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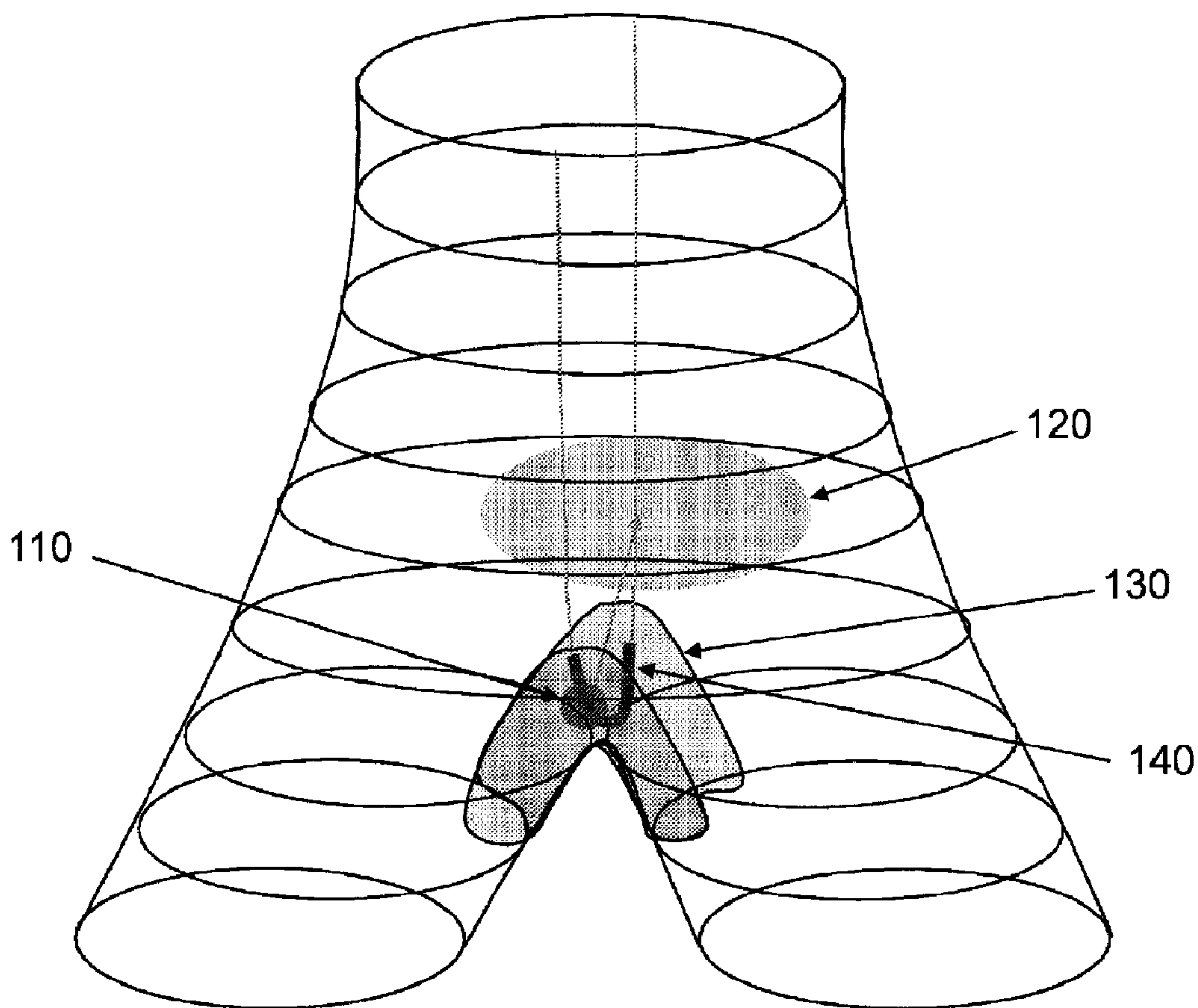
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(54) Titre : PROCÉDE ET SYSTÈME POUR MESURER LE DOMMAGE TISSULAIRE ET LE RISQUE DE MALADIE

(54) Title: METHOD AND SYSTEM FOR MEASURING TISSUE DAMAGE AND DISEASE RISK



(57) Abrégé/Abstract:

This invention relates to a method of quantitatively measuring lung tissue damage by measuring the mineral density deviations and/or mineral composition deviations from low exposure regions in a CT scan and combining this with measurements of global or local measurements of lung obstruction.



ABSTRACT OF THE DISCLOSURE

This invention relates to a method of quantitatively measuring lung tissue damage by measuring the mineral density deviations and/or mineral composition deviations from low exposure regions in a CT scan and combining this with measurements of global or local measurements of lung obstruction.

TITLE: METHOD AND SYSTEM FOR MEASURING TISSUE DAMAGE AND DISEASE RISK

CROSS REFERENCE TO RELATED APPLICATIONS

Not applicable.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

No federal government funds were used in researching or developing this invention.

NAMES OF PARTIES TO A JOINT RESEARCH AGREEMENT

Not applicable.

REFERENCE TO A SEQUENCE LISTING

Not applicable.

BACKGROUND

Field of the Invention

[001] This invention relates to a system, software, and method for quantitatively measuring lung tissue damage by measuring the mineral density deviations and/or mineral composition deviations from normal in a CT scan. This can be used in measuring lung exposure, damage, disease risk, and response to therapy using radiological techniques in combination with data analysis. The methods described here can also be applied to other diseases that involve mineralization including COPD, esophageal cancer, cardiovascular diseases, and osteoarthritis.

[002] Background of the Invention

[003] According to the National Cancer Institute, the number of new cases of lung cancer in 2007 (both non-small cell and small cell combined) is estimated to be 213,380, and the number of deaths is estimated to be 160,390. There currently is no reliable method for measuring an individual's lung damage and risk for developing lung cancer. Lung cancer

screening trials rely on age and individual reported exposure to cigarette smoke and other carcinogens to identify a high risk screening population. This method of lung cancer risk assessment provides a crude estimate of carcinogenic exposure and does not take into account (a) the damage the specific individual has sustained as a result of a wide range of potential lung tissue insults and (b) the variation in individual response to the exposure. An objective method for measuring the amount of lung tissue damage an individual has sustained would be of great benefit to effectively monitor and manage lung cancer risk groups and personalize disease monitoring and treatment of lung cancer patients.

[004] Computed tomography scanning technology has improved dramatically in the last 10 years. Most health care institutions in the United States are now able to routinely obtain thin slice CT scans of the entire lung within a few seconds. The detailed x-ray attenuation measurements these scans produce have the potential to reveal important information relating to the progression and management of lung cancer, chronic obstructive pulmonary disease (COPD), and other smoking related diseases. Numerous studies have revealed important CT imaging features that provide important clinical information that is now important to the early management of thoracic diseases. Thin slice CT allowed for the differentiation of part-solid lung lesions, which must be managed more aggressively due to their high probability of malignancy when detected at baseline. In addition, high resolution CT measurements of airway wall thickness and the extent of emphysema is providing new insight into the management of COPD.

[005] The fields of environmental health and aerosol sciences have also studied the fundamental mechanisms leading to lung cancer. These studies have found that the deposition of particulate matter in the lung, as occurs when smoking, has particular patterns of distribution. Of particular importance is the analysis of air flow patterns in human airways. Several studies have shown that certain structures in the airways, particularly the carinal ridge at airway bifurcations, receive significantly more particulate deposition than other locations in the lung. Smoking population studies have further revealed that for some exposures airway branching levels above three or four receive significantly more particulate load than other airway regions. It is these high exposure

locations that both receive a disproportionate amount of particulate load and have the potential to provide an early indication of the level of damage sustained throughout the rest of the lung.

[006] It is further well known that airways contain large amounts of hyaline cartilage which has the property that it mineralizes, i.e. calcifies, with various forms of repeated stress and age.

BRIEF SUMMARY OF THE INVENTION

[007] The invention described here provides a method of quantitatively measuring lung cancer risk by measuring the mineral density deviations and/or mineral composition deviations from normal or less stressed region in a CT scan. Since mineralization is a common response to stress across many tissues in the human body, such as ligaments, tendons, vascular tissues, and the various forms of cartilage, the methods herein may be used to measure damage and risk and have applicability to other diseases including COPD, esophageal cancer, cardiovascular diseases, aging of ligaments and tendons, and osteoarthritis.

[008] In another preferred embodiment, the invention includes a method of quantitatively measuring lung tissue damage, comprising the steps of i) obtaining a high resolution CT lung scan of an individual; ii) analyzing the CT scan and measuring density deviations of airway tissue locations having the highest particle deposition, wherein the density deviations are obtained using either airway geometry analysis or fluid flow analysis; iii) measuring the subjects local and/or global degree of airway obstruction (e.g. FEV1/FVC is a global lung function measurement and CT wall thickness and emphysema measurements are local) and v) combining any or all of these measurements into a lung disease risk index.

[009] In preferred embodiments, the method includes (a) wherein analyzing the CT scan and measuring density deviations further comprises measuring the sum of the logs of maximum HU density deviations from nearby low exposure regions along the airway tree

in a CT scan; or (b) wherein the location of highest particle deposition comprise one or more bifurcation locations or curved regions, and wherein the step of combining the measurements further comprises placing a greater influence over the measurement of lung damage from the one or more bifurcation locations or curved regions; or (c) wherein the CT scan is a multiple energy CT scan and provides features to further distinguish individual response to exposure; or (d) where it further comprises the step of comparing changes between one or more assessments of lung cancer risk index, and using said comparison to determine a measured response to therapy; or (e) wherein combining measurements into a lung cancer risk index further comprises adjusting the metric for additional clinical data such as age, gender, smoking history, comorbidity, and family history, as is other important diagnostic tests; and / or (f) wherein combining measurements into a lung cancer risk index further comprises adding other CT analysis data to the metric such as COPD wall thickness and emphysema score as both are measures of pulmonary obstruction which is correlated strongly with lung cancer.

[0010] In one preferred embodiment, the therapy is lung cancer therapy.

[0011] In another preferred embodiment, the density and composition CT measurements are taken from hyaline cartilage tissue located at the articular surface of a bone, and can be further used to provide therapeutic and/or clinical information regarding osteoarthritis of an individual. Accounting for and subtracting the mineralization response of non-disease related processes and utilizing a model of mineralization damage response (e.g. exponential mineralization in response to damage requires a log function to estimate tissue damage) will thus reveal the damage and risk level of osteoarthritis.

[0012] In another preferred embodiment, the density and composition CT measurements are taken from vascular wall regions and adjacent areas and can be further used to provide therapeutic and/or clinical information regarding cardiovascular disease of an individual. Accounting for and subtracting the mineralization response of non-disease related processes and utilizing a model of mineralization damage response (e.g. exponential mineralization in response to damage requires a log function to estimate

tissue damage) will thus reveal the damage and risk level of cardiovascular disease including Coronary Artery Disease.

[0013] In another preferred embodiment, the density and composition CT measurements are taken from ligaments and tendons in order to damage and risk of failure. Accounting for and subtracting the mineralization response of non-disease related processes and utilizing a model of mineralization damage response (e.g. exponential mineralization in response to damage requires a log function to estimate tissue damage) will thus reveal the damage and risk level of tissue failure including knee ligament risk of injury.

[0014] The invention described herein also provides a system for quantitatively measuring lung tissue damage by measuring the mineral density deviations and/or mineral composition deviations from normal in a CT scan at high exposure locations such as the Hyaline cartilage found at bifurcations and airway cartilage rings and combining this with lung function information, such as FEV1 and FVC.

[0015] In another preferred embodiment, the invention provides a system for quantitatively measuring lung tissue damage, comprising: i) means for obtaining a high resolution CT scan of lung tissue of an individual; ii) means for analyzing the CT scan and measuring density deviations of airway tissue locations having the highest particle deposition, wherein the density deviations are obtained using either airway geometry analysis or fluid flow analysis; and iii) means for combining measurements into a lung cancer risk index.

[0016] In preferred embodiments, the system includes (a) wherein means for analyzing the CT scan and measuring density deviations further comprises means for measuring the average deviation in HU density along the airway tree in a CT scan; or (b) wherein the location of highest particle deposition comprise one or more bifurcation locations or curved regions, and wherein the means for combining the measurements further comprises a means for placing a greater influence over the measurement of lung damage from the one or more bifurcation locations or curved regions; or (c) wherein the CT scan is a multiple energy CT scan and provides material composition features to further distinguish individual response to exposure; (d) further comprising means for comparing

changes between one or more assessments of lung cancer risk index, and using said comparison to determine a measured response to therapy; (e) wherein the means for combining measurements into a lung cancer risk index further comprises means for adjusting the metric for additional clinical data such as age, gender, smoking history, comorbidity, and family history, as is other important diagnostic tests; and / or (f) wherein means for combining measurements into a lung cancer risk index further comprises means for adding other CT analysis data to the metric such as COPD wall thickness and emphysema score as both are correlated strongly with lung cancer.

[0017]In one preferred system, the therapy is lung cancer therapy.

[0018] In another preferred system, the density and composition CT measurements are taken from hyaline cartilage tissue located at the articular surface of a bone, and can be further used to provide therapeutic and/or clinical information regarding osteoarthritis of an individual.

[0019]In another preferred embodiment all regions of the lung are analyzed with a computer program to identify dangerous combinations of obstruction and calcification. Locations of partial or complete obstruction in the airway and the parenchyma (e.g. Bullae) are detected and the physician is notified. This information can be used to determine if a surgical or therapeutic intervention is necessary to reduce the risk of developing lung cancer and other diseases.

[0020]In another preferred embodiment the patterns of mineralization found at bifurcations are analyzed to provide information on the type and extent of particulate exposure including the mass, shape, and charge of the particle that caused the damage to the lung.

[0021]In another preferred embodiment the lung cancer risk index is used to create a personalized lung cancer screening protocol that optimizes the number of visits, the radiation dose, screening cost, and cancer detection rate. A baseline CT scan combined with FEV1/FVC data is combined to form the LCRI and follow-up screening plans are then calculated to verify the projected risk of the patient over time. Since obstruction and mineralization change slowly, the frequency and duration of screening can be optimized

to the individual. It should be possible to perform some follow-up screening visits for low baseline risk patients by measuring lung function (FEV1/FVC) more often than a full high resolution CT scan, thereby reducing the cost and dose required for lung cancer screening.

[0022]In another preferred embodiment, the LCRI is combined with measurements and attributes of a suspected lung cancer lesion to determine the probability of malignancy of the lesion. This is useful to establish before performing a potentially dangerous needle biopsy.

[0023]In another preferred embodiment a surgical planning tool analyzes lung tissue calcification and potential resection and interventional options to provide the surgeon with the best therapeutic method for ensuring that lung cancer and other disease risk is minimized. This could advise on the lung cancer risk associated with each of several therapeutic options.

[0024]The invention described herein also provides a computer program product, directly loadable into the RAM of a digital computer, comprising software code portions for implementing the steps of the method(s) as set forth herein, when said product is run on said digital computer.

[0025]In preferred embodiments, the software code portions are downloadable from a network.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026]FIGURE 1 is a representative drawing of an airway bifurcation. FIGURE 1 shows details of a bifurcation measurement method.

[0027]FIGURE 2 is a simulation showing the enhancement of particle deposition at a bifurcation location.

[0028]FIGURE 3 is a panel of CT images showing significant calcification at a bifurcation.

[0029]FIGURES 4A-4H constitute a spreadsheet of individual patient data, their CT measurements, lung function measurements, measurement correction values, and a calculated lung cancer risk index. FIGURES 4A-4H extend over eight pages in landscape page orientation. The data reported here provides evidence that careful measurement of mineral deposits at airway locations combined with a measurement of airway obstruction can provide a metric for determining an individual patient's lung cancer risk status.

[0030]FIGURE 5 is a graph of lung cancer risk index results. FIGURE 5 shows the damage index plotted against the patient's age. FIGURE 5 shows that a lung cancer risk threshold can be established, from which diagnostic and therapeutic determinations can be made.

[0031] FIGURE 6 is a graph of LCRI risk distribution. FIGURE 6 shows frequency plotted against the lung cancer risk index (LCRI). FIGURE 6 shows that the cancer and the normal populations show separation along the index .

[0032] FIGURE 7 is a CT scan of a knee where average CT density of the cartilage is measured. FIGURE 7 shows that mineralization measurements can assist in determinations of osteoarthritis.

[0033]FIGURE 8 is a CT scan of an esophagus where increased mineralization is present. FIGURE 8 shows that mineralization occurs in G.I. tissues, e.g. esophagus, and can assist in determinations of gastrointestinal conditions, such as cancer, GERD, Barrett's, etc. where tissue damage has resulted in increased mineralization.

[0034]FIGURE 9 is a scatter plot / graph showing BDI on the vertical axis plotted against FEV1/FVC plotted on the horizontal axis. FIGURE 9 shows the cancer regression line used to establish the LCRI.

[0035]FIGURE 10 is a scatter plot / graph showing pack years on the vertical axis plotted against age on the horizontal axis. FIGURE 10 shows the age and pack year distribution.

[0036]FIGURE 11 is a scatter plot / graph showing BDI on the vertical axis plotted against FEV1/FVC plotted on the horizontal axis, but does not show the regression line.

[0037]FIGURE 12 is a bar graph showing mean LCRI values on the vertical axis against ranges of ages within age-related groups of pack year data. FIGURE 12 shows the difference between the control groups and the cancer groups.

[0038]FIGURE 13 is a scatter plot / graph of LCRI on the vertical axis plotted against Age on the horizontal axis. FIGURE 13 also shows cancer data points against a range of controls from 10-29 PY, 30-49 PY, 50-69 PY, and >70 PY.

[0039]FIGURE 14 is a box and arrow chart showing the pipeline for airway segmentation.

[0040]FIGURE 15 (top) is a CT image “slice” showing contours from airway segmentation; (bottom left) shows medial airway surface line extracted using the LA04 method; and (bottom right) shows how bifurcations on the medial line are automatically extracted and parent/child relationships are computed.

[0041]FIGURE 16 is a combination of box and arrow diagram placed above four images, (i) the airway surface, (ii) embedded voronoi diagram, (iii) medial extraction line, and (iv) topology analysis. These are used to identify bifurcations of the medial line and carinal ridges at each bifurcation.

[0042]FIGURE 17 is an enhanced image showing the location of the carinal ridge (red) and the CD calculation (blue plane).

DETAILED DESCRIPTION OF THE INVENTION

[0043]DEFINITIONS

[0044]The following definitions are provided as an aid to understanding the detailed description of the present invention.

[0045] The term HYALINE CARTILAGE refers to a protective matrix found within an individual at locations involving movement of body parts, i.e. respiratory system, joints, etc.. It contains no nerves or blood vessels, and its structure is relatively simple. Except where it coats the articular ends of bones, it is covered externally by a fibrous membrane, the perichondrium. This membrane contains vessels that provide the cartilage with

nutrition. If a thin slice is examined under the microscope, it will be found to consist of cells of a rounded or bluntly angular form, lying in groups of two or more in a granular or almost homogeneous matrix. The cells, when arranged in groups of two or more, have generally straight outlines where they are in contact with each other, and in the rest of their circumference are rounded. They consist of clear translucent protoplasm in which fine interlacing filaments and minute granules are sometimes present; embedded in this are one or two round nuclei, having the usual intranuclear network. The cells are contained in cavities in the matrix, called cartilage lacunae; around these the matrix is arranged in concentric lines, as if it had been formed in successive portions around the cartilage cells. This constitutes the so-called capsule of the space. Each lacuna is generally occupied by a single cell, but during the division of the cells it may contain two, four, or eight cells. Hyaline cartilage also contains chondrocytes which are cartilage cells that produce the matrix. Hyaline cartilage matrix is mostly made up of type II collagen and Chondroitin sulfate, both of which are also found in elastic cartilage.

[0046] The term AIRWAY refers to those parts of the respiratory system through which air flows, to get from the external environment to the alveoli. The airway begins at the mouth or nose, and accesses the trachea via the pharynx. The trachea branches into the left and right main bronchi at the carina, situated at the level of the second thoracic vertebra. The bronchi branch into large bronchioles, one for each lobe of the lung. Within the lobes, the bronchi further subdivide some 20 times, ending in clusters of alveoli.

[0047] The term LUNG CANCER RISK INDEX is addressed below. The impact of small carcinogenic particles on lung tissue has been extensively studied over the last decade. Numerous studies have reported that the flow of air in the airways results in certain airway locations receiving a disproportionate deposition of particulate matter. In particular, bifurcation locations in the airway tree receive significantly more particulate deposits and, when the deposits are damaging to tissue, also sustain some of the greatest damage in the lung. The cumulative result of this damage can result in lung cancer forming preferentially in the locations that receive the greatest particle deposition load.

[0048] Measurement of airway bifurcations in CT scans is difficult due to the rapid decrease in airway size as branching progresses. The size of a bifurcation region between two airway branches quickly reduces to less than the size of CT scanner Point Spread Function (PSF) at a certain branching level. Without the use of advanced CT analysis methods, the CT density of bifurcations is only able to be reliably measured at the first few, i.e 3 to 4 airway branching levels. Manual measurement of maximum CT density at seven branching locations was performed to estimate lung cancer risk. A Lung Cancer Risk Index (LCRI) is performed by measuring the average density deviation of a plurality of bifurcation regions in the airways. At each bifurcation the log of the maximum CT density minus the average density of a low stress cartilage region near the bifurcation (ie. $\text{Log}(\text{bifurcation} - \text{comparison})$) is performed. A log function is used to estimate the damage associated with an exponential calcification response. The subtraction of a comparison region measurement is performed in order to remove the influence of other calcification processes that can occur in the bifurcation region such as a global increase in calcification or a widespread influence of mechanical stress. The selection of the comparison region should be made to avoid locations in the airway that have a propensity not to calcify. This includes regions that are near large moving structures such as the esophagus, the heart or the aorta that can potentially palpate the cartilage and inhibit calcification. A more advanced method for measuring the comparison region would track the average density of cartilage rings above and below the bifurcation and spatially estimate the comparison densities across the bifurcation, if not the entire airway tree. The measurement of maximum density at a bifurcation was performed by identifying two 26 connected voxels in the bifurcation region that produced the largest average CT density. Orthogonal reformatting of the CT scan is permitted in order to enable the review of maximum calcification in all dimensions, but is not strictly required. The two pixel requirement was used in order to set a size threshold for a focal increase in CT density and to help combat the influence of scanner noise. This is particularly important when large patients are scanned at low dose. The LCRI may also be used to establish threshold values for diagnostic and therapeutic determinations, as described further herein.

[0049] Referring now to the figures, FIGURE 1 is a representative drawing of an airway bifurcation. FIGURE 1 shows details of a bifurcation measurement method. FIGURE 2 shows the expected particle deposition load at the location of an airway bifurcation as shown.

[0050] Computed Tomography (CT) scans are able to obtain high resolution images of the human airway and provide detailed measurements of X-ray density (expressed as Hounsfield Units or HU) along the entire airway lumen and surrounding tissues. Given the preferential carcinogen load that certain airway regions receive, particularly airway bifurcations, it is reasonable to expect that these regions will exhibit changes from normal tissue. It is further expected that early changes in these locations will represent an early indication of lung cancer risk well before changes are visible in other lung areas. It is also possible that the increased calcification is in part due to the sequestration of carcinogens and other substances that are harmful and need to eventually be cleared from the lungs.

[0051] An analysis of high resolution CT scans of individuals with high exposure to cigarette smoke reveals that the CT density of bifurcation and other high curvature regions in the airways appears to increase. The method shown in FIGURE 1 includes determining the maximum intensity region (110) in the bifurcation region(s) (140) and subtracting the comparison intensity. The comparison region (-1/4 of airway circumference) (120) is a region of the airway, i.e the cartilage rings, from which measurements are taken to compare against the measurements at the carinal ridge, i.e. the area of the bifurcation having the maximum exposure / mineralization. The comparison intensity is the measurement taken from the comparison region (120). For the purposes of Figure 1, Bifurcation Max = Mean of maximum 2 edge/vertex connected voxels. For the purposes of Figure 1, Comparison Intensity = Mean cartilage density above or below the bifurcation. For the purposes of Figure 1, the Bifurcation Deviation Measure = $\log(\text{Bifurcation Max} - \text{Comparison intensity})$. For the purposes of Figure 1, Manual LDI = Mean of main bifurcation and 2 maximum Deviation measures in each lung.

[0052] FIGURE 2 is a computational fluid dynamics (CFD) simulation showing the enhancement of particle deposition at a bifurcation location.

[0053]FIGURE 3 shows slices from a high resolution CT scan of an individual with a high CT density response at bifurcation locations as described in particle flow studies. Analysis of several smoker CT scans shows generally a less intense, but clear density increase. The arrow indicates where, on the CT scan, that significant calcification has been determined to exist.

[0054]Further to this, publications on the deposition of asbestos fibers also point out the higher level of exposure sustained at the location of airway bifurcations [3].

[0055]A literature search did not reveal any reporting of the use of measurements of x-ray density increases at bifurcation locations (and other high exposure areas), probably because this is primarily observable with quantitative tools and using more recently available CT scans with sufficient resolution. Thus a quantitative method to assess lung tissue damage in CT images, and by other imaging methods, appears to be novel.

[0056]Without being held to one particular theory, the mechanism by which damage translates into higher density is likely related to continuous inflammatory response of the affected tissues. Hyaline cartilage, which is the type that is a major component of the human airway, is known to mineralize or ossify with repeated stress and age. In addition, the Interleukin-6 and Interleukin-7 pathways represent a potential mechanism by which a repeated inflammatory response could result in increased calcification and CT density. The inflammation pathway is implicated in smoking and asbestos exposure suggesting a common pathway toward increased density.

[0057]In one preferred embodiment, the invention is to quantitatively measure deviations in CT density at the locations of highest particle deposition. One embodiment of the invention is to analyze a CT scan of the lung and extract the full airway tree down to the limits of detection. A complete analysis of density deviations (from all other potential sources of cartilage mineralization) can be done to determine the overall individual response to all forms of exposure. Modeling and subtraction of various forms of biological stress (e.g. renal issues), biomechanical stress, and all forms of particulate deposition stress can be performed and help understand the type and extent of lung risk and injury. A further analysis can be performed by measuring the locations of highest

particle deposition, using either airway geometry analysis or fluid flow analysis. Once this has been done, the measurements can be combined into a global or local lung tissue exposure response score. Additional analysis of airway shape and texture can be performed throughout the airway and an overall lung cancer risk score can be formed by combining this information with standard airway function tests and emphysema scoring methods. Scanning with a multi energy CT scanner should reveal additional information regarding the composition of minerals in the damaged areas. This should provide additional classifications of damage response that could potentially provide additional information on the amount of lung cancer risk and provide guidance on the best methods of treatment. A further refinement of the approach is to measure deviations from age and gender matched control group. This would be necessary if there is a natural increase in density as a result of normal aging.

[0058] Another use of the method is to measure the response of an individual to therapy or chemoprevention. A decrease in CT density at these preferential locations or increase in lung function could signal early response to treatment and potentially predict continued treatment response.

[0059] FIGURES 4A-4H comprise a spreadsheet of individual patient data, their CT measurements, lung function measurements, measurement correction values, and a calculated lung cancer risk index. The data reported here provides evidence that careful measurement of mineral deposits at airway locations combined with a measurement of airway obstruction can provide a metric for determining an individual patient's lung cancer risk status. The spreadsheet of FIGURES 4A-4H shows the pack-years, gender, age, and thickness of subjects that were measured with the lung cancer risk index. This is followed by a individual sample identifier and quantitative measurement data from the main bifurcation location of the lung.

[0060] FIGURES 4A-4H spreadsheet also shows data from the RIGHT bifurcation location, and the LEFT bifurcation location, respectively.

[0061] FIGURES 4A-4H spreadsheet shows the statistical summaries of the findings, and illustrates the connection between high exposure areas (particulate deposition) and lung disease.

[0062] Referring now to the data obtained in FIGURES 4A-4H, the minimal set of steps needed for a preferred embodiment of the invention is:

[0063](1) Obtain a high resolution scan of an airway tree (CT scan is much preferred).

[0064](2) Track the airway tree in the scanned images and identify bifurcation locations in the airway that have the most particulate deposition (high exposure areas).

[0065](3) Take measurements of CT density (expressed in Hounsfield units) at each of the high exposure areas and combine the measurements to form an overall lung cancer risk index.

[0066] In another preferred embodiment, the invention comprises obtaining data. For example, in FIGURES 4A-4H, the spreadsheet data was obtained by specific steps, namely:

[0067](1) Obtain a high resolution 3D CT scan of an airway tree that has the following properties:

[0068](a) No greater than 2mm slice thickness (about .5mm is the best commercially available and is preferred)

[0069](b) Reconstruction kernels should neither perform too much smoothing or sharpening. Bone kernel is preferred for GE scanners.

[0070](c) Pixel spacing in Z should be no greater than slice thickness

[0071](d) Pixel spacing in X and Y should be about .8mm or less – we need the best sampling of the airway tree we can get (and slightly oversampled in the Nyquist sense is preferred).

[0072](e) The tube current of the scanner (expressed as mA) should be set high enough that image noise is kept to a reasonable level. Higher mA is preferred.

[0073](2) Track the airway tree in the scanned images and identify locations in the airway that have the most particulate deposition (high exposure areas).

[0074](a) Inspect and find the bifurcation locations in the airway tree by looking through the stack of CT slices using a medical image viewer that supports orthogonal reformats. The Window/Level image viewing parameters were set to 1500 and -100 respectively.

[0075](b) Geometric modeling methods (e.g. 3D Hessian to identify local shape or skeletonization methods) to automatically track the airway tree and identify the bifurcation locations are contemplated as within the scope of the invention.

[0076](3) Take measurements of CT density (expressed in Hounsfield units) at each of the high exposure areas and combine the measurements to form an overall lung cancer risk index.

[0077](a) Inspect each bifurcation area (which is a wedge-like geometry), including the regions on either side of the wedge and moving up the airway. A 2 voxel region was placed on the location in the bifurcation area that would produce the largest average CT density across both voxels. The connected voxels were required to share a vertex or an edge. A 2 voxel area was chosen so that the measurement would be less susceptible to noise and would obtain a measurement of significant airway damage in a focal area.

[0078](b) Measure the average CT density of cartilage directly above or below the bifurcation (measurement of a cartilage ring spanning $\frac{1}{4}$ of the circumference of the airway is sufficient) and subtract this from the 2 voxel bifurcation value. The log of the resulting value is used to estimate a damage measurement at the bifurcation.

[0079](c) A total of 5 bifurcation measurements were taken per individual including 1 for the main airway bifurcation and 2 for the left airway and 2 for the right airway.

[0080](d) All 5 measurements are averaged to form the average amount of damage sustained by the bifurcations in the lung.

[0081](e) The average of the damage values in the lung are combined with a patients FEV1/FVC ratio to form an overall lung cancer risk index. Higher FEV1/FVC ratios (likely representing higher air velocity and therefore greater focal deposition) require greater amounts of mineralization for the subject to be considered high for lung cancer risk. A simple classifier (e.g. linear or polynomial) is sufficient to assign risk for individuals with FEV1/FVC lung function.

[0082] There is a preferred region to take this measurement which is at the periphery of the bifurcation wedge (but the maximum densities may not be in this region, so only taking the measurements there could be problematic). Think of the wedge as getting wider at each end, similar to a saddle for a horse. Each wider end of the bifurcation is the preferred region to take the measurement. The reason this site is better is that the region receives some of the highest exposures and is thick enough to be able to get a good measurement. Very thin walled structures in the middle of the wedge have their CT densities diminished greatly by partial volume artifact, a well understood problem in scanning systems. Also contemplated as within the scope of the invention is taking into account the partial volume artifact and quantitatively estimating what the CT density had to have been to produce the lower densities we see at the thin bifurcation zones. The contribution of air to the convolution of the scanner PSF and the bifurcation tissue can be estimated and corrected.

[0083] Another preferred embodiment includes performing a flow analysis of the individual's airway tree and either (a) determining the particle deposition load at each of the maximum CT density locations identified above or (b) measuring the density at the places of highest particle load. The particle deposition amount is then used to weight the individual density measurements. Similarly, we know that partial volume artifact reduces CT density measurements, so we weight each measurement based on the size of the airway being measured. Combining both flow analysis and CT scanning physics (i.e. accounting for partial volume artifact, noise, etc) is a good approach for this measurement problem.

[0084] Another preferred embodiment includes analyzing patterns of mineralization to estimate the mass, shape, and charge of the particles that damaged the lung. Higher mass particles will create more focal areas of mineralization at bifurcation locations. For example, asbestos fibers tend to settle in the lower lobes of the lungs due to the influence of gravity.

[0085] Another preferred embodiment includes creating a personalized lung cancer screening protocol based on the key components of the lung cancer risk index.

Measurement of FEV1/FVC can be used for low risk patients to obtain their expected risk trajectory and status over several years and this can be used to reduce the number and coverage of CT scans.

[0086] Another preferred embodiment includes measuring the probability of malignancy of a lung cancer lesion based on a combination of lesion attributes and the lung cancer risk index, including global and local indices.

[0087] Finally, a variant of this method could be applied to other organ systems that operate through the use of flowing liquids, air/gas, or solid/liquid mixtures, such as in the case of the digestive track or the lymphatic system.

[0088] FIGURE 5 is a graph of lung cancer risk index results and shows the damage index plotted against the patient's age. FIGURE 5 shows that a lung cancer risk threshold can be established, from which diagnostic and therapeutic determinations can be made.

[0089] FIGURE 5 shows female cancers against female controls, and male cancers against male controls. FIGURE 5 also shows the risk progression of 15 pack-year to 40 pack-year, to 60 pack-year, to 90 pack-year, to 100 pack-year patients. Within this progression, a lung cancer risk threshold can be determined. Thus, for example, an individual patient's position can be determined on this progression. Thus, a 47-old moving from LCRI of 2.0 to 2.4 over the course of a five year period has a high probability of developing cancer. Given the position and trajectory of an individual, a physician can advise the patient on therapies, detection strategies, and behaviors to reduce their probability of developing cancer, and increase the probability of detecting it at an early stage.

[0090] FIGURE 6 is a histogram of LDI risk distribution. FIGURE 6 shows frequency plotted against the lung damage index (LDI), and shows that the cancer and the normal populations show separation along the index. FIGURE 6 shows the cancer patient LDI distribution is higher than the control PCRI distribution, taking into account that they have matched with control subjects with roughly the same age, gender, and Pack-Year characteristics. This separation takes into account the normal, biomechanical mineralization processes. Drawing a vertical line at 2.6 yields a sensitivity of 69% and specificity of 77%, yielding a valuable diagnostic test.

[0091] Referring now to FIGURE 7, a CT scan of a knee is shown. Using high resolution, the CT will provide both information about mineral density and composition. The results of this analysis, when compared to average, or normal, mineral densities or compositions, provides essential information concerning inflammation and osteoarthritis of the knee, and for other joints of the body as well.

[0092] From the CT scan of a knee and from measuring the average CT density of the cartilage, and hyaline in particular, it provides the ability to measure increased mineral density and mineral composition with high resolution CT, note that osteophytes or bone spurs tend to form in high inflammation areas of the knee: see e.g. http://en.wikipedia.org/wiki/Bone_spur.

[0093] Of course, hyaline cartilage is the most common form of cartilage and changes in its mineral composition and density could serve many purposes including use as an early biomarker of disease and potentially used to measure therapy response.

[0094] Hyaline cartilage and other structures (ligaments and tendons) respond to stress and aging by ossifying (increasing minerals). In most people this is a natural and regular process that also includes reducing water content and other things that could change CT density measurements.

[0095] There are locations throughout our body that give a natural and measurable response to aging. When we stress those areas more, such as particle deposition at bifurcations in the lung and subsequent inflammation, the tissue mineralizes faster. It also likely adds different kinds of minerals depending on the type of damage and stress and the microenvironment.

[0096] It is also considered that carcinogenic or toxic compounds are sequestered within the mineralization of these tissues. This appears to be a highly common mechanism in the body, and our ability to measure it can be used to measure a very wide range of diseases and processes in the body.

[0097] The impact of hazardous substances and irritants on the lung can result in several different types of diseases. This includes multiple forms of Chronic Obstructive Pulmonary Disease (COPD), lung cancer, and cardiac conditions. Tracking the path of an

individual through the various lung risk features we are capable of measuring (image based features and pulmonary function tests) is useful in understanding the type and severity of disease(s) the individual currently has or is likely to attain at a time in the future. For example, an individual that has rapidly increasing mineralization at airway bifurcations but relatively little loss in pulmonary function will more likely be stricken with lung cancer than COPD.

[0098] It is particularly useful to decompose each of the main components of risk, obstruction and deposition/mineralization, into different subtypes. Airway obstruction can be caused by (a) airway wall thickening, (b) emphysema (both of which I can measure in CT), or (c) other factors. Pulmonary function tests consist of many different types and measurements that can further be used to understand the type of obstruction and functional issues occurring in the lung.

[0099] Mineralization measurements can be decomposed into the (a) overall airway mineralization, (b) measurement of the degree of calcification at the bifurcation, or (c) different patterns of calcification throughout the lung. In particular, mineralization patterns around bifurcation and their global distribution can tell us a lot about the carcinogen/irritant and the body's reaction to it. For example, larger asbestos particles will undergo sedimentation and tend to form at the base of the lung due to the effect of gravity. Dual energy CT information will further tell us more about the type of carcinogen/irritant and the individual's reaction to it.

[00100] Mapping the position and trajectory of an individual through each of these measurements over time will give useful information on the types of disease the individual currently has and is likely to face in the future. This would be highly useful in managing and treating patients for lung cancer, COPD, and other respiratory diseases. This information may also be useful (alone or in combination with additional cardiac measurements) in understanding the current status and future status of cardiac diseases and cardiac function.

[00101] Methods are contemplated herein for measurement of aging at several sites across the body using this process. CT is one way to measure it, but biopsies and other

scanning methods could also be used for these diagnostic tests. There appears to be support for measuring many diseases including the following.

[00102] LUNG CANCER:

[00103] Measure the bifurcations and other locations and measure the amount and rate of mineralization. This appears to be correlated with lung cancer.

[00104] OSTEOARTHRITIS:

[00105] Measure small changes in mineral content of the hyaline cartilage at joint and other locations.

[00106] The following article describes the literature that supports an ossifying process in articular/hyaline cartilage. <http://www.peprotech.com/content/focusarticles.htm?id=72>

[00107] And the following article demonstrates that immobilization of a limb (causes stress on cartilage) will cause increased mineralization that can be measured with CT:

[00108] [http://www.scielo.br/scielo.php?](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-879X2004000400006)

[script=sci_arttext&pid=S0100-879X2004000400006](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-879X2004000400006). Another article describes the

ability measure mineralization in micro-CT: [http://www.sciencedirect.com/science?](http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WP3-4CHRY50-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=1c87e9e52f0252b0fcbeb069bb27f0f8)

[_ob=ArticleURL&_udi=B6WP3-4CHRY50-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=1c87e9e52f0252b0fcbeb069bb27f0f8](http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WP3-4CHRY50-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=1c87e9e52f0252b0fcbeb069bb27f0f8) .

[00109] It appears that studying osteoarthritis, and specifically, the subtle mineralization processes occurring in cartilage processes provide for the determination of deviations from normal, and which provides a viable way to measure disease, progression, and therapy response.

[00110] CARDIAC AND VASCULAR DISEASE:

[00111] It is also contemplated to be able to determine the natural mineralization process of vascular and cardiac tissues to measure subtle changes there, especially locations where hyaline cartilage is involved.

[00112] GASTROINTESTINAL TRACT

[00113] It appears that the esophagus/digestive track is also another site we can measure stress through quantification of mineralization. <http://www.springerlink.com/content/>

h071q457134h1311/. This can be observed in a similar manner as that described herein for analyzing CT cases for lung.

[00114] FIGURE 8 shows an image of an example of esophageal calcification. The red contour shows the site of calcification. FIGURE 8 is a CT scan of an esophagus where average CT density of the cartilage is measured. FIGURE 8 shows that mineralization detection can assist in determinations of gastrointestinal conditions, including cancer, GERD, Barrett's, and so forth, where tissue damage has resulted in increased mineralization.

[00115]DIAGNOSTIC SYSTEMS

[00116]In another embodiment, a system is provided which includes a medical imaging device known in the art for generating a plurality of images, specifically a computed tomography (CT) system.

[00117] During a CT imaging session, an individual lies horizontal and is exposed to a plurality of x-rays measured with a series of X-ray detectors. A beam of x-rays passes through a particular thin cross-section or "slice" of the individual. The detectors measure the amount of transmitted radiation. This information is used to compute the x-ray attenuation coefficient for sample points in the body. A gray scale image is then constructed based upon the calculated x-ray attenuation coefficients. The shades of gray in the image contrast the amount of x-ray absorption of every point within the slice. The slices obtained during a CT session can be reconstructed to provide an anatomically correct representation of the area of interest within the body that has been exposed to the x-rays.

[00118] Once initial CT images have been obtained, the images are generally segmented. The segmentation process classifies the pixels or voxels of an image into a certain number of classes that are homogeneous with respect to some characteristic (i.e. intensity, texture, etc.). For example, in a segmented image of the brain, the material of the brain can be categorized into three classes: gray matter, white matter, and cerebrospinal fluid. Individual colors can be used to mark regions of each class after the segmentation has been completed. Once the segmented image is developed, surgeons can use the segmented images to plan surgical techniques.

[00119] Generally, creating a segmented CT image involves several steps. A data set is created by capturing CT slices of data. Through the segmentation process, a gray scale value is then assigned to each point in the data set and different types of tissues will have different gray scale values. Each type of material in the data is assigned a specific value and, therefore, each occurrence of that material has the same gray scale value. For example, all occurrences of bone in a particular image may appear in a particular shade of light gray. This standard of coloring allows the individual viewing the image to easily understand the objects being represented in the images.

[00120] One embodiment of a medical imaging system includes a CT imaging device or scanner, a processor and an interface unit. The CT imaging device generates a plurality of image data sets. In the context of CT, acquisition of image data is generally referred to as "scans". A processor is configured to perform computations in accordance with embodiments of the present invention and is also configured to perform computation and control functions for well-known image processing techniques such as reconstruction, image data memory storage, segmentation and the like. The processor may comprise a central processing unit (CPU) such as a single integrated circuit, such as a microprocessor, or may comprise any suitable number of integrated circuit devices and/or circuit boards working in cooperation to accomplish the functions of a central processing unit. The processor desirably includes memory. Memory within the processor may comprise any type of memory known to those skilled in the art. This includes Dynamic Random Access Memory (DRAM), Static RAM (SRAM), flash memory, cache memory, etc. The memory may be a single type of memory component or may be composed of many different types of memory components. The processor is also capable of executing the programs contained in memory and acting in response to those programs or other activities that may occur in the course of image acquisition and image viewing. As used herein, "adapted to", "configured" and the like refer to mechanical or structural connections between elements to allow the elements to cooperate to provide a described effect; these terms also refer to operation capabilities of electrical elements such as analog or digital computers or application specific devices (such as an application

specific integrated circuit (ASIC)) that are programmed to perform a sequel to provide an output in response to given input signals.

[00121] An interface unit is coupled to the processor and is adapted to allow human users to communicate with system. The processor is further adapted to perform computations that are transmitted to the interface unit in a coherent manner such that a human user is capable of interpreting the transmitted information. Transmitted information may include images in 2D or 3D, color and gray scale images, and text messages regarding diagnosis and detection information. The interface unit may be a personal computer, an image work station, a hand held image display unit or any convention image display platform generally grouped as part of a CT system.

[00122] All data gathered from multiple scans of the individual is to be considered one data set. Each data set can be broken up into smaller units, either pixels or voxels. When the data set is two-dimensional, the image is made up of units called pixels. A pixel is a point in two-dimensional space that can be referenced using two dimensional coordinates, usually x and y. Each pixel in an image is surrounded by eight other pixels, the nine pixels forming a three-by-three square. These eight other pixels, which surround the center pixel, are considered the eight-connected neighbors of the center pixel. When the data set is three-dimensional, the image is displayed in units called voxels. A voxel is a point in three-dimensional space that can be referenced using three-dimensional coordinates, usually x, y and z. Each voxel is surrounded by twenty-six other voxels. These twenty-six voxels can be considered the twenty-six connected neighbors of the original voxel.

[00123] In an embodiment of the present invention, a computer-aided system for use in the diagnosis and detection of disease comprises an image acquisition device for acquiring a plurality of image data sets and a processor adapted to classify selected tissue types within the image data sets based on a hierarchy of signal and anatomical models. The processor is further adapted to differentiate anatomical context of the classified tissue types for use in the diagnosis and detection of a selected disease. The system further comprises an interface unit for presenting the classified tissue types within the image data

sets and anatomical context of the classified tissue types for aiding an interpretation of the processed image data sets. The anatomical models are parametric, mathematical representations of anatomical tissues. The anatomical context comprises at least one of lung nodules indicative of lung cancer, healthy lung tissue, diseased lung tissue indicative of chronic obstructive pulmonary disease (COPD) and other pathological descriptions of tissue that can be characterized by radiologists and further modeled mathematically.

[00124] In an exemplary embodiment, the imaging device is a x-ray CT scanner. A CT system is particularly well adapted to acquire a plurality of images, or alternatively slices, of a region of interest. Also, in this exemplary embodiment, the imaging object is a lung.

[00125]EXAMPLE - A Quantitative Method for Estimating Individual Lung Cancer Risk

[00126]In this example, the performance of a novel method for estimating individual lung cancer risk is evaluated based on the combined measurement of CT calcification density at airway bifurcations and FEV1/FVC.

[00127]Thirteen early lung cancer patients were selected from a CT screening study based on the availability of low dose, whole lung CT data with ≤ 1.25 mm slice thickness and good image quality. 91 cancer-free control subjects were also selected with these criteria plus the requirement that each subject's age was within ± 10 years and pack years was within ± 10 years of a cancer case. 7/13 (54%) cancer positive and 70/91 (77%) cancer negative scans were performed with 1.0mm slice thickness. 2 cancer cases and 14 control cases were female. Siemens scanners and the B60f reconstruction kernel were used, except for 2 control cases that used the B80f kernel. Pulmonary function tests were administered at CT scan time according to ATS spirometry guidelines. A quantitative method was developed to calculate a lung cancer risk index (LCRI) based on airway bifurcation CT density and FEV1/FVC. A single reader manually performed all CT image measurements.

[00128]LCRI measurement of all 104 cases achieved a lung cancer detection sensitivity and specificity of 69% and 79%, respectively. Mean LCRI values for 10-29, 30-49, 50-69, and ≥ 70 pack years controls were 2.34, 2.46, 2.60, and 2.59, respectively. 54/91

(59%) control cases had an LCRI value below the lowest cancer positive LCRI value. This increased to 55/74 (74%) when applied to the subset of cases where FEV1/FVC was above 50% and CT slice thickness was 1.0mm.

[00129]EXAMPLE – BIFURCATION DAMAGE MEASUREMENT METHOD

[00130]Each HRCT scan was measured by Mr. Avila using a medical data review application (VolView 3.0) with standard image review features. To maintain measurement consistency a window/level setting of 1500 and -100 was used to review each dataset.

[00131]The main tracheal bifurcation was measured and a visual search was performed on axial slices for two bifurcations in each lung exhibiting maximal calcification. Thus 5 bifurcations were measured in each patient. The two 26-connected voxels with the greatest CT density either along the carinal ridge or a small downstream region were averaged to form a starting Bifurcation Density (BD). Two voxels were averaged to avoid image noise biases. A search for evidence of cartilage rings just above the bifurcation was performed and the average density of a representative region of cartilage roughly spanning $\frac{1}{4}$ the circumference of the airway was measured. This average density will be referred to as the Comparison Density (CD). Care was taken during the measurement of CD to avoid partial volume artifacts and other factors that influence calcification (e.g. The posterior half of the trachea has a tendency not to calcify). The CD value was subtracted from the BD value in order to remove the influence of factors not related to focal PM deposition. A log function was then applied to the (BD-CD) value in order to reflect the amount of damage the tissue sustained. This was in part driven by the literature on biological calcification, which describes calcification as a crystal growth process that can progress rapidly in response to small changes in the tissue microenvironment. The mean value of all five bifurcations was computed and a final constant scanner Correction Factor (CF) was applied to account for varying scanner types and protocols. This mean value after correction is referred to as the Bifurcation Damage Index (BDI) and was used to estimate the individual's lung cancer risk. The BDI calculation is summarized by the equation in Table 1.

[00132]EXAMPLE – SCANNER CORRECTION FACTORS

[00133]In this example, scanner correction factors were constructed based on an analysis of the mean BDI values for 69 control subjects that were scanned with at least 1.25mm slice thickness. The correction factors in Table 1 are used to account for partial volume artifact on the Siemens scanners used herein

[00134]It is also recognized that more robust forms of scanner calibration may be used, including a method that leverages phantom analysis and accounts for scanner Point Spread Function (PSF) as well as the orientation of the bifurcation with respect to CT slices.

[00135]

$$(1) \text{BDI} = \frac{\text{CF}}{n} \times \sum_{i=1}^n \log(\text{BD}_i - \text{CD}_i)$$

<u>Scanner Model</u>	<u>Slice Thickness</u>	<u>Correction</u>
Definition	1.00 mm	0.9676
Sensation 64	1.00 mm	1.0000
Volume Zoom	1.00 mm	1.0264
Volume Zoom	1.25 mm	1.0703

Table 1: Scanner correction factors.

[00136]

[00137]EXAMPLE - Bronchiole & Alveolar Damage Measurement

[00138]This example discloses a method for estimating lung cancer risk and requires that FEV1 and FVC scores are obtained near the time of the HRCT scan. It is particularly important that these respiratory maneuvers are performed according to ATS guidelines for performing spirometry measurements, including supervision by trained personnel. The ratio of FEV1/FVC, a commonly used metric for assessing respiratory health, was used to estimate lung cancer risk. No corrections were made to the FEV1/FVC values despite the apparent presence of airway wall thickening, scarring, and airway remodeling.

[00139]EXAMPLE – Computing Lung Cancer Risk Index

[00140]In this example, a plot of the BDI and FEV1/FVC values computed for cancer patients in the development dataset, described herein, revealed a near linear trend for the 6/13 patients that were scanned with 1mm slice thickness and had FEV1/FVC values greater than 55%. This plot is shown in FIGURE 9. A linear regression was computed for these cancer data points and distance to this line was used to compute the LCRI. It should be noted that four cancer cases had FEV1/FVC scores greater than 55%, but were scanned at 1.25mm slice thickness. Consistent with the 1mm slice thickness cancer data linear regression, the 1.25mm slice thickness data points had a similar slope but had lower BDI values. This was likely due to an inability of the scanner correction method to fully account for partial volume artifact.

[00141]EXAMPLE - Age and pack year distribution.

[00142]Referring to FIGURE 10, HRCT data and FEV1/FVC data were obtained and the manual measurement technique was applied. Here, the BD and CD measurements were largely obtained in one reading session and without knowledge of the cancer status or FEV1/FVC values of the individual.

[00143] EXAMPLE - BDI and FEV1/FVC values.

[00144] Referring now to FIGURE 11, HRCT scans of early lung cancer cases were reviewed along with four to five age, gender, and pack year matched control cases for each cancer case plus some additional HRCT cases. All subjects were scanned as part of an early lung cancer screening study. Most of the cases were male. Due to a lack of a clear gender distinction in the early results, gender was not used in the LCRI method or the reporting of results. Datasets with a slice thickness greater than 1.25mm or those that contained excessive image noise or motion were not measured. All cases were scanned at low dose on the Siemens scanners shown in Table 1 (except for 1 Somatom Plus4 scan not measured due to poor coverage). A B60f reconstruction kernel was used, except for a few B80f cases. A total of 15 cancer cases and 122 control cases were provided for analysis, but 22 were not analyzed due to insufficient slice thickness or poor image quality. Of these 22, two cancer cases were excluded, one due to a 3mm slice thickness and the other due to limited coverage of the lung. The age and pack years distribution for this data collection is shown in FIGURE 10.

[00145] FIGURE 11 shows a plot of BDI and FEV1/FVC scores for all cancers and controls that were measured. There is a trend in this measurement space that places healthy uninjured lungs in the bottom right corner and highly damaged lungs toward the top left corner.

[00146] EXAMPLE - LCRI versus age.

[00147] Referring now to FIGURES 12 and 13, FIGURE 12 shows the mean LCRI values for subjects with varying pack years. Only cases scanned with 1.0 mm slice thickness were used for this analysis in order to avoid variability associated with partial volume artifact. The control cases appear to show increasing LCRI values. All seven cancer cases had an LCRI value of 2.70 or greater. Finally, a plot of LCRI versus age for all cases is shown in FIGURE 13. Pack year groups are shown in different colors and appear to demonstrate a progression of risk with increasing age and smoking exposure.

[00148]EXAMPLE – An automated method.

[00149]In this example, there is provided an automated method for estimating an individual's risk of developing lung cancer. Using the Lung Cancer Risk Index (LCRI) which consists of a combined measurement of maximal bifurcation calcification in HRCT and a corresponding FEV1/FVC score, we replace the manual method of measuring bifurcation calcification with a more robust and automated solution. This fully automated method allows for much faster experimentation and refinement of the method and also removes the inter- and intra-reader variability of a manual method. An automated method for computing the LCRI involves 4 main steps. First, the full 3D airway tree down to 5 branching levels is fully segmented from the CT scan. Second, the location of each bifurcation and the 3D extent of its carinal ridge is robustly identified. Third, an analysis of the maximal calcification in the vicinity of the carinal ridge as well as an estimate of the average calcification burden around the bifurcation is measured. An estimate of the full distribution of bifurcation calcification burden in the airways is established when all bifurcations have been processed and a Bifurcation Damage Index (BDI) for the patient is then computed. Fourth, the patient's FEV1/FVC score and BDI are combined using a linear classifier to form an overall Lung Cancer Risk Index (LCRI).

[00150] EXAMPLE - Airway Segmentation Software

[00151]In this example, a software module to automatically detect and track the airway tree in low dose HRCT scans is provided. Highly accurate airway segmentation is important since failures in segmentation will degrade the estimation of the distribution of bifurcation calcification. The resulting segmentation is then utilized to identify bifurcations and serve as scaffolding for defining the regions of pixels that are used for estimating the LCRI.

[00152]Airway segmentation is based on the two main characteristics of airways: tubular shape and HU intensity values similar to air. The tubular shape is measured with the method proposed by Sato et al, [1998, Medical Image Analysis 2:143-168] based on the Eigen analysis of the image Hessian matrix computed at multiple scales. The scales which are considered are those in the range of diameters expected for the airways between the first and fifth branching levels. For every pixel this method computes a tubularness value. For every given pixel in the image, the values of HU intensity and tubularness are used as positions in a 2D parametric space. The airways structure are extracted by using a region growing method combining spatial connectivity in the 3D CT scan with a similarity criterion based on proximity in the 2D parametric space of HU intensity and tubularness. The seed points for the region growth are selected automatically based on the large expected radius of the Trachea, which provide a very unique signature in the CT dataset.

[00153]The output of the parametric region growing filter is a binary image, which unfortunately produces staircase effects when iso-surface extraction is performed. These staircases generate artifacts in the subsequence bifurcation analysis and therefore, to prevent them, an Anti-Alias level-set-based filter is added at the end of this pipeline to smooth the image before the final surface extraction. The Anti-Alias filter guarantees that the surface will not be displaced by more than one voxel [29]. FIGURE 14 illustrates the image processing pipeline consisting mostly of filters that are currently available in the ITK toolkit. Segmentation results are shown in FIGURE 15. The top image of Figure 15 shows a CT slice with contours resulting from airways segmentation. The bottom left image of Figure 15 shows a medial airway surface line extracted using the [LA04] method. The bottom right image of Figure 15 shows bifurcations (red) on the medial line are automatically extracted and parent/child relationships are computed. It is contemplated that when dataset anomalies are found, they will be analyzed and algorithm corrections will be developed. Cycles of algorithm evaluation and algorithm correction may then be performed iteratively until all major segmentation issues are resolved.

[00154]EXAMPLE - The pipeline for airway bifurcations and carinal ridge.

[00155]Referring now to FIGURE 16, there is provided a pipeline that is used to identify the airway bifurcations and carinal ridge. A module is then developed that automatically identifies each bifurcating and carinal ridge down to 5 branching levels. Human airways, and particularly those of aging smokers, exhibit a large degree of variation in airway geometry including a very wide range of airway branching angles, changes in airway diameter, curvature along airway segments and at bifurcations, and as many as 4 branches occurring simultaneously. In addition, the presence of ridges, sputum, and locations of partial airway narrowing adds further complexity to this task.

[00156]This method is based on prior work on the analysis of geometry of bifurcating vascular trees [Antiga et al., 2004 IEEE Trans. Medical Imaging 23:704-713]. Here, there is shown a surface enclosing the segmentation of the airway, up to the 5th level. The surface is capped if necessary to ensure that it is closed. The medial line of this surface is extracted as outlined in Antiga et al.. This involves computing the embedded voronoi diagram of the points in the airway surface, from their Delaunay tessellation. The embedded voronoi diagram is the a subset of the voronoi diagram, internal to the object and is obtained by removing from the Delaunay tessellation, the tetrahedra whose circumcenter falls outside the airway surface. The medial line is guaranteed to lie on the boundaries of the voronoi polygons. The next step is to solve the Eikonal equation on this voronoi diagram, with a speed function inversely proportional to the radius of the voronoi spheres using the fast marching method. This method produces an accurate depiction of the medial line, its accuracy determined by the mesh resolution, which is denser than the image resolution. The radius at each point along with the medial line is given by the radius of the voronoi spheres. The topology of the resulting medial-line tree is analyzed to detect splits and the parent, children at each bifurcation. FIGURE 16 illustrates this image processing pipeline. All of these methods are currently available in ITK [www.itk.org], VTK [www.vtk.org] and VMTK [www.vmtk.org], under a BSD license.

[00157]To evaluate the dataset, tree like geometries are constructed analytically, whose carinal ridges can be analytically computed and which use these to validate the carinal ridge extraction algorithm. Evaluation on the development datasets may also be done visually by checking if the medial line is extracted correctly, and that the carinal ridge(s) at each bifurcation are computed.

[00158]EXAMPLE - Bifurcation Calcification Analysis

[00159]As described herein, calculation of the Bifurcation Damage Index (BDI) requires accurate measurement of (i) a Bifurcation Density (BD); (ii) a Comparison Density (CD); and (iii) a scanner Correction Factor (CF). In this example, there is provided an automated method used to calculate the BDI. With a fully automated algorithm, measurement of all upper airway bifurcations in a case is possible and which fit a distribution function to estimate the full distribution of damage. Where this data is represented by a standard statistical distribution, an analysis of the upper tail of this distribution may create a BDI for the entire lung region in the patient. This distribution may be expected to be more resilient to a few outlier bifurcation values.

[00160]EXAMPLE – Comparison Density

[00161]In this example, there is provided another improve of the BDI, namely with the calculation of CD. First, a solution is implemented performs similar operations as the manual measurement. Then, measurements are taken of increasing amounts of cartilage surrounding the bifurcation and spatially interpolating these values to determine the CD value at the location of BD. This prevents a single cartilage ring with unrelated density values from dominating the CD calculation and therefore results in a more robust BDI measurement.

[00162]In practice, CD is obtained since a segmentation of the airway down to the 5th generation as well as the segmentation of the carinal ridge near each bifurcation has already been found. The Insight ToolKit (ITK) [31] has iterators which allow neighborhoods of an image to be walked and manual operations to be applied at each of the voxels within the neighborhood. The carinal ridge segmentation is used as the neighborhood to be walked, and calculated from each voxel of the image in the neighborhood is the maximum 26-connected pair to arrive at the BD value for the bifurcation. To get CD, the airway is walked up a distance c from the bifurcation using a previously calculated center line. A perpendicular plane will be used to cut the image perpendicular to the airway tree at this location and a distance map will be generated that gives the radial distance r from the airway boundary.

[00163]The algorithm may be evaluated in two parts. First, a set of digital phantoms is developed with known BDI and predetermined airway and bifurcation segmentations are used to validate the mathematics of the system. Second, given the development data set and the segmentations of the airway tree and bifurcations from the previous sections, a number of the bifurcation BDI values are hand-calculated and compared to the values computed by the program.

[00164]EXAMPLE - Lung Cancer Risk Estimation

[00165]In this example, there is disclosed a method and system for estimating the overall LCRI by analysis of FEV1/FVC and BDI values for various groups in the development dataset and by establishing the geometry and direction needed to create an increasing risk index. Linear regression strategy is used to determine the direction of increasing lung cancer risk, but more advanced classification methods such as linear discriminant analysis and support vector machine analysis, are also contemplated as within the present inventive subject matter. These methods may include the data collected from the automated algorithm and/or available clinical information such as individual FEV1 and FVC values as well as pulmonary function test prediction percentages and clinical data such as age, pack years, and presence of emphysema.

[00166]EXAMPLE - Evaluating the Automated Lung Cancer Risk Method

[00167]In this example, there is provided a method for evaluating the automated lung cancer risk method. Two metrics may be used to measure the performance of the automated LCRI method versus manual measurement. The first metric is the ability of the method to separate cancer cases from age and pack year matched controls. In addition, a good estimate of risk for developing lung cancer should correlate with increasing tobacco exposure. Thus the second metric is the degree of correlation between the calculated LCRI and self-reported pack years. A receiver operator characteristic (ROC) approach, including the calculation of the area under the curve (AUC) will be employed to fully understand the performance of the automated LCRI method versus the manual measurement method on the development dataset. A leave-one-out cross-validation approach may also be employed to better understand the confidence interval associated with the ROC curves.

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[00170][2] Imre Balásházy, Werner Hofmann and Thomas Heistracher, "Local particle deposition patterns may play a key role in the development of lung cancer," J Appl Physiol 94: 1719-1725, 2003.

[00171][3] Official Statement of the American Thoracic Society, "Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos," Am J Respir Crit Care Med Vol 170. pp 691-715, 2004.

[00172]The references recited herein are incorporated herein in their entirety, particularly as they relate to teaching the level of ordinary skill in this art and for any disclosure necessary for the commoner understanding of the subject matter of the claimed invention. It will be clear to a person of ordinary skill in the art that the above embodiments may be altered or that insubstantial changes may be made without departing from the scope of the

invention. Accordingly, the scope of the invention is determined by the scope of the following claims and their equitable Equivalents.

CLAIMS

I claim:

- [Claim 1] A method of quantitatively measuring mineralization of tissue in an individual comprising: measuring in a CT scan the mineral density deviations and/or mineral composition deviations of said tissue; comparing said deviations against normal or less stressed regions of tissue in the CT scan.
- [Claim 2] The method of claim 1, wherein the mineral density deviations and the mineral composition deviations are associated with hyaline cartilage-associated tissues selected from the group consisting of tissue on the ventral ends of ribs; in the larynx, trachea, and bronchi; and on the articular surface of bones.
- [Claim 3] The method of claim 1, further comprising the step of determining osteoarthritis damage and risk level of osteoarthritis by accounting for and subtracting the mineralization response of non-disease related processes and utilizing a model of mineralization damage response where exponential mineralization in response to damage requires a log function to estimate tissue damage.
- [Claim 4] The method of claim 1, further comprising the step of determining cardiovascular damage and risk level of cardiovascular disease including coronary artery disease by accounting for and subtracting the mineralization response of non-disease related processes and utilizing a model of mineralization damage response where exponential mineralization in response to damage requires a log function to estimate tissue damage
- [Claim 5] The method of claim 4, further comprising wherein the density and composition CT measurements are taken from vascular wall regions and adjacent areas and are used to provide therapeutic and/or clinical information regarding cardiovascular disease of an individual.
- [Claim 6] The method of claim 2, wherein the tissue damage index indicates a disease selected from the group consisting of COPD, esophageal cancer, cardiovascular disease, and osteoarthritis.

- [Claim 7] The method of claim 2, further comprising wherein the density and composition CT measurements are taken from ligaments and tendons in order to assess damage and risk of failure by accounting for and subtracting the mineralization response of non-disease related processes and utilizing a model of mineralization damage response where exponential mineralization in response to damage requires a log function to estimate tissue damage, and therefore revealing the damage and risk level of ligament and tendon tissue failure.
- [Claim 8] The method of claim 8, further comprising wherein the ligament is a knee ligament.
- [Claim 9] A method of quantitatively measuring lung tissue damage, comprising: obtaining a high resolution CT lung scan of an individual; analyzing the CT scan and measuring density deviations of airway tissue locations having the highest particle deposition, wherein the density deviations are obtained using either airway geometry analysis or fluid flow analysis; measuring the subjects degree of airway obstruction using a local lung function measurement and/or a global lung function measurement; and combining any or all of these measurements into a lung disease risk index.
- [Claim 10] The method of claim 9, further comprising wherein the global lung function measurement is FEV1/FVC and wherein the local lung function measurement is selected from CT wall thickness measurement, emphysema measurement, or both.
- [Claim 11] The method of claim 9, further comprising wherein analyzing the CT scan and measuring density deviations further comprises measuring the sum of the logs of maximum HU density deviations from nearby low exposure regions along the airway tree in a CT scan.
- [Claim 12] The method of claim 9, further comprising wherein the location of highest particle deposition comprise one or more bifurcation locations or curved regions, and wherein the step of combining the measurements further comprises

placing a greater influence over the measurement of lung cancer risk from the one or more bifurcation locations or curved regions.

[Claim 13] The method of claim 9, further comprising wherein the CT scan is a multiple energy CT scan and provides features to further distinguish individual response to exposure.

[Claim 14] The method of claim 9, further comprising the step of comparing changes between one or more assessments of lung cancer risk index, and using said comparison to determine a measured response to therapy.

[Claim 15] The method of claim 9, further comprising wherein combining measurements into a lung cancer risk index further comprises adjusting the metric for additional clinical data such as age, gender, smoking history, comorbidity, and family history.

[Claim 16] The method of claim 9, further comprising wherein combining measurements into a lung cancer risk index further comprises adding other CT analysis data to the metric, said CT analysis data comprising COPD wall thickness and emphysema scores.

[Claim 17] The method of claim 9, further comprising the steps of comparing mineral composition of hyaline cartilage tissue, and comparing mineral composition deviation against control values of mineral composition, and identifying areas of hyaline cartilage tissue damage where the mineral composition of the tissue is increased.

[Claim 18] The method according to any of claims 9- 17 , further comprising the step of comparing changes between one or more assessments of lung cancer risk index, and using said comparison to estimate the future lung cancer risk profile for the subject or to determine a measured response to therapy.

[Claim 19] The method of claim 18 , wherein the therapy is lung cancer therapy.

[Claim 20] An imaging system, comprising: a CT scanner; and a computer programmed to: quantitatively measure mineralization of tissue in an individual by measuring in a CT scan the mineral density deviations and/or mineral

composition deviations of said tissue; compare said deviations against normal or less stressed regions of tissue in the CT scan; and determine a tissue damage index.

[Claim 21] The system of claim 20, wherein the mineral density deviations and the mineral composition deviations are associated with hyaline cartilage-associated tissues selected from the group consisting of tissue on the ventral ends of ribs; in the larynx, trachea, and bronchi; and on the articular surface of bones.

[Claim 22] The system of claim 20, further comprising the step of determining osteoarthritis damage and risk level of osteoarthritis by accounting for and subtracting the mineralization response of non-disease related processes and utilizing a model of mineralization damage response where exponential mineralization in response to damage requires a log function to estimate tissue damage.

[Claim 23] The system of claim 20, further comprising the step of determining cardiovascular damage and risk level of cardiovascular disease including coronary artery disease by accounting for and subtracting the mineralization response of non-disease related processes and utilizing a model of mineralization damage response where exponential mineralization in response to damage requires a log function to estimate tissue damage.

[Claim 24] The system of claim 23, further comprising wherein the density and composition CT measurements are taken from vascular wall regions and adjacent areas and are used to provide therapeutic and/or clinical information regarding cardiovascular disease of an individual.

[Claim 25] The system of claim 20, wherein the tissue damage index indicates a disease selected from the group consisting of COPD, esophageal cancer, cardiovascular disease, and osteoarthritis.

[Claim 26] The system of claim 20, further comprising wherein the density and composition CT measurements are taken from ligaments and tendons in order to assess damage and risk of failure by accounting for and subtracting the

mineralization response of non-disease related processes and utilizing a model of mineralization damage response where exponential mineralization in response to damage requires a log function to estimate tissue damage, and therefore revealing the damage and risk level of ligament and tendon tissue failure.

[Claim 27] The system of claim 26, further comprising wherein the ligament is a knee ligament.

[Claim 28] An imaging system, comprising: a CT scanner; and a computer programmed to: quantitatively measure lung tissue damage by obtaining a high resolution CT lung scan of an individual; analyze the CT scan and measuring density deviations of airway tissue locations having the highest particle deposition, wherein the density deviations are obtained using either airway geometry analysis or fluid flow analysis; measure the subjects degree of airway obstruction using a local lung function measurement and/or a global lung function measurement; and combine any or all of these measurements into a lung disease risk index.

[Claim 29] The system of claim 28, further comprising wherein the global lung function measurement is FEV1/FVC and wherein the local lung function measurement is selected from CT wall thickness measurement, emphysema measurement, or both.

[Claim 30] The system of claim 28, further comprising wherein analyzing the CT scan and measuring density deviations further comprises measuring the sum of the logs of maximum HU density deviations from nearby low exposure regions along the airway tree in a CT scan.

[Claim 31] The system of claim 28, further comprising wherein the location of highest particle deposition comprise one or more bifurcation locations or curved regions, and wherein the step of combining the measurements further comprises placing a greater influence over the measurement of lung cancer risk from the one or more bifurcation locations or curved regions.

- [Claim 32] The system of claim 28, further comprising wherein the CT scan is a multiple energy CT scan and provides features to further distinguish individual response to exposure.
- [Claim 33] The system of claim 28, further comprising the step of comparing changes between one or more assessments of lung cancer risk index, and using said comparison to determine a measured response to therapy.
- [Claim 34] The system of claim 28, further comprising wherein combining measurements into a lung cancer risk index further comprises adjusting the metric for additional clinical data such as age, gender, smoking history, comorbidity, and family history.
- [Claim 35] The system of claim 28, further comprising wherein combining measurements into a lung cancer risk index further comprises adding other CT analysis data to the metric, said CT analysis data comprising COPD wall thickness and emphysema scores.
- [Claim 36] The system of claim 28, further comprising the steps of comparing mineral composition of hyaline cartilage tissue, and comparing mineral composition deviation against control values of mineral composition, and identifying areas of hyaline cartilage tissue damage where the mineral composition of the tissue is increased.
- [Claim 37] The system according to any of claims 28-36 , further comprising wherein the computer is programmed to perform the step of comparing changes between one or more assessments of lung cancer risk index, and using said comparison to estimate the future lung cancer risk profile for the subject or to determine a measured response to therapy.
- [Claim 38] The system of claim 37, wherein the therapy is lung cancer therapy.
- [Claim 39] A computer program product, directly loadable into the RAM of a digital computer, comprising software code portions for implementing the steps of the method as set forth in any of claims 1-28, when said product is run on said digital computer.

- [Claim 40] The computer program product of claim 39, wherein the software code portions are downloadable from a network.
- [Claim 41] A computer-readable medium encoded with a data structure for implementing the steps of the method as set forth in any of claims 1-28.
- [Claim 42] A system for the computer aided detection of locations that represent high lung cancer risk, comprising: a CT scanner; and a computer programmed to perform the method of any of claims 9-19.
- [Claim 43] A computerized system for therapy planning analysis, comprising: a computer programmed to: determine a lung disease risk index from analysis of CT scan measurements; and suggest the form of therapy that will yield the lowest potential lung cancer and COPD risk.
- [Claim 44] A method for minimizing the number of scans needed to detect early lung cancer, comprising: measuring the change in LCRI over time; and creating a lung cancer risk monitoring protocol, whereby the number of scans needed to detect early lung cancer is minimized compared to a method which does not measure the change in LCRI over time.
- [Claim 45] The method of claim 44, further comprising wherein the lung cancer risk index is used to create a personalized lung cancer screening protocol that optimizes the number of visits, the radiation dose, screening cost, and cancer detection rate, wherein a baseline CT scan combined with FEV1/FVC data is combined to form the LCRI and follow-up screening plans are then calculated to verify the projected risk of the patient over time, and wherein since obstruction and mineralization change slowly, the frequency and duration of screening is optimized to the individual.
- [Claim 46] The method of claim 45, further comprising wherein personalized lung cancer screening protocol comprises follow-up screening visits for low baseline risk patients by measuring lung function (FEV1/FVC) more often than a full high resolution CT scan, thereby reducing the cost and dose required for lung cancer screening.

- [Claim 47] The method of claim 9, further comprising wherein the LCRI is combined with measurements and attributes of a suspected lung cancer lesion to determine the probability of malignancy of the lesion.
- [Claim 48] A lung cancer therapy device, comprising: a unit that vibrates/palpates the lung of a patient in need thereof, wherein the vibration/palpation is sufficient to accelerate the removal of mineralization from the lung, and wherein the unit actuates the vibration/palpation using a mechanism which employs sound or mechanical stimulus.
- [Claim 49] A method of analyzing lung cancer risk, comprising: obtaining a high resolution CT lung scan of an individual; analyzing the CT scan and measuring density deviations of airway tissue at bifurcation locations; comparing these measurements to measurements from a lung disease risk index database; and determining information on the type and extent of particulate exposure including the mass, shape, and charge of the particle that caused the damage to the lung.
- [Claim 50] A method of providing risk assessment information to a patient, comprising: (i) tracking the path of an individual's medical condition through a plurality of measurable risk features, and (ii) determining the type and severity of disease(s) the individual currently has or is likely to attain at a time in the future, wherein the medical condition involves pulmonary, cardiac, and/or gastrointestinal tissues or organs, wherein the measurable risk features are obtained from (a) image based mineralization features and (b) from organ function tests, and wherein the risk features being measured comprise the degree of obstruction within the tissues or organ, and the deposition / mineralization of the tissues or organ as seen from a CT scan.
- [Claim 51] The method of claim 50, further comprising wherein the condition is pulmonary, and the organ function test is a pulmonary function test, and wherein a risk feature indicating an individual that has rapidly increasing mineralization at airway bifurcations but relatively little loss in pulmonary function will provide an

assessment that an individual is more likely be stricken with lung cancer than COPD.

[Claim 52] The method of claim 51, wherein the image-based mineralization features include (a) airway wall thickening, (b) emphysema, or (c) both.

[Claim 53] The method of claim 51, wherein the image-based mineralization features comprise (a)(1) overall airway mineralization, (a)(2) measurement of the degree of calcification at the bifurcation, or (a)(3) different patterns of calcification throughout the lung.

[Claim 54] The method of claim 53, further comprising wherein mineralization patterns around bifurcation and their global distribution provides information about a specific carcinogen/irritant and the body's reaction to it.

[Claim 55] The method of claim 54, wherein the carcinogen / irritant is asbestos.

Application number / numéro de demande: 2711986

Figures: 2-3-7-8-15-16-17

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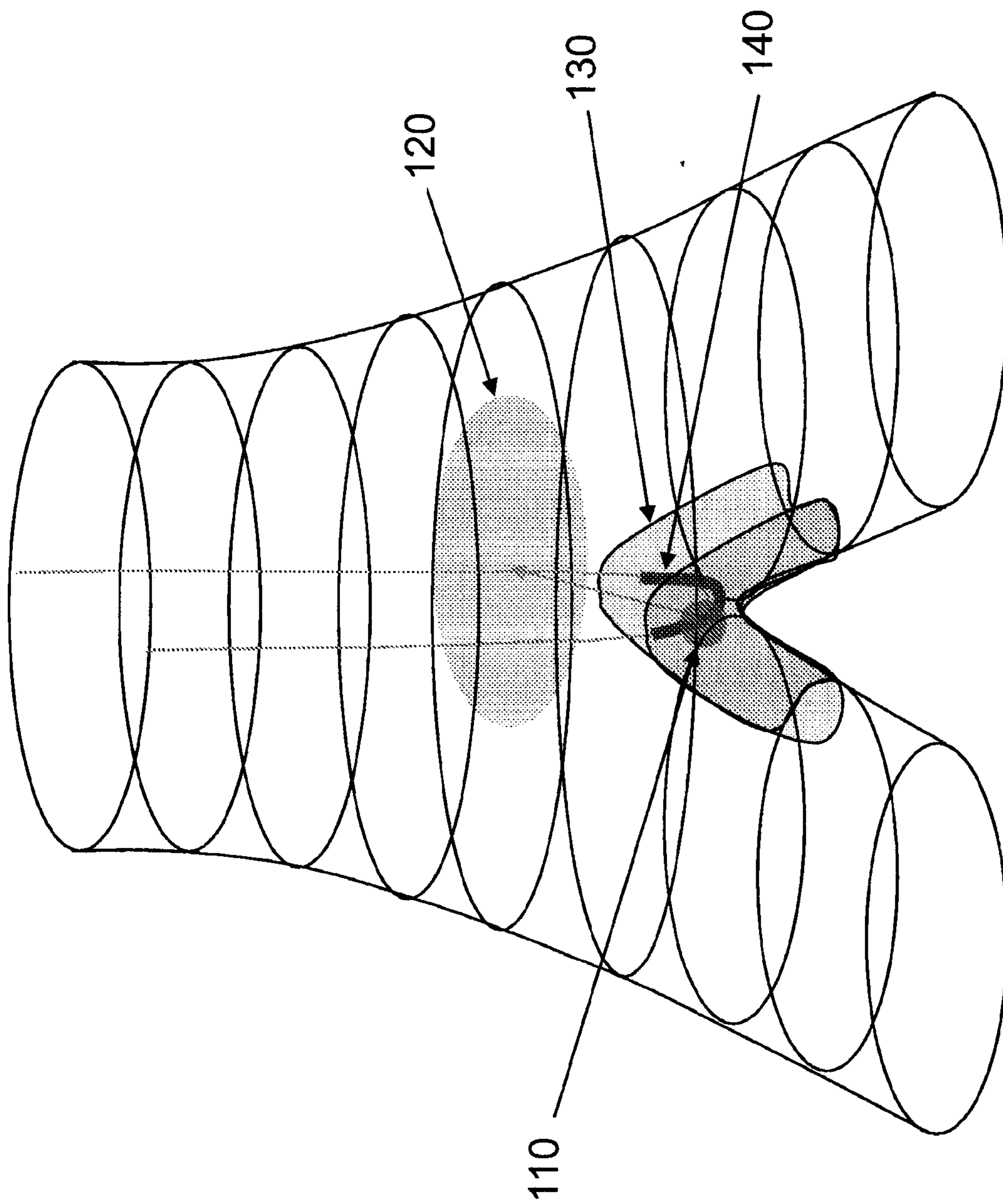


Fig. 1

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#	Age	Gen	PY	Patient Code	Number	Scanner Correction	Main		R1		R2	
							Err	Comp Damage	Err	Comp Damage	Err	Comp Damage
1	49	F	26.35	876	1	1.07	452	2.48	494	105	319	123
	51	F	28	210		1.03	484	2.51	1275	89	1265	135
	51	F	28	862	3	0.97	710	2.66	586	228	1638	124
	55	F	26	141	4	1.00	383	2.32	460	190	471	274
	52	F	2.5	1124		1.07						2.29
2	53	F	72	554	5	1.03	1631	3.09	1206	386	1157	496
	54	F	75	1403	6	1.00	435	2.38	623	181	494	234
	59	F	20	581		1.00	576	2.57	472	212	469	200
	60	F	19.5	1082	8	1.00	486	2.47	367	149	561	145
	62	F	80	530	9	1.00	292	0.00	706	67	1204	134
	62	F	80	632								3.03
	64	F	67.5	1406	10	1.00	499	2.39	542	224	1394	156
	66	F	100	1680								3.09
	76	F	60	548	11	1.03	1082	2.76	750	439	1164	411
	76	F	20	812	12	1.03	382	2.44	419	82	678	150
3	76	F	30	1431	13	1.00	1224	1.31	1903	704	2075	251
	88	F	142	159		1.07			1198	416		2.89
												2.88

Fig. 4A

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L1		Comp Damage		FEV1/ FVC		Lung Fun Correction		All PY		Lung Cancer Risk Index		Scanner Adj LDI Non Cancers		LDI Average		STDV		Airway	
				73		0.16 65													
363	110	2.40	316	153	2.21	78	0.90			2.30		2.56	2.39	0.15	128				
1016	226	2.90	1183	202	2.99	74	0.93	2.77		2.77		2.98	2.91	0.23	162				
684	207	2.68	587	134	2.66	71	0.95			2.53		2.66	2.75	0.25	188				
590	122	2.67	557	156	2.60	80	0.88			2.17		2.46	2.46	0.17	183				
1047	371	2.83	1110	526	2.77	84	0.85			2.70		2.96	2.88	0.13	435				
629	129	2.70	620	186	2.64	68	0.98			2.49		2.56	2.56	0.15	185				
652	192	2.66	519	158	2.56	59	1.05	2.65		2.65		2.53	2.53	0.10	193				
560	211	2.54	548	181	2.56	81	0.87			2.19		2.51	2.51	0.11	175				
551	193	2.55	552	168	2.58	74	0.93			2.04		2.19	2.19	1.24	171				
1557	299	3.10	675	140	2.73	74	0.93								215				
						75	0.92			2.54		2.76	2.76	0.33					
							1.52												
1172	464	2.85	733	326	2.61	57	1.06			2.97		2.79	2.72	0.16	428				
722	251	2.67	1039	162	2.94	89	0.81			2.21		2.73	2.66	0.19	150				
1741	456	3.11	1139	614	2.72	81	0.87			2.35		2.70	2.70	0.80	646				
1445	411	3.01				47	1.14	3.62		3.62		3.16	2.95	0.09	414				
						0.16 60.00													

Fig. 4B

47	M	42	1118	1	1.00	810	224	2.77	695.5	203	2.69	772.5	99	2.83
48	M	40	1172a	2	1.07	437.5	101	2.53	362	121	2.38	440.5	142	2.47
48	M	40	1172b	3	1.00	573	181	2.59	614.5	172	2.65	841	238	2.78
48	M	39	1369	4	1.07	813	279	2.73	480.5	156	2.51	415.5	36	2.58
49	M	40	1078	5	0.97	850.5	135	2.85	1061.5	182	2.94	794.5	68	2.86
51	M	37.5	787	6	1.07	444	158	2.46	659	88	2.76	406	68	2.53
46	M	12.5	892	7	1.07	306.5	123	2.26	499.5	163	2.53	445	22	2.63
46	M	16	949	8	1.07	489	203	2.46	360	115	2.39	354.5	64	2.46
48	M	17	1148	9	1.07	1060	156	2.96	494.5	169	2.51	460	108	2.55
51	M	15	289	10	0.97	976	239	2.87	674	168	2.70	561	171	2.59
54	M	17.5	893											
49	M	20	393a											
49	M	20	393b											
53	M	60	1433	12	1.00	1162	201	2.98	580	148	2.64	570	158	2.61
61	M	60	77	13	1.00	531.5	155	2.58	455	196	2.41	594	242	2.55
54	M	62.5	694	14	1.03	520.5	149	2.57	592	150	2.65	418	121	2.47
57	M	63	1001	15	1.07	800	86	2.85	400.5	149	2.40	433.5	112	2.51
54	M	66	540	11	1.07	360.5	129	2.36	370.5	120	2.40	356	127	2.36
57	M	60	1607											
54	M	32	1191	16	1.00	558.5	170	2.59	710.5	88	2.79	557	93	2.67
56	M	30	1530	17	1.00	956.5	172	2.89	667.5	190	2.68	676	88	2.77
57	M	30	663	18	1.03	675	285	2.59	867.5	180	2.84	572.5	202	2.57
57	M	30	1361	19	1.00	1316	548	2.89	703.5	180	2.72	633.5	87	2.74
53	M	90	1322	20	1.00	811	251	2.75	790	114	2.83	734	60	2.83
59	M	90	762	21	1.00	603	333	2.43	549	185	2.56	469.5	130	2.53
60	M	92	652	22	1.07	620.5	208	2.62	895	139	2.88	510.5	83	2.63
62	M	92	527	23	1.03	1136	204	2.97	1102	195	2.96	615	65	2.74
64	M	87.5	1270	24	0.97	1230	109	3.05	1052	193	2.93	684.5	153	2.73
57	M	67.5	621	25	1.03	380.5	112	2.43	562.5	75	2.69	452.5	127	2.51
57	M	70	692	26	1.03	452	160	2.47	523	124	2.60	579	113	2.67
57	M	70	1644	27	1.00	987	303	2.84	538.5	172	2.56	499	206	2.47

Fig. 4C

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743.5	119	2.80	530	81	2.65	79	0.85	2.33	2.75	2.75	0.07	145
						74	0.89					
614	133	2.68	406.5	128	2.44	74	0.89	2.38	2.68	2.50	0.11	125
767	73	2.84	522	212	2.49	84	0.81	2.16	2.67	2.67	0.14	175
474.5	124	2.54	446.5	76	2.57	74	0.89	2.46	2.77	2.59	0.08	134
753	248	2.70	926.5	147	2.89	81	0.83	2.30	2.76	2.85	0.09	156
461	127	2.52	363.5	105	2.41	76	0.87	2.37	2.71	2.54	0.13	109
299.5	251	1.69	444	72	2.57	85	0.80	2.00	2.50	2.33	0.39	126
384.5	83	2.48	502	49	2.66	76	0.87	2.32	2.66	2.49	0.10	103
405.5	180	2.35	411	114	2.47	71	0.91	2.51	2.75	2.57	0.23	145
704.5	47	2.82	729	89	2.81	78	0.86	2.28	2.67	2.76	0.11	143
						69	0.93					
						69	0.93					
577.5	135	2.65	712.5	58	2.82	71	0.91	2.50	2.74	2.74	0.16	140
592	286	2.49	526.5	187	2.53	73	0.90	2.25	2.51	2.51	0.06	213
609	94	2.71	495	76	2.62	62	0.98	2.63	2.67	2.60	0.09	118
453	73	2.58	391.5	98	2.47	78	0.86	2.35	2.74	2.56	0.18	103.6
418.5	78	2.53	455	111	2.54	72	0.90	2.36	2.61	2.44	0.09	113
						44	1.13					
532.5	69	2.67	658.5	79	2.76	86	0.79	2.14	2.70	2.70	0.08	100
979	100	2.94	724	70	2.82	68	0.94	2.64	2.82	2.82	0.10	124
918.5	86	2.92	622.5	95	2.72	67	0.94	2.64	2.80	2.73	0.15	170
541.5	262	2.45	693	160	2.73	58	1.02	2.75	2.70	2.70	0.16	247
726.5	134	2.77	739	112	2.80	71	0.91	2.55	2.80	2.80	0.04	134
665	156	2.71	543	170	2.57	61	0.99	2.54	2.56	2.56	0.10	195
469.5	202	2.43	386	149	2.37	68	0.94	2.59	2.77	2.59	0.20	156
500.5	97	2.61	501	133	2.57	67	0.94	2.68	2.84	2.77	0.19	139
1001.5	149	2.93	780.5	201	2.76	72	0.90	2.52	2.79	2.88	0.13	161
548	65	2.68	468	58	2.61	54	1.05	2.78	2.65	2.59	0.11	87
545	112	2.64	470	110	2.56	76	0.87	2.31	2.65	2.59	0.08	124
630	117	2.71	660	72	2.77	66	0.95	2.54	2.67	2.67	0.15	174

Fig. 4D

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57	M	105	1318	28	1.00	1329	479	2.93	886.5	225	2.82	1541.5	133	3.15
56	M	84	1591	29	0.97	437.5	156	2.45	760.5	185	2.76	656	139	2.71
57	M	82	1679	30	1.07	584	122	2.66	464.5	171	2.47	438.5	112	2.51
65	M	100	1134	31	1.00	743.5	166	2.76	1139.5	100	3.02	868	165	2.85
57	M	45	1639	32	1.00	805	174	2.80	1632.5	165	3.17	1969.5	272	3.23
60	M	45	1010	33	1.00	694.5	155	2.73	630.5	153	2.68	603	145	2.66
58	M	75	867	34	1.00	401	137	2.42	561	185	2.57	344.5	156	2.28
58	M	76	1109	35	1.00	1051.5	244	2.91	1156.5	88	3.03	576	210	2.56
61	M	75	960		1.07									
61	M	74	1154											
59	M	64.5	1073											
61	M	55	1716b	36	0.97	514.5	150	2.56	518.5	195	2.51	616.5	187	2.63
60	M	58.5	248		1.07	380	127	2.40	582	197	2.59	531	136	2.60
62	M	66	358	38	1.07	1144.5	196	2.98	806.5	153	2.82	436.5	175	2.42
58	M	64.5	1345	39	0.97	1164	791	2.57	1397	232	3.07	1102	92	3.00
64	M	66	171		1.07	388	77	2.49	481.5	94	2.59	487	213	2.44
60	M	21	1199											
60	M	20	1364		1.00									
61	M	20	1105	41	1.03	470.5	147	2.51	436.5	81	2.55	433	198	2.37
61	M	21	1331	42	1.00	574	191	2.58	660.5	122	2.73	653	182	2.67
62	M	21	1416	43	1.00	855	226	2.80	582	245	2.53	498	147	2.55
60	M	60	1206	44	1.07	538	102	2.64	520.5	181	2.53	456	102	2.55
61	M	65	1716a											

Fig. 4E

1280	190	3.04	732	240	2.69	77	0.86	2.53	2.93	2.93	253
632	118	2.711	507	127	2.58	68	0.94	2.39	2.56	2.64	145
						63	0.98				
396	101	2.47	352	91	2.42	60	1.00	2.68	2.68	2.51	119
646.5	95	2.74	700	204	2.70	67	0.94	2.65	2.81	2.81	146
1105.5	333	2.89	1181.5	446	2.87	81	0.83	2.49	2.99	2.99	278
721.5	123	2.78	770.5	105	2.82	55	1.04	2.84	2.73	2.73	136
540	63	2.68	525	101	2.63	82	0.82	2.07	2.52	2.52	128
662	120	2.73	740.5	61	2.83	68	0.94	2.63	2.81	2.81	145
						70	0.92				
						72	0.90				
589	80	2.71	589	160	2.63	72	0.90	2.28	2.52	2.61	154
633.5	139	2.69	641	118	2.72	72	0.90	2.52	2.78	2.60	143
699	148	2.74	456	100	2.55	71	0.91	2.64	2.89	2.70	154
993.5	137	2.93	776	160	2.79	68	0.94	2.60	2.78	2.87	282
358	80	2.44	417	102	2.50	53	1.06	2.82	2.67	2.49	113
						77	0.86				
						85	0.80				
545	93	2.66	355.5	155	2.30	69	0.93	2.36	2.54	2.48	135
974.5	110	2.94	716.5	165	2.74	81	0.83	2.27	2.73	2.73	154
548	160	2.59	507	152	2.55	39	1.17	3.04	2.60	2.60	186
490	81	2.61	462.5	53	2.61	77	0.86	2.39	2.77	2.59	104
						72	0.90				
							1.48				

Fig. 4F

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62	M	60	858	45	1.07	687	107	2.76	371	139	2.37	375	120	2.41
62	M	31.25	1365											
64	M	33	910	46	1.00	692.5	132	2.75	813	65	2.87	781.5	157	2.80
66	M	35	759	47	1.03	390.5	154	2.37	494	146	2.54	510	67	2.65
67	M	37	1682	48	0.97	1333	265	3.03	1303.5	291	3.01	814.5	101	2.85
64	M	3	830	49	1.03	403.5	120	2.45	543	112	2.63	399.5	169	2.36
64	M	2	1115	50	1.07	434.5	122	2.49	461	145	2.50	389	97	2.47
64	M	5	979	51	1.07	574	225	2.54	555	142	2.62	512	91	2.62
64	M	75	926	52	1.07	764	165	2.78	701.5	129	2.76	454	117	2.53
66	M	75	1254	53	1.00	497	187	2.49	644.5	218	2.63	578.5	153	2.63
68	M	72	235		1.07	509	130	2.58	563	70	2.69	527	207	2.51
65	M	60	1310	55	1.00	708.5	165	2.74	535	186	2.54	530.5	228	2.48
67	M	60	780	56	1.00	706	246	2.66	2127.5	391	3.24	701	276	2.63
69	M	60	161		1.07	421.5	140	2.45	475.5	108	2.57	412.5	78	2.52
61	M	61.5	1531	58	1.00	540.5	120	2.62	690.5	164	2.72	619.5	182	2.64
74	M	60	1259	59	1.00	829.5	146	2.83	685	199	2.69	577.5	147	2.63
76	M	60	795	60	1.03	1019	161	2.93	537	150	2.59	630.5	131	2.70
66	M	82	102	61	1.00	1716	387	3.12	776.5	288	2.69	611	51	2.75
70	M	76.5	1385											
72	M	75	1084	62	1.00	958.5	154	2.91	630.5	150	2.68	666.5	200	2.67
74	M	75	532		1.07	397.5	135	2.42	467.5	35	2.64	427	125	2.48
79	M	65	1572	64	1.00	671.5	182	2.69	594	110	2.68	858.5	95	2.88
80	M	68.75	984a											
80	M	50	1076	65	1.07	279	180	2.00	393	113	2.45	354	126	2.36
82	M	68.75	984b											
60.3544		53.33		79		317	2.5011							

Cornell Partsolids

45	F	SM0070	1	1.06	440	101	2.53	573	32	2.73	518.5	73	2.65
		SM0055	2										
45	F	SL0074	3	1.06	1043	198	2.93	891	82	2.91	394	77	2.50

GiveAScan

62	F	0	P0006	1	1.20	174.5	42	2.12	981.5	22	2.98	747	4.8	2.87
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Fig. 4G

410.5	117	2.47	423.5	147	2.44	75	0.88	2.34	2.66	2.49	0.16	126
682.5	176	2.70	521.5	145	2.58	71	0.91					135
463.5	143	2.51	463	204	2.41	67	0.94	2.59	2.74	2.74	0.11	143
951.5	271	2.83	682.5	186	2.70	69	0.93	2.38	2.56	2.50	0.11	223
449.5	139	2.49	348	162	2.27	48	0.93	2.59	2.79	2.88	0.14	140
422	67	2.55	362.5	155	2.32	55	1.10	2.75	2.51	2.44	0.14	117
465.5	99	2.56	353.5	97	2.41	64	1.04	2.74	2.64	2.47	0.09	131
554	138	2.62	497	94	2.61	75	0.97	2.64	2.73	2.55	0.09	129
583	198	2.59	477	97	2.58	73	0.88	2.50	2.84	2.66	0.11	171
642.5	103	2.73	531.5	80	2.65	75	0.90	2.31	2.58	2.58	0.06	118
685	73	2.79	769	144	2.80	78	0.88	2.48	2.82	2.63	0.09	159
676.5	200	2.68	1495.5	152	3.13	48	0.86	2.28	2.67	2.67	0.15	253
568.5	113	2.66	587	148	2.64	45	1.10	3.14	2.87	2.87	0.29	117
824.5	159	2.82	740	142	2.78	76	1.12	3.08	2.75	2.57	0.09	153
675	99	2.76	758.5	138	2.79	79	0.87	2.37	2.72	2.72	0.09	146
621.5	170	2.65	548.5	111	2.64	36	0.85	2.32	2.74	2.74	0.08	145
911.5	131	2.89	567	185	2.58	76	1.19	3.31	2.77	2.70	0.13	208
						52	0.87	2.45	2.81	2.81	0.21	
							1.06					
663.5	142	2.72	637.5	108	2.72	74	0.89	2.43	2.74	2.74	0.10	151
478	45	2.64	461.5	112	2.54	71	0.91	2.48	2.72	2.54	0.10	90
637.5	204	2.64	515	112	2.61	66	0.95	2.57	2.70	2.70	0.11	141
378	117	2.42	388	73	2.50	56	1.03					122
						44	1.13	2.83	2.51	2.34	0.20	
						56	1.03					
						68	0.94					
465	99	2.56	599	99	2.70			H	2.79	2.63	0.09	81
655	76	2.76	515	89	2.63			H	2.91	2.75	0.18	104
862.5	61	2.90	667	117	2.74	81	0.87	2.85	3.27	2.72	0.35	49

Fig. 4H

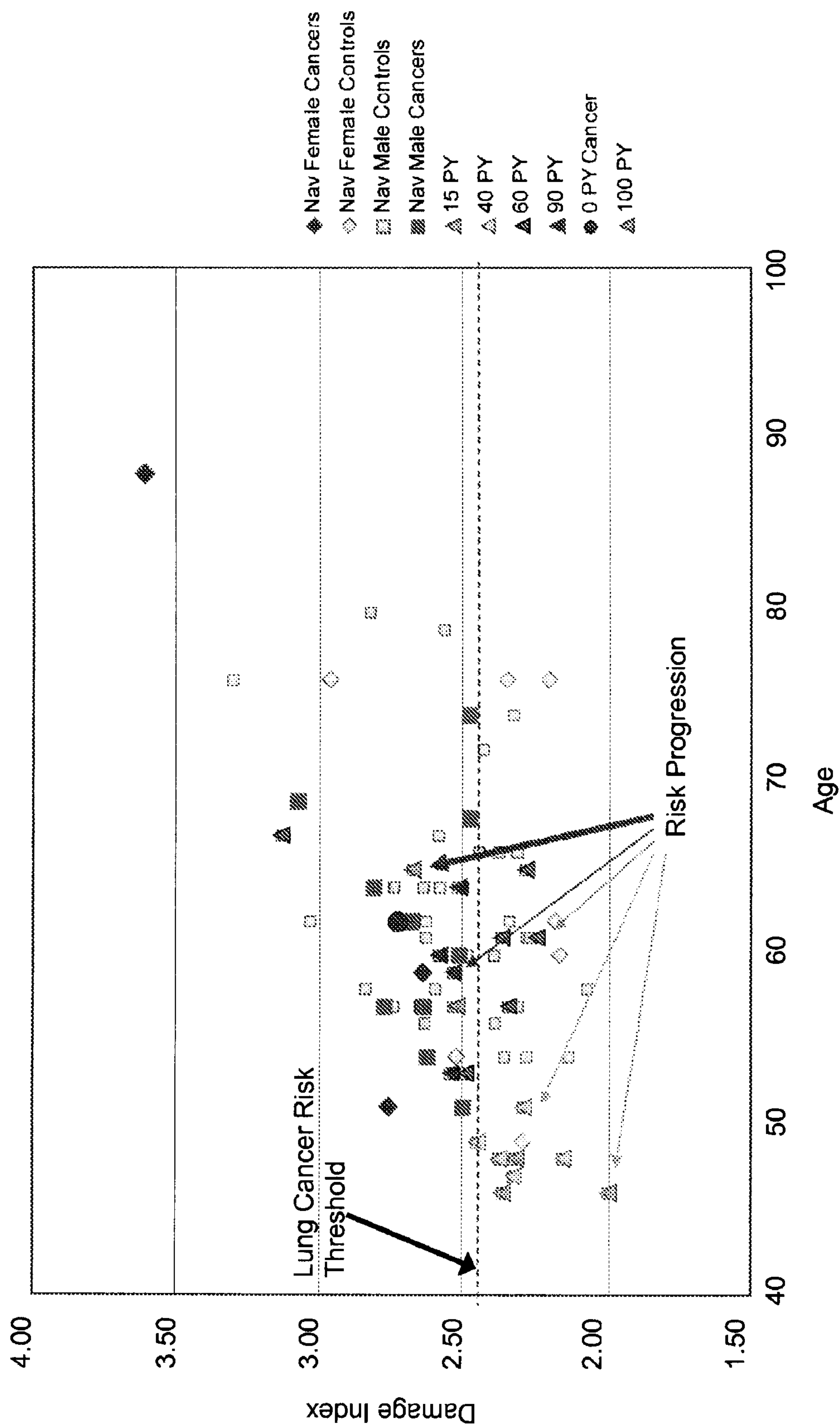


Fig. 5

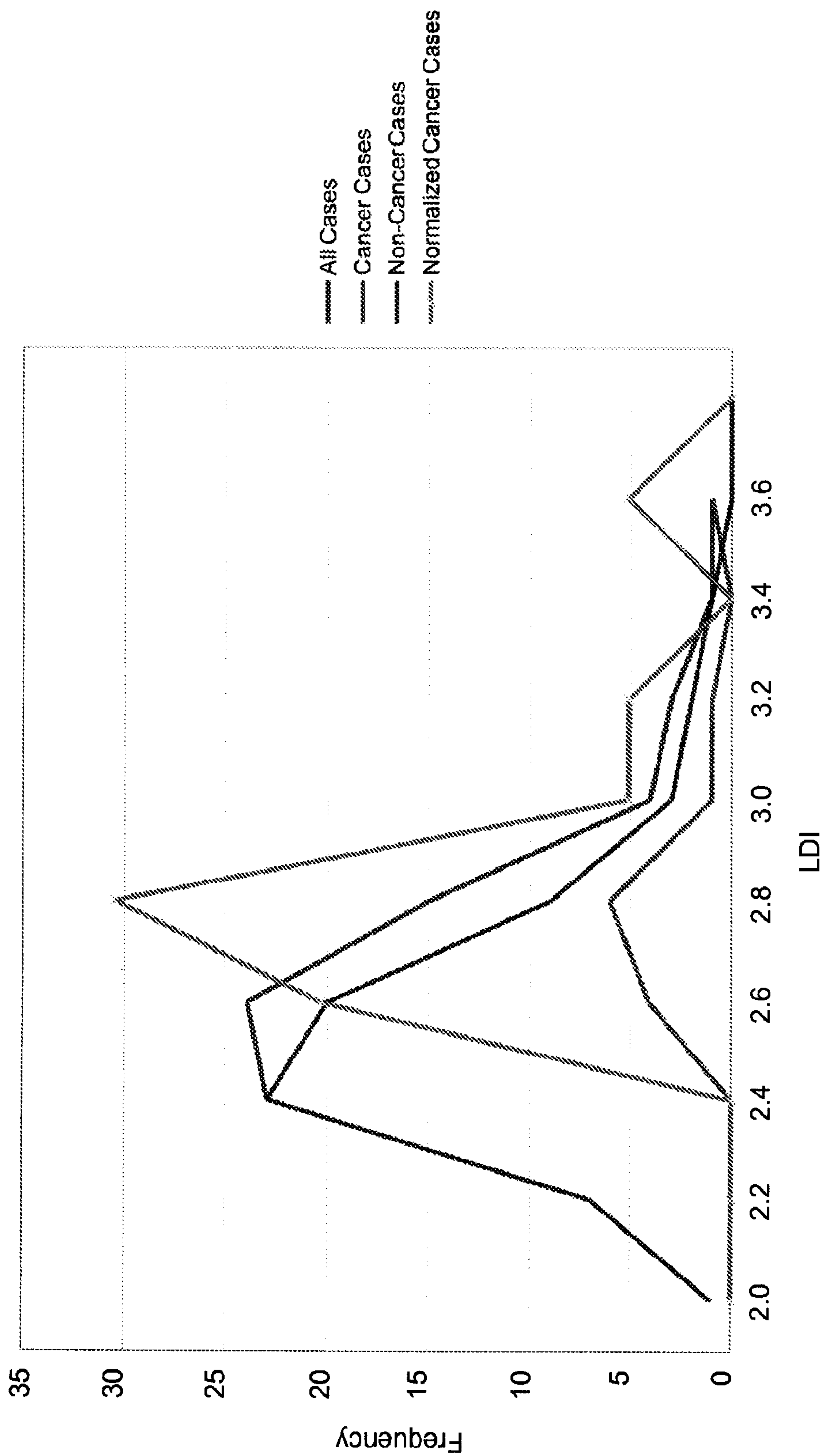


Fig. 6

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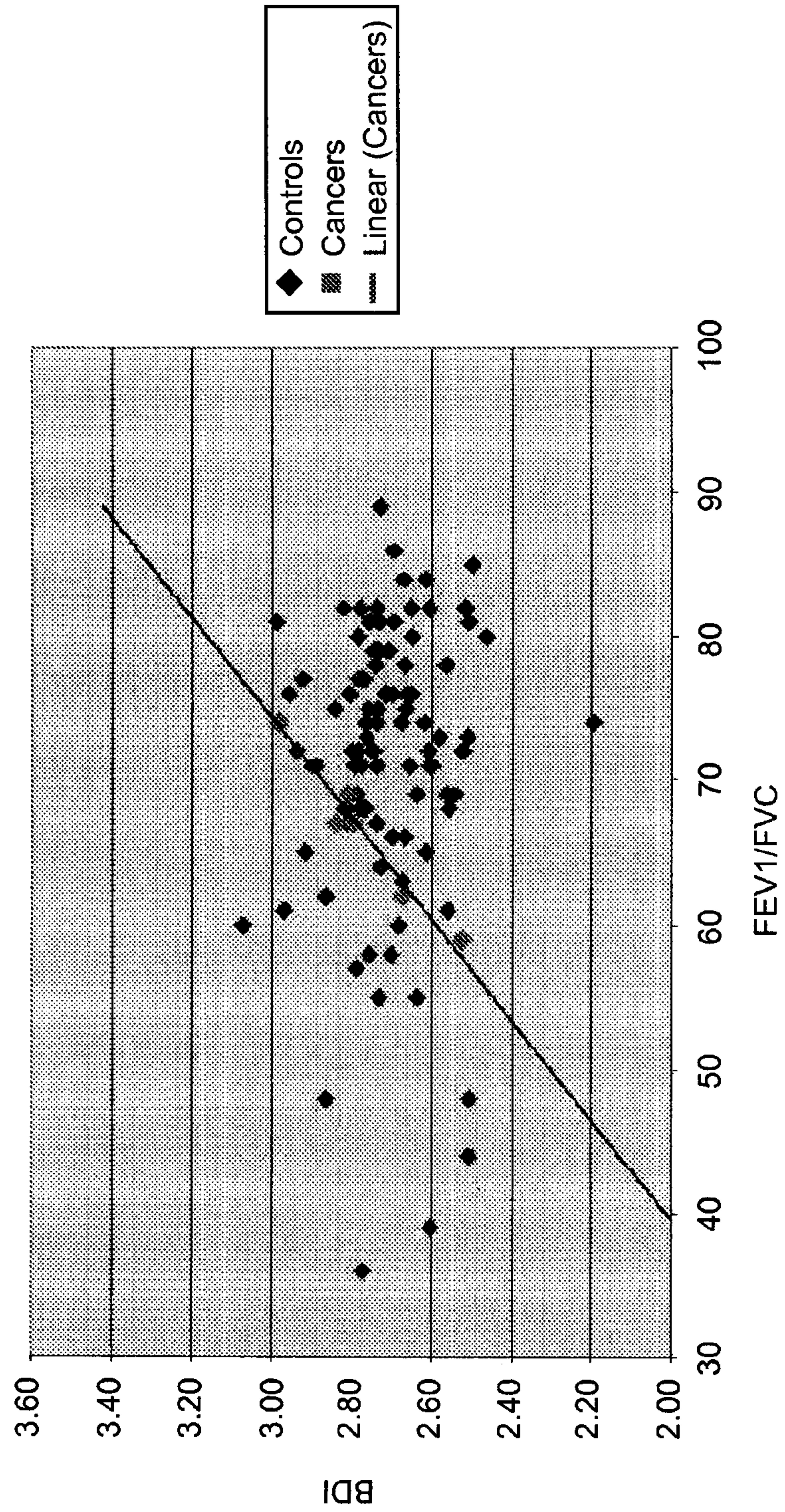


Fig. 9

PCT/US09/34021 02-10-2009

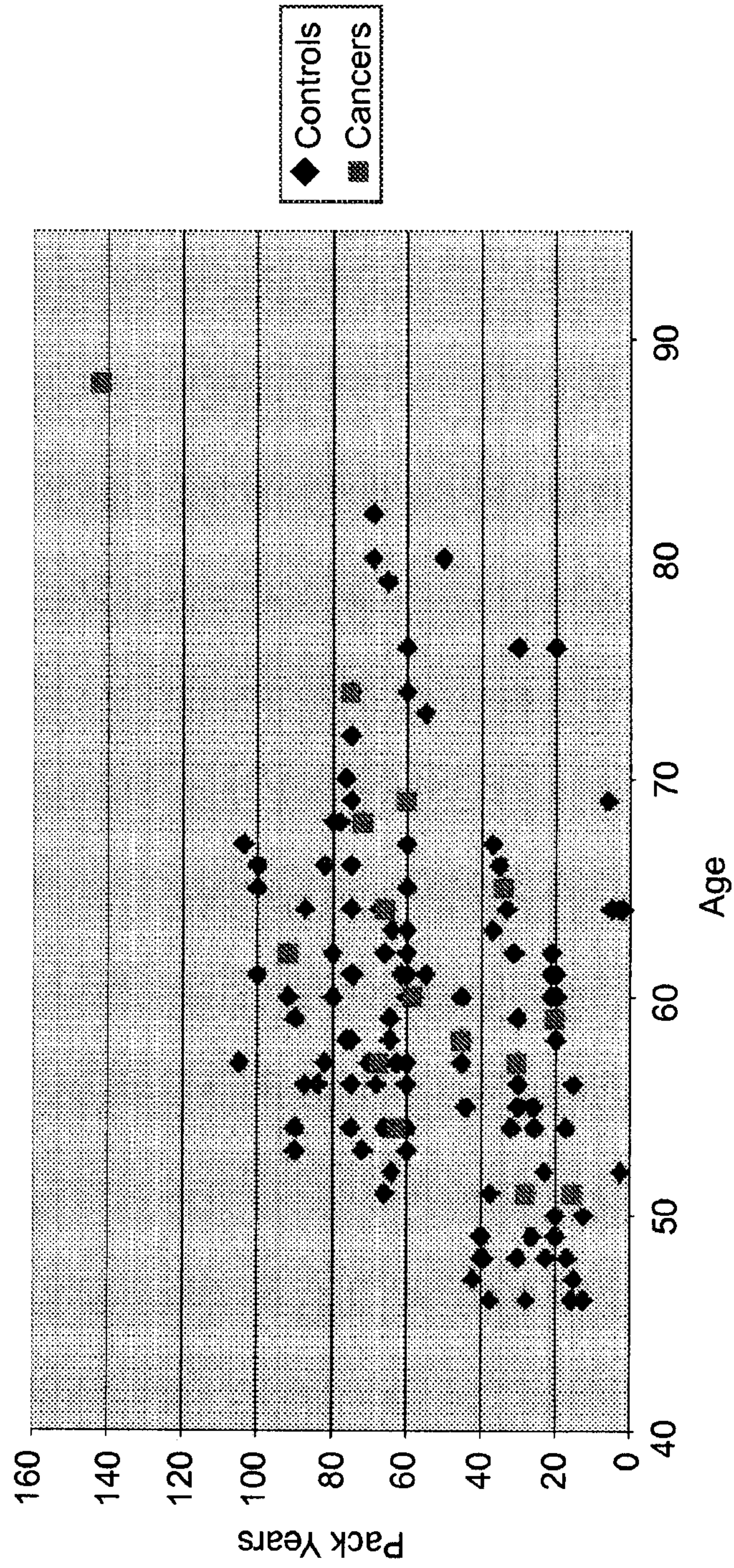


Fig. 10

PCT/US09/34021 02-10-2009

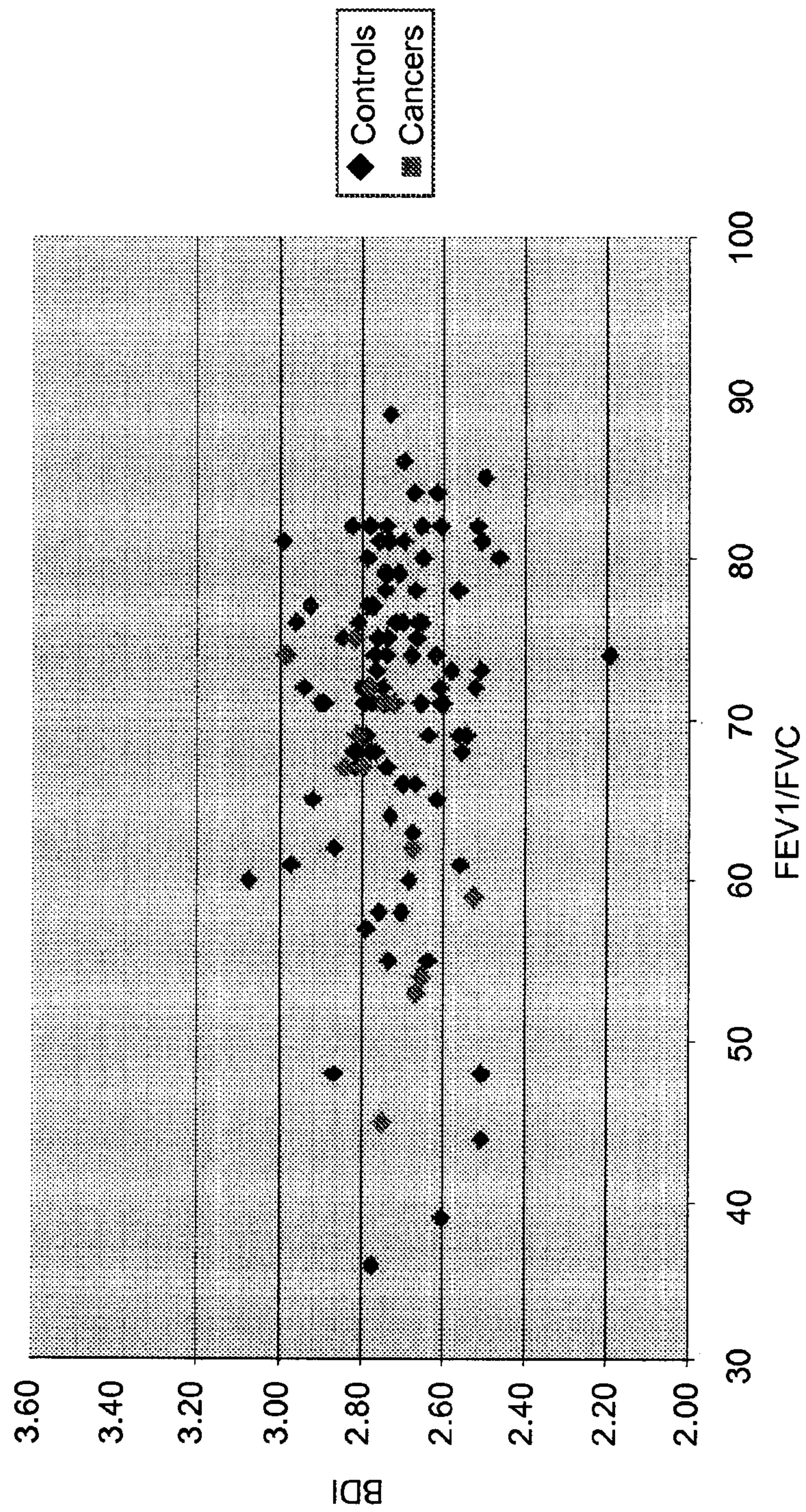


Fig. 11

PCT/US09/34021 02-10-2009

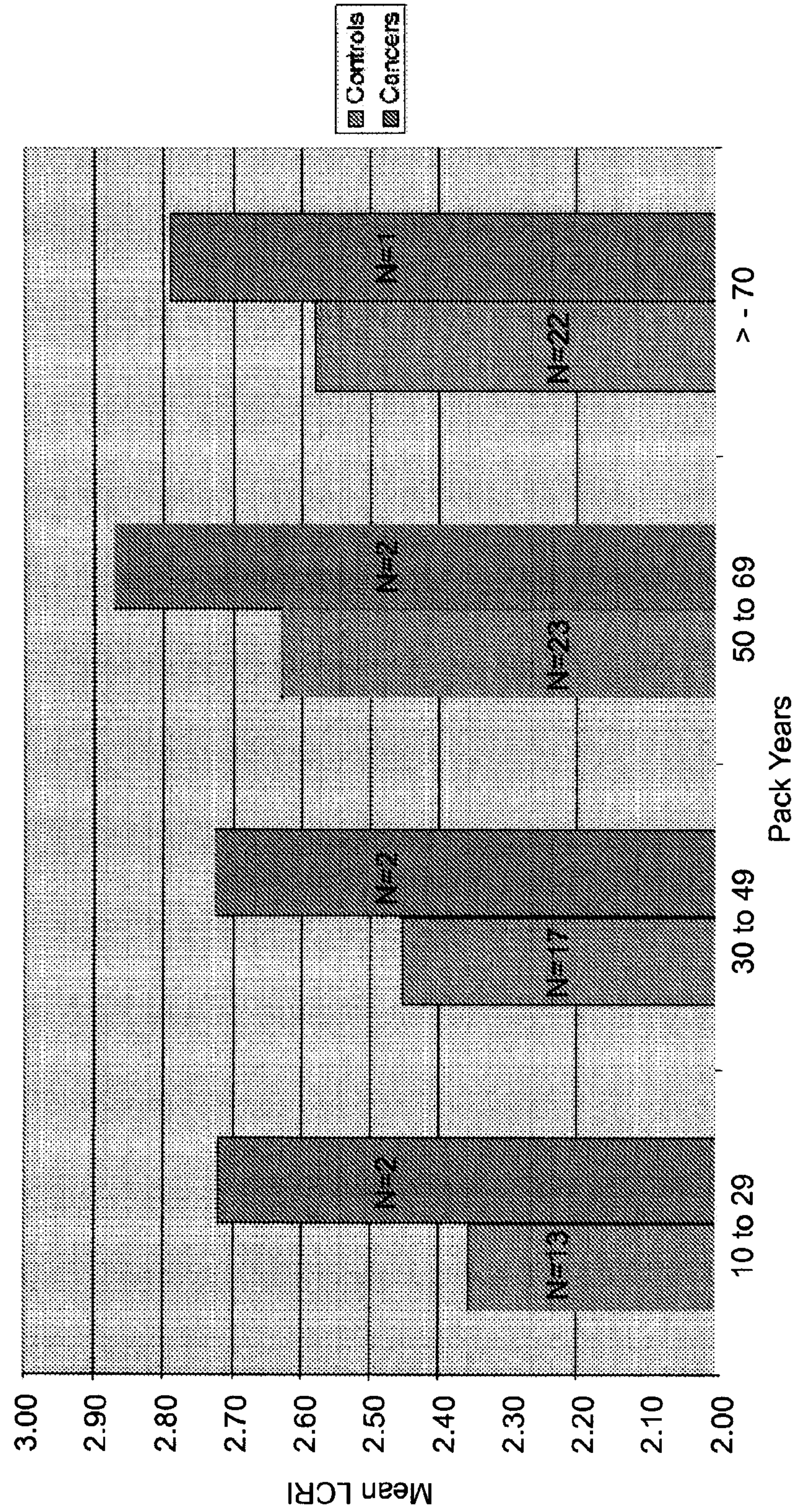


Fig. 12

PCT/US09/34021 02-10-2009

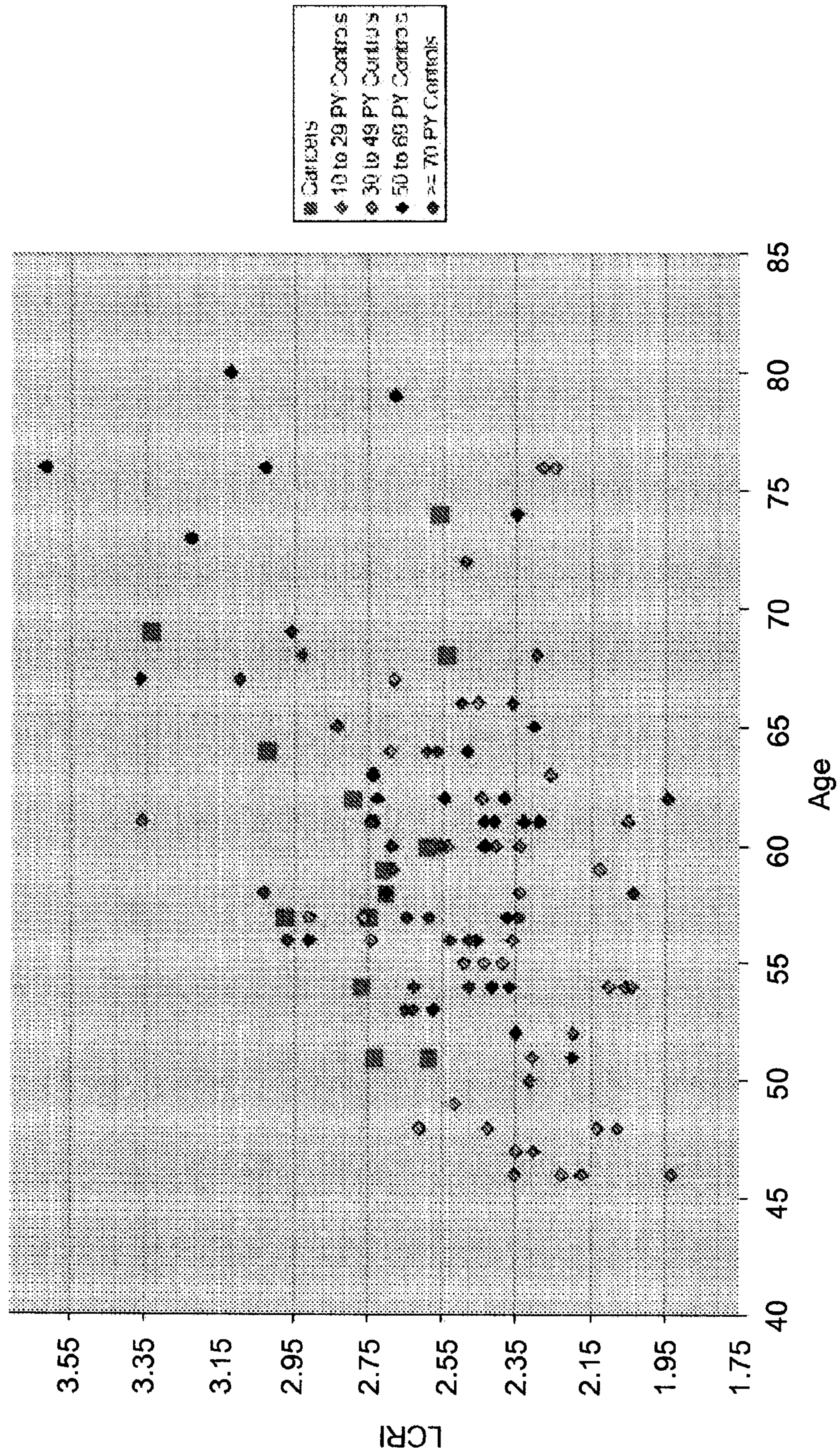


Fig. 13

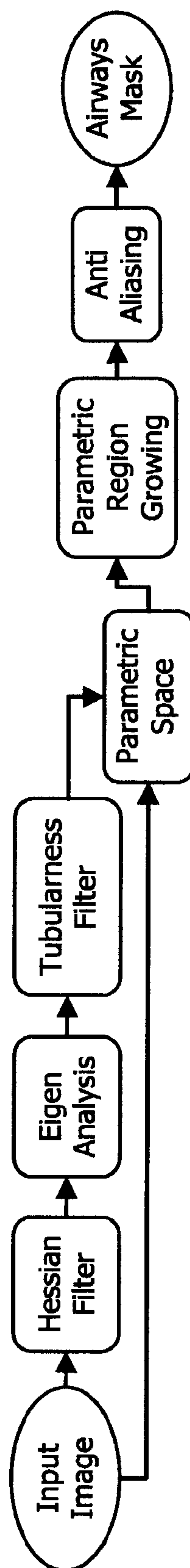


Fig. 14

