METHODS AND SYSTEMS FOR ASSESSING CLINICAL OUTCOMES

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 61/039,721, filed March 26, 2008, which application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Conventional methods for assessing a patient's clinical outcome are primarily based on clinicians' judgment and past experience. The conventional methods generally involve laboratory tests, patient surveys and office visits at isolated time points, all of which are not scalable for a time series analysis, especially for one that tracks or predicts the trend of a patient's clinical outcome in real time. Intrinsic to the conventional methodologies is the profound drawback that a relatively small set of information such as a single clinician's personal preference is taken into consideration in reaching a clinical decision. As such, under the existing medical system, patient care becomes increasingly difficult when multiple variables are involved. In particular, there lacks a system and method to effect a multi-dimensional analysis in which a large set of biomarkers are used to aid in the diagnosis, prognosis, and treatment of a clinical outcome or the design and execution of a clinical trial.

[0003] Multivariate statistics are generally concerned with determining a statistical distribution of an outcome or a series of outcomes based on multiple variables. Inherently, most medical conditions and treatments are multivariate due to the complexities of the physiology. The discoveries of a vast number of disease biomarkers and the establishment of miniaturized analytic systems have made a new paradigm of patient care that makes multivariate analysis feasible. A desirable new paradigm would provide rapid access to information characterizing clinical outcome and then automatically linking that information through customized communication channels so that the desired medical actions (adaptive dose ranging, clinical decision making and so forth) can be performed. Also desirable is the ability to integrate information from an individual's blood tests with other physiologically relevant factors, and present that information in an actionable format. The technology described herein satisfies these needs and provides related advantages as well.

SUMMARY OF THE INVENTION

[0004] The present disclosure provides a medical information system for subject data analysis. In one aspect, a system as disclosed is particularly useful for advancing the future of blood testing and data analysis. For example, the system can be part of an integrated infrastructure built around real-time, point-of-care consumer blood monitoring devices which analyze a small blood sample (e.g., 500 ul, 50 ul, 25 ul, 10 ul or even less) and wirelessly transmit that information to a database which integrates real-time data with stored data from disparate databases (patient record,

genetic/ genomic information, data from pivotal trials) into one central repository. The system then allows for the automatic application of multivariate, multidimensional mathematics to the data repository to perform specific commands or tasks, e.g., mapping real-time PK/PD dynamically in the context of the pathophysiology of a given medical condition.

[0005] In another aspect, a system as disclosed can be used to improve the label of key drugs through adaptive clinical studies which generate publications for label expansions for new indications, patient subpopulations, and for ameliorating safety concerns. The development of such a system for home, real-time blood monitoring has significant implications which allow one to collect information which is otherwise not available through the use of the conventional laboratory testing.

[0006] The medical information system typically comprises (a) an input device for receiving subject data and in communication with a processor; (b) storage unit in communication with the processor having a database for: (i) storing data corresponding to a probability space defined by a set of discrete clinical outcomes, each of which is characterized by statistical distribution of at least one biological marker; and (ii) storing subject data corresponding to the at least one biological marker; (c) a processor that calculates the position of said subject data in said probability space as a way of assessing the probability of a discrete clinical outcome of said subject; and (d) an output device that transmits information relating to the discrete clinical outcome of c) to an end user.

[0007] Non-limiting clinical outcome that the system is adapted to predict can be selected from the group consisting of but not limited to: complete response (CR), partial response (PR), stable disease (SR), non-response(NR), adverse drug effect (ADR), and drug toxicity. In using the medical information system, the end user can be a medical personnel or the subject himself or herself. In some instances, the end user is from a pharmaceutical company.

[0008] As disclosed, the processor of the system calculates the position of said subject data in said probability space as a way of assessing the probability of a discrete clinical outcome of said subject.

[0009] As disclosed, the input device of the system comprises a touch screen. Where desired, the input system can comprise a data entry portal or a keyboard. The subject data to be input into, processed by, or transmitted as an output by the system can be textual, numeric or a category. Where desired, the textual or numeric information is solicited from the end user.

[0010] In some instances, the subject data represent measurements of the at least one biological marker present in a bodily fluid. In some instances, the measurements are obtained by a point-of-care device that is operated by the subject. The measurements can be taken at various time points to yield a trajectory within the probability space, wherein said trajectory represents a time series of the assessed clinical outcome. The various time points can cover a period of less than or about 24 hours

[0011] As disclosed, the medical information system comprises an output device having an automatic alert system. The automatic alert system can be programmable by the end user. Where desired, the automatic alert system is programmable based on a predefined protocol for a clinical

trial. As disclosed, the output device of the system transmits selected portions of the subject data and the probability space in response to instructions from the end user. In yet another aspect, the information transmitted by the output device is encrypted. In still another aspect, the information transmitted by the output device represents an assessment of the clinical outcome of said subject at a single time point. The information transmitted by the output device can represent a time series of the assessed clinical outcome.

[0012] As disclosed, the input device and/or the output device of the system comprises a user interface that can remotely access the network.

[0013] As disclosed, the medical information system comprises a network.

[0014] As disclosed, the storage unit of the system stores historical reference data of a plurality of subjects in relationship to the at least one biological marker. Where desired, the data stored in the storage unit are selected from the categories consisting of pathology, anatomy, treatment option, treatment outcome, pharmacological parameter, pharmacokinetics parameter, psychological parameter, and genomic information. The database can be public, internal.

[0015] The end user of the medical information system can be a health care provider, including without limitation a Health Maintenance Organization (HMO).

[0016] The present disclosure further provides a method for characterizing the probability of a clinical outcome of a subject. The method comprises the steps of (a) constructing a probability space defined by a set of discrete clinical outcomes, each of which is characterized by a statistical distribution of at least one biological marker; (b) obtaining subject data corresponding to the at least one biological marker; and (c) calculating the position of said subject data in said probability space, thereby characterizing the probability of the clinical outcome of said subject.

[0017] Also provided is a method of characterizing a clinical outcome of a subject comprising: (a) constructing a probability space within a server, wherein the probability space is defined by a set of discrete clinical outcomes, each of which is characterized by the statistical distribution of at the least one biological marker; (b) entering data of a subject into the server, said data corresponding to the at least one biological marker; and (c) calculating the position of said subject data in said probability space thereby characterizing the clinical outcome of the subject. In some embodiments, in practicing the subject methods, at least steps b and c are repeated at various time points to yield a trajectory within a probability space, wherein said trajectory is indicative of the likelihood of progression to the clinical outcome. The subject methods can comprise the step of notifying a medical personnel or the subject of a need for taking a medical action upon assessing or characterizing the position of said subject data in said probability space. In some instances, the medical action involves at least one action selected from the group consisting of altering a dosage of an existing therapeutic agent administered to said subject, administering a different a therapeutic agent, and administering a different combination of therapeutic agents. Notification of a medical action can be electronically

transmitted, e.g., wirelessly transmitted. The subject methods can further comprise step of, upon selection of the at least one action, performing an outcome analysis for assessing a result of said selected action, and automatically updating the probability of a discrete clinical outcome of said subject.

[0018] Further provided in the present disclosure is a computer readable medium comprising computer readable instructions, which when executed cause a processor to: a) provide a probability space defined by a set of discrete clinical outcomes, each of which is characterized by a statistical distribution of at least one biological marker; b) obtain subject data corresponding to the at least one biological marker; and c) calculate the position of said subject data in said probability space to assess the probability of a clinical outcome of said subject. In general, the instructions operate in a software runtime environment. As disclosed, the instructions when executed further causes a processor to provide a user defined alert condition based on an assessment of trajectory parameters of the subject data in the probability space, wherein said trajectory parameters are at least one of speed, acceleration, direction, and position.

[0019] As disclosed, a method is provided herein of predicting the occurrence of a medical condition that requires medical intervention, the method comprising: (a) measuring concentrations of a first set of biomarkers present in a subject and measuring one or more physiological indicators of said subject at a given frequency, wherein the first set of biomarkers are suspected to be predictive of the medical condition; (b) based on the concentrations measure in (a), generating from the first set a subset of biomarkers that are more correlative with the occurrence of the medical condition and/or a new frequency of measurement of the biomarkers; and (c) measuring concentrations of the subset of (b) and/or following the new frequency of measurement of one or more biomarkers, thereby predicting the occurrence of the medical condition.

[0020] In some instances, a method further comprises analyzing data reflecting the concentrations and/or the physiological indicators with multivariate statistical software. In some instances, the biological markers are present in a biological sample of said subject. The biological sample can be diluted by an appropriate fold to ensure, e.g. the appropriate range of concentration level is detected.

[0021] As disclosed, a method of monitoring sepsis development of a subject comprises: measuring at least two parameters selected from the group of (1) body temperature of said subject, (2) protein C concentration of said subject, (3) interleukin 6 (IL-6) concentration of said subject, multiple times to yield a trend of temperature, protein C trend, and/or IL-6; and wherein an increase beyond normal body temperature, a decrease in protein C concentration and/or an increase in IL-6 concentration is indicative of the development of sepsis in said subject. As disclosed, a decrease in protein C and an increase of IL-6 can be indicative of the development of sepsis in said subject. In some other aspects, a decrease in protein C and an increase of IL-6 and an increase beyond normal body temperature can be indicative of the development of sepsis in said subject. In some instances,

an at least about 10-fold increase in IL-6 concentration in said subject is indicative of the occurrence of sepsis in said subject. In a further instance, an at least about 100-fold increase in IL-6 concentration in said subject is indicative of the occurrence of sepsis in said subject. This method may further comprise the step of increasing frequency of measuring IL-6 concentration upon an increase beyond normal body temperature and/or a decrease in protein C concentration. For example, the frequency of IL-6 measurement can be increased to once a day, once every 12, 8, 6, or 4 hours. A determination of the occurrence of sepsis may be promptly followed by an appropriate medical intervention.

[0022] Also described herein is a method for characterizing a medical condition of a subject, comprising: obtaining a first set of subject data comprising at least one biological marker and at least one physiological parameter from the subject; determining the probability of a medical condition of the subject using the first set of subject data obtained; selecting a second set of subject data from the probability of the medical condition; and obtaining the second set of subject data from the subject, thereby characterizing the medical condition of the subject.

[0023] In yet another aspect, a method is disclosed for characterizing periodicity of a clinical condition of a subject, the method comprises: identifying a set of biomarkers for a clinically relevant condition; obtaining longitudinal subject data corresponding to at least one biomarker in said set to obtain a trend of the subject data; analyzing said trend to identify periodic changes in the at least one biomarker; measuring values of peak measurements of the periodic changes of the trend; and characterizing the values of the peaks thereby characterizing the periodicity of the clinically relevant condition. In some instances, the analyzing step comprises developing an ARIMA model to determine a differencing lag in the underlying model. The differencing lag can be used to de-trend the trend and establish a stationary trend. In some instances, the analyzing step comprises calculating an autocorrelation function and the measuring step comprises identifying the statistically significant peaks in the autocorrelation function. In some instances, the analyzing step comprises calculating spectral density and the calculating spectral density is performed using a Fast Fourier Transform. The measuring step can comprise identifying the power spectrum of the maximum spectral density frequency.

[0024] As disclosed, a method for monitoring subject response to therapy comprises: obtaining longitudinal subject data corresponding to at least one biomarker in a set of biomarkers for a clinically relevant condition to obtain a trend of the subject data, wherein the subject data is obtained from a subject receiving a therapy; monitoring periodicity of the trend; and corresponding the periodicity to a response to the therapy received by the subject. In some instances, the therapy is a periodic dosing regimen. In some instances, the response to the therapy is characterized by a time-dependent behavior of peak levels of the trend. In some instances, the time-

dependent behavior is substantially constant. In other instances, the time-dependent behavior is changing linearly. In yet other instances, the time-dependent behavior is changing exponentially.

[0025] In an aspect, there is provided a method for clinical trial design by characterizing the emergence of clinically relevant subpopulations of patients exposed to a therapeutic agent, the method comprising: identifying a set of biomarkers in a blood sample that act as surrogate markers for the therapeutic agent; receiving subject data regarding the set of biomarkers measured longitudinally from a group of patients exposed to the therapeutic agent; identifying distinct clusters in a multivariate clustering space of the measured values of the set of biomarkers from the group of patients; determining the rate of separation of the distinct clusters and measuring the distance between the distinct clusters in a statistical manner; obtaining patient information from the group of patients to classify the patients in clinically relevant subpopulations; and comparing the distinct clusters to the clinically relevant subpopulations to characterize sensitivity and specificity of the distinct clusters to predict the clinically relevant subpopulations. In some instances, the method further comprises identifying a second set of biomarkers configured to improve the characterization of the emergence of distinct clusters to predict the clinically relevant subpopulations. In some instances, the group of patients exposed to the therapeutic agent are participants in a clinical trial. In some instances, the clinical trial is a dose ranging trial. In other instances, the clinical trial is a part of an adaptive clinical trial. The adaptive clinical trial can be designed to characterize an optimal dosing regimen or can be designed to characterize an optimal responder population. In some instances, the measuring the distance step comprises measuring the Mahalanobis distance between the distinct cluster centroids. In other instances, the measuring the distance step comprises measuring the nearest-neighbors distance between the distinct clusters. In yet other instances, the measuring the distance step comprises measuring a Euclidean distance measure between the distinct clusters. In some instances, the measuring the distance step measuring a Manhattan distance measure between the distinct cluster.

INCORPORATION BY REFERENCE

[0026] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] Many features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which many principles of the invention are utilized, and the accompanying drawings of which:

[0028] Fig. 1 illustrates a general representation of the Mahalanobis distance method and the representative ellipses. The figure also includes the Mahalanobis distance mathematical equation.