (336). The risk or probability of hyperglycemia (HbA1c >48mmol/mol) is estimated after fixing the values of network variables to 'low' or 'elevated'.

By way of illustrative example as shown in Figure 4, imaging metrics including parameters and quantitative measurements are derived from abdominal multi-parametric MRI scans. To assess the level of risk of cardiovascular hospitalisation, quantitative measurements of liver fibro-inflammation (iron-corrected T1, cT1) and liver fat (PDFF) were calculated, alongside quantitative measurements of pancreatic

fibro-inflammation (scanner-referenced T1, srT1). All imaging metrics are standardised to be comparable across scanner manufacturers and field strengths. Imaging metrics are combined with parameters including the participants' age and BMI. Blood biochemistry is used to calculate levels of circulating biomarkers aspartate aminotransferase (AST), alanine aminotransferase (ALT), glycated haemoglobin (HbA1c) and C-reactive protein. Each of the metrics above (with the exception of age) are turned into thresholded variables using clinically defined cutoffs. In addition, each metric is independently associated with an increased risk of cardiovascular disease-related hospitalisation.

Thus, a categorical risk model comprises combining metrics with outcome data. One example is a Cox proportional hazard model. This model links changes in metrics to the rate of outcomes. As such, it allows for the calculation of predicted hospitalisation-free survival probability for any combination of input metrics. As a further step, an individual's predicted 3-year survival probability is used as an easy to interpret risk score. The relative impact of different treatment approaches can be easily analysed by modifying input variables based on its expected effect on modifiable input variables. In the present example, a drug that normalised HbA1c values alone would have less effect than a drug which was able to reduce fibro-inflammation in the liver and pancreas.

By way of illustrative example, the method is used to estimate an individual's risk of developing diabetic macular oedema (DMO). This is a complication of diabetes mellitus affecting the eyes which can lead to vision loss. A number, *k*, of imaging metrics are collected from an individual undergoing clinical assessment and multi-parametric MRI scan, including quantitative measurements of liver fibro-inflammation (iron-corrected T1, cT1) and pancreatic fibro-inflammation (scanner-referenced T1, srT1), liver fat (PDFF) and parameters covering demographics, medical history, blood and urine biochemistry. All the imaging metrics are standardised to be comparable across scanner manufacturers and field strengths. A relevant population pool is identified from various data sources, in which the indication of interest (DMO) is present along with controls without the indication. The *k* metrics from the individual which underwent the clinical assessment are selected from the relevant population pool, to create a truncated dataset. Based on the truncated dataset, a logistic regression model is defined with DMO status as the dependent variable, *y*, and all *k* independent variables included at the beginning to comprise the with the full model. A stepwise backwards

variable selection process is utilised, and independent variables are removed one at a time sequentially to identify the most parsimonious model based on Akaike Information Criterion (AIC) optimisation, i.e. the final model. The final model summarising the association between the dependent variable (DMO) and the key independent variables, is used to predict the probability of DMO in the case of the individual's characteristics. The individual's probability score can be statistically transformed and presented in a visual manner to contextualise the relative risk of the disease indication and improve patient and clinician understanding.

The invention has been described by way of examples only. Therefore, the foregoing is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described, and accordingly, all suitable modifications and equivalents may be resorted to, falling within the scope of the claims.

Claims:

1. A computer implemented **method** of estimating a risk of a multi-organ pathology in a person, comprising:

collecting medical metrics from the person, the medical metrics comprising quantitative parameters of phenotype of the person, and one or more quantitative measures of each one of a plurality of organs of the person from at least one MRI scan performed to obtain MRI data of the organs,

using the metrics to assess a state of each one of the organs, and selecting a plurality of the states and at least one of the quantitative parameters to estimate the risk of the multi-organ pathology in the person.

2. A method of estimating the risk according to claim 1 wherein the states selected include other than those of the organs that the multi-organ pathology directly affects plus those that the multi-organ pathology directly affects.

3. A method of estimating the risk according to claim 2 selecting the states of the organs that the multi-organ pathology directly affects according to levels of the quantitative parameters or quantitative measures of blood, liver, and biliary tree required for autoimmune liver disease.

4. A method of estimating the risk according to claim 2 wherein the multi-organ pathology is cardiovascular or cardiac and the organs other than those that the multi-organ pathology directly affects include the liver and pancreas, and those the multi-organ pathology directly affects include the heart.

5. A method of estimating the risk according to any preceding claim assessing the state of each of the organs using a weighted sum of the metrics.

6. A method of estimating the risk according to any preceding claim assessing the respective state of each of the organs using a weighted sum of a plurality of the quantitative measures.

7. A method of estimating the risk according to claim 5 or 6 using a logistic regression model having a dependent variable dependent upon independent variables, wherein the dependent variable is for status of the multi-organ pathology and the independent

variables are respective to each one of the medical metrics.

8. A method of estimating risk according to claim 7 reducing the logistic regression model by removing from the logistic regression model at least one of the independent variables by a stepwise backwards selection process removing the independent variables one at a time sequentially to identify a parsimonious model based on Akaike Information Criterion optimization.

9. A method of estimating the risk according to any preceding claim using a point in a space having a number of dimensions equal to how many there are of the quantitative measures of the each of the organs, wherein an n-cube that represents the states that are normal healthy is calculated, and clustering is performed within the space to quantify the sensitivity of the risk to each of the quantitative measures of each of the individual organs.

10. A method of estimating the risk according to any preceding claim using a Bayesian network in which the metrics for each of the organs are nodes, assigning a categorical value to each of the nodes, and propagating the categorical values through the Bayesian network to estimate the risk.

11. A method of estimating the risk according to any preceding claim wherein the risk is of future occurrence of the multi-organ pathology developing in the person to require treatment of the multi-organ pathology.

12. A method of estimating the risk according to any preceding claim turning all of the metrics except age into thresholded categorical variables using clinically defined cutoffs.

13. A method of estimating the risk according to any preceding claim including:

identifying a relevant population pool of people who are initially healthy and monitoring over time the same medical metrics and the state of each of the same organs of each one of the people of the relevant population pool as are collected from the person,

recording quantitative levels of the metrics and the state of each of the organs of the of the people in the relevant population pool over time, and

correlating a rate of change in each of the metrics and the state of each of the organs of the people in the relevant population pool with a rate of occurrence of the multi-organ pathology in the people and using the correlation to adjust the estimate of the risk of the multi-organ pathology in the person.

14. A method of estimating the risk according to any of claims 1 to 12 including:

identifying a relevant population pool of people in which an indication that the multi-organ pathology is present develops over time from an initial indication that the multi-organ pathology is not present, and

identifying a control population pool without the indication that the multi-organ pathology is present,

collecting the same medical metrics and assessing the same states for the people in the relevant population pool and for people in the control population as are collected from the person, and

determining a difference between the states in the people in the relevant population compared to the control population, correlating each difference with a rate of occurrence of the multi-organ pathology in the relevant population pool over the time, and using the correlation to adjust the estimate of the risk of the multi-organ pathology in the person.

15. A multi-organ pathology risk estimation **system** to execute the method of estimating a risk of a multi-organ pathology in a person according to any of claims 1 to 14 comprising a computer, a data receiving device by which the computer receives the quantitative parameters and the quantitative measures of a plurality of organs of the person from at least one MRI scan, a display by which the computer shows a numerical or graphical visualization of the risk, and a computer program directly loadable into a memory of the computer for controlling the method when the program is run on the computer.