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Real Time Clinical Decision Support System

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1. Introduction

Information technology (IT) and Web-based facility have become the major backbone of the modern hospital information systems (HIS) since the beginning of 21st century. Associated with the rapid evolution of medical informatics, the clinical decision support system (CDSS) is playing an important role to help physicians and other healthcare professionals in making decisions while determining diagnosis of patient data. For the routine treatment procedure, the physicians usually take much time to study patients' clinical records (PCRs) prior to explain abstruse clinical markers to patients in clinics. Particularly, for chronic and traceable diseases, they also need to refer patients' quality of life (QOL) and their patient-reported outcomes (PROs) for prescribing the proper therapies. Therefore, a real time clinical decision support system (RTCDSS) is proposed for patient- and clinician-oriented interface as well as patient-to-clinician (P2C) communication, mostly for the chronic diseases with traceable clinical markers. The system provides accurate medical informatics with efficient process for presenting immediately analytical diagram through graphical interface based on patients' and clinicians' requirements.

The major cancer therapy usually brings numbers of side effect in addition to destroy tumors. It implies that QOL is deeply impacted by uncertainty and after-effect due to treatment of oncology clinic. Healthcare people probably make incorrect judgments because patients embarrass on answering private questions or hiding actual conditions. The past studies showed improvements for drug dosing, preventive care, and other economic aspects of medical care, but not convincingly for diagnosis, as reviewing computer-based CDSS on clinician performance and patient outcome (Johnston et al., 1994; Hunt et al., 1998). Obviously, it is not easy to create a universal system for varied clinical requirements. However, it would be possible to build up a platform with expandable components for specified clinical purpose due to customized rules. Therefore, the proposed RTCDSS can be induced by developing a patient-oriented interface with healthcare function to collect real time PROs and PCRs according to practical requirements of hospitals. For example, the assessment of QOL utilizes questionnaires provided by the EORTC[1] to highlight physicians' awareness of patients' status and greatly facilitate physician-patient communication (Detmar et al., 2002). Recently, an interactive assessment system named clinical infometrics

[1] European Organization for Research and Treatment of Cancer

was established with information and psychometrics technology for measurement, statistical modeling, informatics and practice, in palliative care with computerized procedure to improve clinical assessment (Chang et al., 2007; Chang, 2008). Applied for measurement and management of PROs, infometrics technique can assist clinicians to more precisely recognize actual response of patients and improve the quality of care with instant process and real time outcomes statistics (Lin et al., 2010). With graphical diagrams, clinicians thus can convince patients by presenting PRO instantly with other PCR.

In clinical practice, furthermore, clinicians meet a number of common problems when it comes to improving quality of clinical treatments as follows: (1) clinicians may take several hours, or even a couple of days, to review PCRs but only have a few minutes to explain their opinions to patients; (2) patients typically find difficulty to understand their condition since clinicians may only explain the disease adequately using written descriptions; (3) the CDSS is computerized, but it may not have online capability in many clinics; (4) real-time analysis is not supported by many commercial computational tools. From clinical data tracking to real-time decision making tools, the flexible Web-based CDSS with online evidence-based medicine (EBM) progress is a growing trend in advanced clinical care The past research indicated that publicly released clinical evidence data assist to improve patient care quality at the hospital level (Fung et al., 2008). Numerous CDSS platforms have been constructed for a variety of clinical approaches. To facilitate the treatments, many studies suggested analytical tools to assist clinicians in estimating the relative pretreatment parameters and for tracking the proper diagnostic guidelines on visualized interfaces (Holmes-Rovner et al., 2005; Walter & Covinsky, 2001; Dorfman et al., 2010). Thus, a clinician-oriented interface with real-time online analysis may improve accuracy and efficiency of decision support. Many clinicians hence are in need of an expandable RTCDSS with an interactive diagrammed interface to efficiently evaluate instant informatics and to make clinical decisions (Lin et al., 2011). It is feasible to take chronic diseases with traceable markers as the case study of RTCDSS.

In order to solidify real time functions of the proposed system, the clinical guideline with medical evidences is recommended for appropriate treatments. The Web-interfaced process has been developed for graphical guidelines that allow users to traverse the algorithm by flowcharts in an interactive fashion (Liem et al., 1995). The clinical benefits were highlighted by rapid knowledge acquisitions, shareable guideline models, and robust information systems while evaluating its impacts on outcomes (Zielstorff, 1998). Thus the electronic guidelines improved decision quality and physician-patients interaction significantly (Hsu et al., 2005). However, many obstacles were encountered as practicing guidelines for the management of workflow integration would be the most difficult tasks (Maviglia et al., 2003). Obviously, lots of challenges still exist while integrating a new RTCDSS with the PROs, PCRs, CDSS, and interactive guidelines into the legacy HIS. The framework for interactive clinical guidelines should consider readiness of clinicians for practice, barriers to change as experienced by clinicians, and the target level of interventions (Moulding et al., 1999). To properly integrate electronic clinical guidance into an existing system, the issues of heterogeneous data integration should be practiced in the platform. Numerous studies established models of evidence-based guidelines by using XML (extensible mark-up language) documents (Shiffman et al., 2000; Sanders et al., 2001) and AJAX (asynchronous

JavaScript and XML) technique to supply shareable information and user-friendly search, respectively, with automatic completion. The techniques have been widely utilized to online interactive interface in the past years for acquisition of efficient data transportation.

In this article, prostate cancer, which is familiarly monitored by prostate specific antigen (PSA) and other treatment parameters, is taken to practice the proposed RTCDSS. A Web-based platform is established with clinical infometrics and interactive guidelines for a RTCDSS. Java™ technologies are applied to create patient- and clinician-oriented interfaces with automatic clinical procedure and data transformation.

2. Development of RTCDSS infrastructure

This section will describe the details how the Web-based platform of RTCDSS is built upon novel Internet technologies. The infrastructure involves core models as follows: model view controller (MVC), object oriented mapping (ORM), clinical data warehouse (CDW), Web services (WS), online analytical process (OLAP), and AJAX. Data flows throughout all stages of the structure can be manipulated by Internet services and information techniques.

2.1 Model-view-controller model

The MVC model is a type of design patterns employed in software engineering. It hybridizes the design patterns, and divides system responsibilities into three parts: the model, which maintains program data and logic; the view, which provides a visual presentation of the model; the controller, which processes user input and makes modifications to the model. Herein, it is utilized for generating a modelized architecture systematically with expandable and reusable components of the Web-based platform for efficient and flexible collaboration. The concept of modelized architecture can be driven into Web assessment for acquiring PROs from online infometrics system and adapting PCRs with the legacy HIS in hospital. The architecture reflects the MVC design pattern, which was established in 1970' and included several design patterns to build reliable object-oriented software system (Krasner & Pope, 1988). The public of design patterns was first made by introducing twenty-three patterns related to creational, structural and behavioural models for software design to progress recurrent elements (Gamma et al., 1994). The MVC theoretically hybrids three of them, the "strategy," "observer," and "composite" patterns; and divides system responsibilities into the model, the view, and the controller. The pattern is involved in well-known open-source framework such as "Strut," "Spring," "Hibernate" for development. These frameworks with MVC paradigm use polling for its input control to solve the problems on consuming computation resources when the user is not interacting with the interface and avoid unnecessary performance loss. Due to this architecture, a web-based prototype system built with the open-source framework is available for online infometrics of QOL. Fig 1 presents an architecture consisting of conceptual components organized by three main groups which contain the model, the view, and the controller to provide sole modules but support one another for system requirements.

As extending the MVC-based architecture to the RTCDSS, the built-in elements within the framework should be reusable and extractable to enable clinical analysis and decision support for clinical cares which includes: (a) instantaneous disease evaluation, (b) risk

analysis, and (c) treatment guidance. For these tasks, the infrastructure can be detailed below to complete requests for presentation, management, analysis, and database.

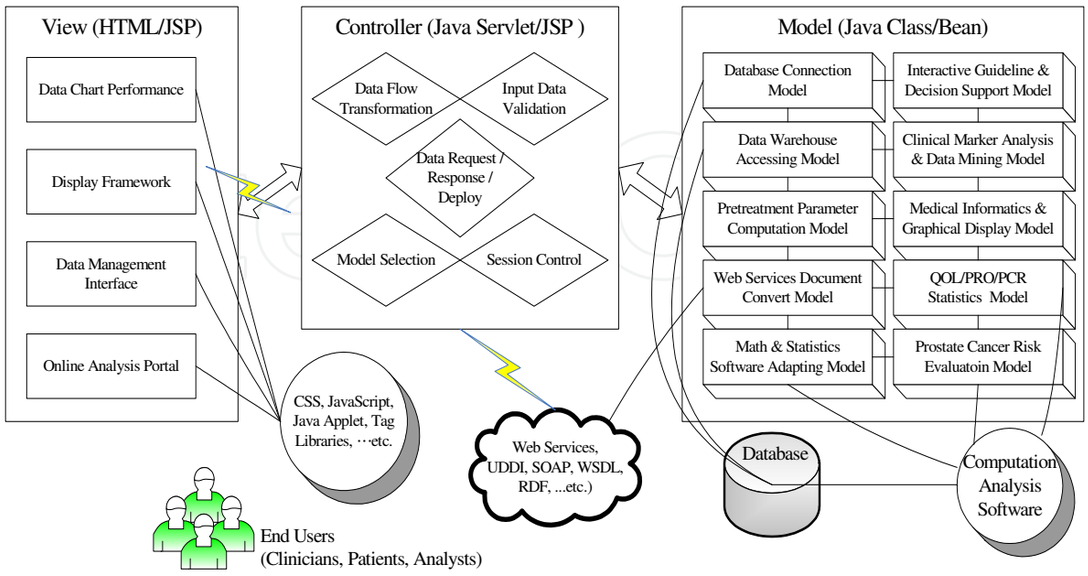

Fig. 1. Web MVC-based Architecture with model-view-controller components.

i. Models:

The models are leading four main groups: disease evaluation, risk analysis, treatment guidance, and data processing models. The first three models are relative to clinical data computation while the last one represents the other IT modules. The disease evaluation contains modules primarily to retrieve clinical variables, calculate pretreatment parameters, and evaluate PROs and PCRs. The risk analysis model drives algorithms to analyze clinical variables and parameters, identify risk indicators and criteria, and so on. The guidance criteria model enables the generation of evidence-based diagrams, online guidance and decision support. The rest of the IT-related modules such as clinical data conversion, database connection, and graphical display, are included in the data processing model.

ii. Views:

The views can implement the patient- and clinician-oriented interfaces directly with the OLAP portal and the EBM informatics for clinicians at the presentation stage. Similarly, the view of management interface provides IT engineers with security administration at the management stage. Meanwhile, all clinical data can be taken care through the analysis view at the analysis and database stages. Based on this consideration, these views are behind the major components of each stage such as real-time diagrams, interactive guidelines, privilege administration, informatics management, data filtering and data analysis tools.

iii. Controllers:

The controllers support interactions among the models and views within the RTCDSS infrastructure. At the presentation stage, the controllers process data flow transformation and data input validation when the clinicians begin online inquiries. At the management

stage, the privilege control and role identification are required when the engineers are conducting system maintenance. Meanwhile, the clinical data at the back stages of analysis and database are coordinated by heterogeneous data transaction.

2.2 Object relation mapping model

Object-relational mapping (ORM) is a programming technique to convert data between incompatible type systems in relational databases and object-oriented languages. It is the automated and transparent persistence of application objects to the tables in a relational database by using metadata that describes the mapping between the objects and the database. The ORM works through reversibly transforming data from one representation to another and is used to unify various data format transformed among the sub systems (Bauger & King, 2005). We can coordinate the infometrics and clinical data flow through the interface of ORM to convert persistent objects and manage data transaction and resource throughout database. The interface includes functional modules of session, session factory, configuration, transaction, query, and criteria to interact XML metadata with application modules of server. In mechanism, the session interface conducts lightweight instances of application in safe as the necessary data are requested on the web tier all the time; the application obtains session instances from a session factory to share many application modules and cache scripted database transaction and other mapping metadata at runtime for data conversion. Then, the configuration interface configures the location of mapping documents and specific properties for data retrieval; thus a transaction interface is optionally selected to keep portable between different execution environments. Furthermore, the query interface performs instances to control data queries against the database, while the criteria interface executes queries under the objected-oriented criterion. Herein, the assessment of QOL questionnaires can be implemented by the ORM model for online analysis to concurrently process and share light weight data over the Web-based system by rearranging storage, organization, and retrieval of structured data.

2.3 Clinical data warehouse model

The data warehouse is known as an integral database for historical data repository with lack of systematic arrangement by information technique. It was initially defined as an integrated, subject-oriented, time-variant and non-volatile database that provides support for decision making (Inmon & Kelley, 1994). The concept of clinical data warehouse obeys the definition above to integrate practical PROs and PCRs with a standard procedure from different hospital databases into the knowledge bank for advanced analysis. To incorporate infometrix data with existing PCR for online analysis, a clinical data warehouse (CDW) is planned and practiced in the RTCDSS. The data warehouse is known as building up an integral database for historical data repository with lack of systematic arrangement by information technique. The critical factor leading to the use of data warehouse is that a data analyst can perform complex queries and analyses without slowing down the operating system. The raw data for clinic in variety of format would be rigorously unified by extract-transform-load (ETL) process into database through extraction, consolidation, filtering, transformation, cleansing, conversion and aggregation (Rob & Cornel, 2004). As planning the data warehouse, fact tables and cube dimensions related to historical data are the key elements. The fact table contains facts that are linked through their dimensions, which are qualifying characteristics that provide additional perspectives to the given facts.

2.4 Web services model

A Web service is an interface describing a collection of operations that are network accessible through standardized XML messaging (Gottschalk et al., 2002). With the Web services model, the criterion for decision support can be retrieved from online data logs for online analysis. Through Web services, the computation model retrieved decision criteria from unified document to create online statistical chart. In order to improve efficiency of data transaction, the intensive database query is executed to remain at the server site and the less-intensive data for online analysis is processed at the client site. The designation of XML schema is the essential factor of Web services for accessing network data. The tree structure with hieratical node elements is created in the document of XML schema to record data from the web server, and then the XML parser can parse the tree structure by subsequent nodes in the schema to retrieve data. The flow chart of parsing process in Fig 2 is separated as three parts: (1) converse data as XML document from database based on the specific schema, (2) parse XML document through SAX (Simple Application-programming-interface for XML) standard, and (3) retrieve data of XML document by scheme definition. The interactive data required by QOL assessment and guideline conduction are then transformed as Web services documents. The historical clinical data redeemed by expert opinions will feedback to data warehouse; and, the online computation models retrieve decision criteria from unified documents to display statistical charts. Herein, the WS model is integrated with the ORM model to share the QOL questionnaires as the over the Web-based system for indexing and reorganizing the clinical database.

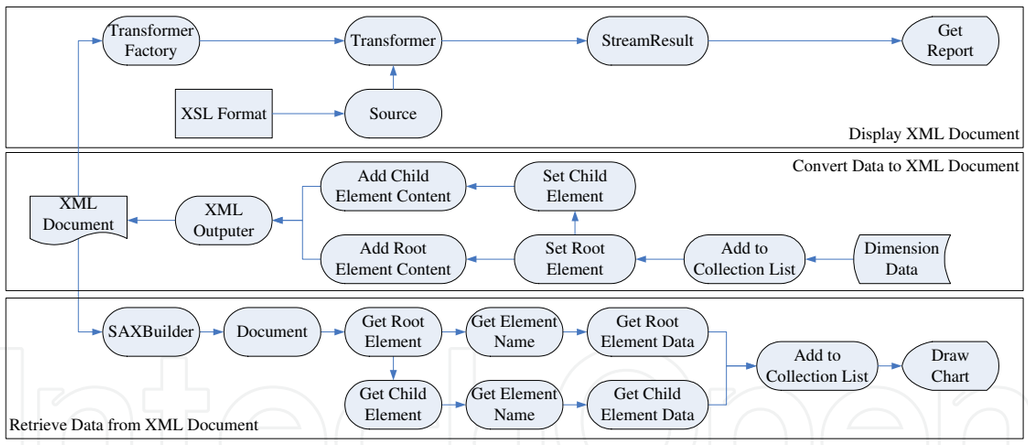

Fig. 2. Parsing procedure for light-weight data with XML schema.

2.5 Online analytical process model

Online analytical process (OLAP) has been embedded on the decision support platform deployed for enterprise system since early period of network boom-up era (Chaudhuri & Dayal, 1997). It provides efficient functionalities with computation algorithm on data warehouse to explore historical data. This model can help in presenting real time analytical information by online graphical diagraph with specific computation modules. In order to manage and analyze infometrix and clinical data cooperatively in the system, the OLAP model crossing over the web server and database leads online computation within the RTCDSS. The PCR queries integrated with heterogeneous databases are primarily

progressed while accessing the database server; thus, the risk evaluations embedded within online session logs are efficiently retrieved as connecting the web server. The progress may keep complex query behind data mining for the knowledge bank but remain simple data transaction through dynamic views in data warehouse. Based on the MVC architecture, the online clinical informatics can be achieved by the OLAP mechanism. For example, the clinician is a decision maker on a presentation stage that performs the components of the interactive guideline and real-time diagrams in clinic.

2.6 Asynchronous JavaScript XML-HttpRequest model

The asynchronous JavaScript XML-HttpRequest (AJAX) technique has been widely applied for online interactive interface in the past years to grab instant information as well as to avoid lag in transportation of client-server data. It can be developed as diverse, convenient, and interactive applications with visualized functions for user-friendly interface design. The basic concept of asynchronous data transformation is storing transient data at client sites to reduce redundant data query with database sites and enhance interactive patient- and clinician-oriented interface. Adaptive with the client-server network architecture, it may process numerous data queries between the database and the web server. Technically, persistent and large data transaction might downgrade the network speed. As the WS and OLAP models communicate with the client browser for adopting light-weight data like QOL questionnaires, risk evaluations or guideline indexes, the AJAX model helps in adjusting data interaction performance. The method doesn't need to request database all the time but load into browser's temporary container at client site. If the client site keeps sessions at online status, the browser is calling JavaScript™ and restoring data. Once the session needs reconnection or updating, the client-server communication is activating. The manner can be approved by AJAX that is a standards-based programming technique to make web-based applications more responsive, interactive, and customizable in addition to reduce network latency and interface complexity for keeping server responsiveness (Smith, 2006).

In short, the proposed RTCDSS remains heavy-weight database query at server site and keeps light-weight data for online analysis at client site to improve clinical data transaction efficiently. In the system, clinical data are analyzed to yield expert opinions for feedback to clinical data warehouse. Through models of ORM, WS and OLAP, the decision criteria and interactive guidance are displayed by AJAX with real time online diagraphs. Based on the MVC and CDW, the web and database servers are collaborative within the network services.

3. Design of patient and clinician oriented interfaces

This section aims to integrate previous models with practical clinical interfaces for both of patients and clinicians. In which, prostate cancer is selected for the sample of modeling since it is the chronic disease with a traceable marker for long-term monitoring. Two types of interfaces are addressed below for processing PRO with clinical infometrics and analyzing PCRs upon the EBM. The entire infrastructure is designed with five primary layers to (1) acquire patient-reported outcomes at the "acquisition", (2) present online clinical diagraph at the "presentation", (3) manage clinical information at the "management", (4) analyze patient's clinical records at the "analysis", and (5) coalesce diverse clinical databases at the "database". The structure is exampled by the project named clinical infometrics for prostate cancer (CIPC) in China Medical University Hospital (CMUH) in Tahchung, Taiwan.

3.1 Patient-oriented interface

The ORM and CDW models are driven for the patient-oriented interface to collaborate clinical measurements with medical informatics through Internet. A knowledge bank is generated in database with feedback of expert opinions that provide clinicians real time guidance. Instant assessment of patients' QOL is acquired to compare with clinical markers.

3.1.1 QOL assessment

Herein, an infometrics system upon real time online assessment is developed for prostate cancer patients. It is employed by the RTCDSS to generate psychometrical modules upon information technique to measure patient's QOL. The assessment results can be instantly reported while patients are conducted to easily complete questionnaires on the interface of patient-oriented design. Compared to importance of survival evaluation, QOL becomes a significant index of healthcare. EORTC creates series of QOL assessments in cancer clinical trials to provide a more accurate evaluation of the well-being of individuals or groups of patients and of the benefits and side-effects that may result from medical intervention. The reliability, validity and sensitivity of assessment are acceptable since questionnaires have been validated by more than 3,000 studies worldwide. The quality of life questionnaire (QLQ) C30 is developed to assess the QOL of cancer patients while the PR25 is designed for prostate cancer patients. In the CIPC, a web-based platform with infometrics system is to serve prostate cancer patients. The questionnaires are adopted from EORTC, thus QLQ C30 and PR25 are the primary assessment modules for volunteer patients in pilot study. The C30 involves 9 multi-item scales for 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and 1 global health QOL scale, while several single-item symptom measures are also included (Aaronson, N.K., et al., 1993). The PR25 is a 25-item questionnaire for use among patients with localized and metastatic prostate cancer. It has subscales assessing urinary symptoms (9 items), bowel symptoms (4 items), treatment-related symptoms (6 items) and sexual functioning (6 items).

3.1.2 Clinical implementation for prostate cancer

QOL is an important healthcare index but patients probably conceal the truth because of private manners. In addition, the traditional paper-based QOL assessment usually causes reading difficulty for patients because of improper font size and print space. Hence the infometrics module of CIPC system is designed for patient orientation through sufficient accessibility and accompanies QLQ with instant PRO analysis and evaluation. In which, the fonts of questionnaires are enlarged for elderly patients who have poor eyesight and the selection buttons are displayed on a touch screen for patients who are not familiar with using computer mouse. Most of prostate caner patients are seniors who initially might not know how to click mouse-button or scroll the browser to navigate the computer; therefore the Web-page design is simplified by one-touch action per question before the users are well trained. Besides, a multimedia function played with head phones is optionally provided for low education level patients who could read questions with limited literacy. Patients are arranged privately in a consulting room to complete the questionnaires while waiting for the clinicians. Then, through automatic computation and statistical models, the clinicians could immediately evaluate the real time reports with online analysis. Based on the system design, clinicians and researchers can immediately access infometrix data after patients

completed the questionnaires. Fig 3 performs the operating procedure, in which the clinician can make cross compare overall treatment information with instant expert opinions for advanced communicate with patients.

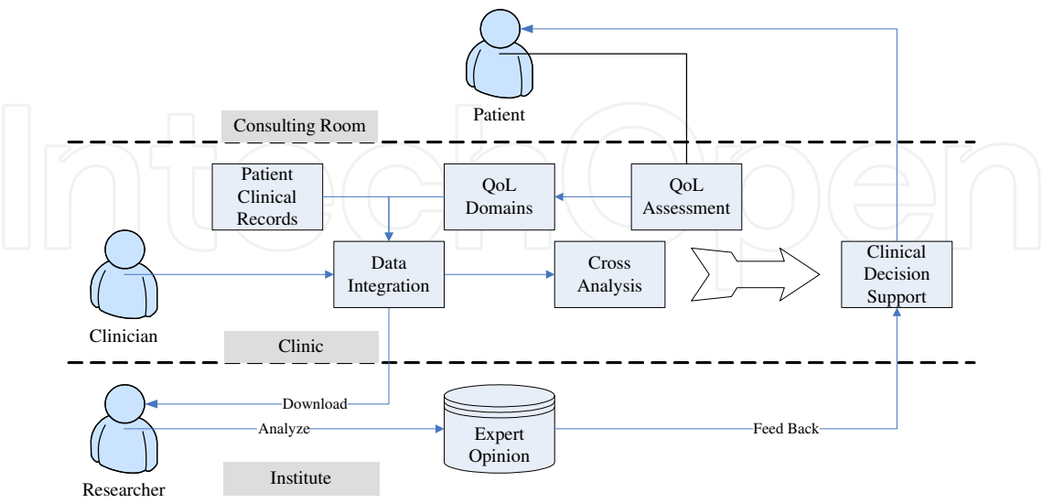

Fig. 3. Clinic progress implemented with clinical infometrics system.

Furthermore, the network of CIPC needs to link hospital and campus networks, but under hospital's information security policy, to collaborate tiers of database, analysis, management, presentation, and acquisition for clinical and research workflows. As shown in Fig 4, the database tier supports clinical and infometrix data warehouse; the analysis tier assists analysts analyzing data and feeds back statistical results as resource of the

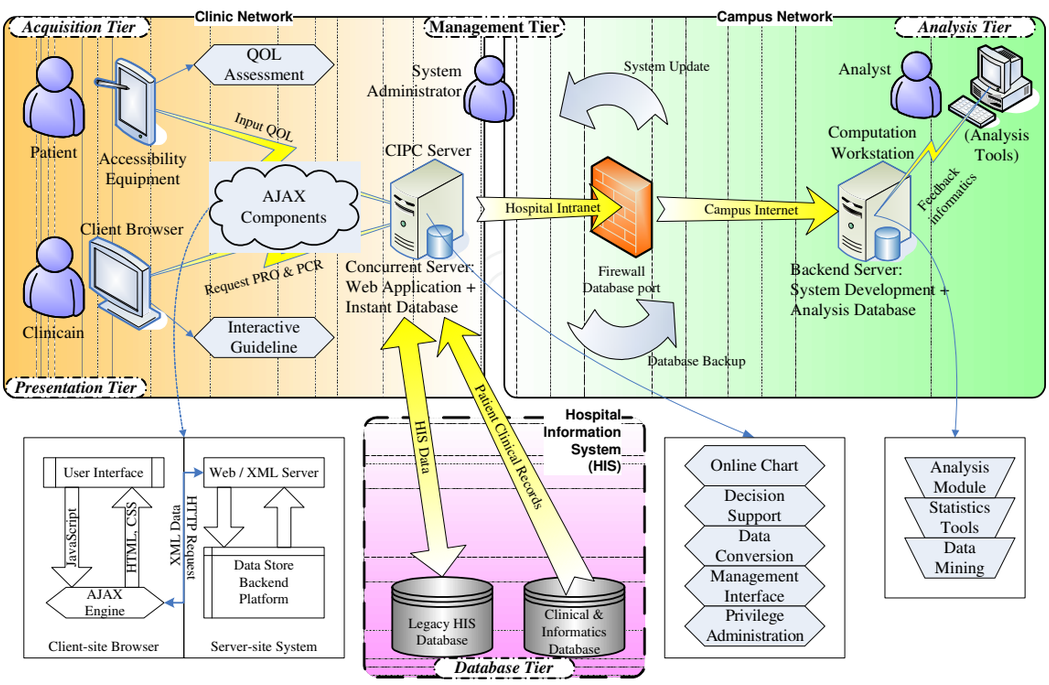

Fig. 4. Network infrastructure of the CIPC system with RTCDSS components.

knowledge bank; the management tier is the control center for administrating data flow throughout the entire system; the presentation tier presents real-time functions for online decision support and interactive guideline on a friendly interface for P2C communication; the acquisition tier becomes the data collector to execute online QOL assessment with accessibility interface. The infrastructure bridges both networks of clinics and campus through the firewall to routinely backup clinical data and maintain the CIPC system.

3.2 Clinician-oriented interface

The clinician-oriented interface is established by MVC model to help analyzing pretreatment parameters for clinical evidences. The system can be constructed by the open source frameworks with the graphical diagrams to combine PCRs and biomarkers from diverse database through networks. In the CIPC, the interface can guide clinicians to concurrently collect and analyze specific clinical markers with instant diagrams for prostate cancer patients. By referring suggestions from participant clinicians for long-term tracking, we herein create computation models based on statistical algorithms to respond expert opinions.

3.2.1 Prostate cancer treatment

Several pretreatment parameters and clinical markers are significant for tracking the disease condition of prostate cancer patients periodically. The CIPC system is proposed in urology clinic for reflecting relationship between QOL and pretreatment parameters such as PSA, clinical classification stage, and Gleason score, etc. Prostate cancer rarely causes symptoms early in the course of the disease. Suspicion of prostate cancer resulting in prostatic biopsy is most often raised by abnormalities found on digital rectal examination (DRE). The presence of systemic symptoms as a result of prostate cancer suggests locally advanced or widely metastatic disease. Growth of prostate cancer into the urethra or bladder neck can result in obstructive and irritative voiding symptoms (Carter et al., 2007). Prostate cancer has greatly benefited from the discovery of tumor markers. Instant observation and comparison of PRO and PCR can be tracked by auto-analysis prior to clinics.

PSA has evolved for the detection, staging, and monitoring of men diagnosed with prostate cancer since its discovery in 1979 to clinical application in the late 1980s through 1990s (Sensabaugh, 1978). Most prostate cancer arises as clinically nonpalpable disease with PSA between 2.5 and 10 ng/mL. The stage regarding how far the tumors have spread for defining prognosis and selecting therapies, and has become an important marker as evaluating prostate cancer. The four-stage TNM system, which includes the size of the tumor (T), the number of involved lymph nodes (N), and the presence of any other metastases (M), indicate how far the cancer has spread for defining prognosis and selecting therapies. Among urologic malignancies, the combination of DRE and serum PSA is the most useful first-line test for assessing the risk of prostate cancer. Particularly, the initial PSA value after a treatment is the most useful clinical information for detecting, staging, and monitoring prostate cancer patients when assessing the risk of prostate cancer (Partin et al., 1997; Pound et al., 1999). The clinical variables can be retrieved from databases of HIS through different networks.

i. PSA Level

The presence of prostate diseases is the most important factor affecting serum levels of PSA (Wang et al., 1981; Ercole et al., 1987). Many studies have made efforts to evaluate other thresholds to maximize the positive biopsy rate of PSA-based screening (Gann et al., 1995). The PSA-related parameters including PSA density (PSAD), PSA velocity (PSAV) and PSA doubling time (PSADT) are considered to improve diagnostic accuracy of PSA. A direct relationship between PSAD and the likelihood of cancer has been documented (Bazinet et al., 1994), and higher PSA densities may be found among groups of men with positive biopsies compared with men with negative biopsies (Uzzo et al., 1995). PCRs can be filtered to rank high risk patients who have relatively smaller prostate volumes when a constant number of biopsies are obtained.

PSAV is the rate of change in serum PSA. A rate in excess of 0.75 ng/mL per year is a significant indicator of prostate cancer for prediction of prostate cancer (Carter et al., 1992; D'Amico et al., 2005). PSAV can be estimated by substituting PSA data into the linear regression equation as Eq.(1) that formulates the arbitrary PSA (P_i) with respect to time (T_i).

$$P_i = \alpha + \beta \times T_i \tag{1}$$

Where, the parameter β represents the slope of equation and is identical to the PSAV while α would be the initial PSA. T_i is available to count by days, months or years.

PSADT is denoted as the duration when the logarithm of PSA doubles and has been evaluated in patients with a rising PSA after local treatment with radiation therapy (Fowler et al., 1994). In Eq. (2), we can substitute the regression equation of PSAV into the half-logarithmic coordinate of $\ln(P_i)$ versus T_i, and a straight line is obtained to calculate doubling PSA at doubling time T_D.

$$\frac{\ln(2 \times P_1) - \ln(P_1)}{T_D - T_1} = \frac{\ln(P_2) - \ln(P_1)}{T_2 - T_1} \quad \text{yields} \quad T_D - T_1 = \frac{\ln(2) \times (T_2 - T_1)}{\ln(P_2) - \ln(P_1)} \tag{2}$$

The relationship of two arbitrary PSAs measured at the time T_1 and T_2 with respect to the doubling time T_D is formulated when $\ln(2*P_1)$ is estimated.

ii. TNM stage

The well-known TNM classification system generally evaluates the size of the tumor (T) by four stages, the extent of involved lymph nodes (N) by two stages, and any metastasis (M) by two stages. For evaluation of the primary tumor: T1 stage presents tumor, but not detectable clinically or with imaging; in T2, the tumor can be palpated on examination, but has not spread outside the prostate; the tumor has spread through the prostatic capsule in T3 stage; and in T4, the tumor has invaded other nearby structures. For evaluation of the regional lymph nodes: N0 present there has been no spread to the regional lymph nodes whereas N1 has been spread. For evaluation of distance metastasis, M0 represent there is no distant metastasis while M1 has that. In this study, version 6 of the TNM system published by the American Joint Committee for Cancer (AJCC) and the International Union against Cancer (UICC) in 2002 is adopted.

iii. Gleason score

The Gleason grading system is based on a low-magnification microscopic description of the architecture of the cancer and is the most commonly used classification scheme for the histological grading of prostate cancer (Gleason, 1966). The predominant pattern that occupies the largest area of the specimen is given a grade between 1 and 5. This number is then added to the grade assigned to the second most dominant pattern; thus, a Gleason sum can be arranged between 2 and 10. This system describes tumors as "well", "moderately", and "poorly" differentiated based on Gleason score of 2-4, 5-6, and 7-10, respectively.

iv. Kaplan Meier survival estimation

The Kaplan-Meier estimator, which is known as the product limit estimator, estimates the survival function from life-time data (Kaplan & Meier, 1958). Let S(t) be the probability that an item from a given group of size N will have a lifetime exceeding t. Corresponding to each t_i is n_i, the number "at risk" just prior to time t_i, and d_i, the number of deaths at time t_i, where i = 1, 2, …, N. Note that t_i is equal or less than ti+1 and the intervals between each time typically will not be uniform. Then, the estimator is with nonparametric maximum likelihood convergence of S(t) in a product of the form

$$S(t) = \prod_{t_i < t} \frac{n_i - d_i}{n_i} \tag{3}$$

When there is no censoring, n_i is the number of survivors just prior to time t_i. With censoring, n_i is the number of survivors less the number of losses. It is only those surviving cases that are still being observed that are "at risk" of an observed death.

v. Cox Proportional Hazard Model

Proportional hazards model is a sub-class of survival models well known in statistics by consisting of two parts: the underlying hazard function to describe how hazard (risk) changes over time; and the effect parameters to describe how hazard relates to other factors, e.g. the choice of treatment, in a typical medical example. The effect parameters estimated by any proportional hazards model can be reported as hazard ratios. The formula in Eq. (4) is recruited for building computation module in the system.

$$h(t, \mathbf{X}) = h_0(t) \exp(\sum_{i=1}^{p} \beta_i X_i), \quad X = (X_1, X_2, \cdots X_p) \tag{4}$$

In which, $h_0(t)$ is the baseline hazard involving t but not X's while X denotes a collection of p explanatory variables X_1, X_2, …, X_p and the model is nonparametric because $h_0(t)$ is unspecified. For PSA variables correlation in prostate cancer treatment, these variables may include age, race, initial PSA, PSAV, PSAD, clinical stage, treatment, and so on.

3.2.2 Instant analytical diagram

The computation models involve statistical modules to achieve pretreatment parameters for clinical requirements. These modules carry out analytical diagrams on the clinician-oriented interface for physicians to instantly study tendency of illness conditions according to the significant pretreatment parameters below.

i. PSA-related information

The PSA-related information such as PSAD, PSAV and PSADT can be calculated due to previous equations and perform real time online analytical diagrams. The graphic interface displays instant diagram of PSA baseline with respect to parameters above. The clinicians can select required item to present possible velocity and doubling time of PSA by checking the date of PSA record from check-box. The diagram can be printed out as the attachment of clinical prescription. Furthermore, the survival and hazard estimation modules are available for instant crossing comparison to avoid time-consuming manual analysis beyond clinics.

ii. Partin table

Gleason grade has been shown to correlate with the pathologic extent of disease but is not sufficiently accurate so that Partin tables are usually referred. The Partin tables include primary clinical stage, serum PSA level, and Gleason score to determine the probability of having a final pathologic stage based on logistic regression analyses for all 3 variables combined (Partin et al., 1993; Partin et al., 2001). The table is important in guiding decisions for prostate cancer. It is a way of predicting cancer's pathologic stage which is determined after the prostate gland has been surgically removed and examined by a pathologist. The probability is referred by following the pathologic stages, due to the tables, as (1) organ-confined disease, (2) established capsular penetration, (3) seminal vesicle involvement, and (4) lymph node involvement. If probability of organ-confined disease is high, then early-stage treatment options are feasible. If the probability of cancer having spread beyond the prostate is high, then other treatment options will need to be considered. Herein, the system adopts the Partin table guided by the National Comprehensive Cancer Network (NCCN).

iii. Risk evaluation criteria

Risk evaluation criteria of prostate cancer is constructed on the basis of large numbers of patients who have undergone radical prostatectomy to aid in the precise prediction of pathologic stage by using multiple clinical parameters as accurate predictors of both cancer extent and long-term outcomes after treatment of the primary tumor (Kleer & Oesterling, 1993). The criteria as shown in Table 1 (D'Amico et al., 2001) can be adopted to stratify patients into low, intermediate, and high risk disease, and to summarize the failure status,

Risk group	Risk factors	Risk (a, b, c) %
Low	T1c or T2a and PSA <= 10 ng/ml and Gleason score <= 6	(<25, 85, 83)
Intermediate	T2b or Gleason score = 7 or PSA > 10 and <= 20 ng/ml	(25-50, 60, 46)
High	T2c or PSA > 20 ng/ml or Gleason score >= 8	(>50, 30, 29)
a. Post-therapy PSA failure at 5 yrs; b. PSA failure-free survival at 5 yrs; c. PSA failure-free survival at 10 yrs		

Table 1. Risk Evaluations for Prostate Cancer (D'Amico et al., 2001; Lin et al., 2011).

Based on the correlations of these pretreatment parameters with the true extent of disease, the RTCDSS can integrate the clinical data and expert opinions available for clinicians to determine the likelihood of disease progression and predict the pathologic stage.

3.3 Integration design

Based on RTCDSS design, the CIPC system is built with open source framework of Java™ technique while Apache Tomcat™ and Oracle™ are selected as Web and database servers,

respectively. The system components with flexible functionality and keep-in-simple-stupid (KISS) interface are designed to enhance the human computer interaction. The system involves database, analysis, management, presentation, and acquisition layers, from right to left in Fig 5, on the modelized architecture by implementing previous methodology.

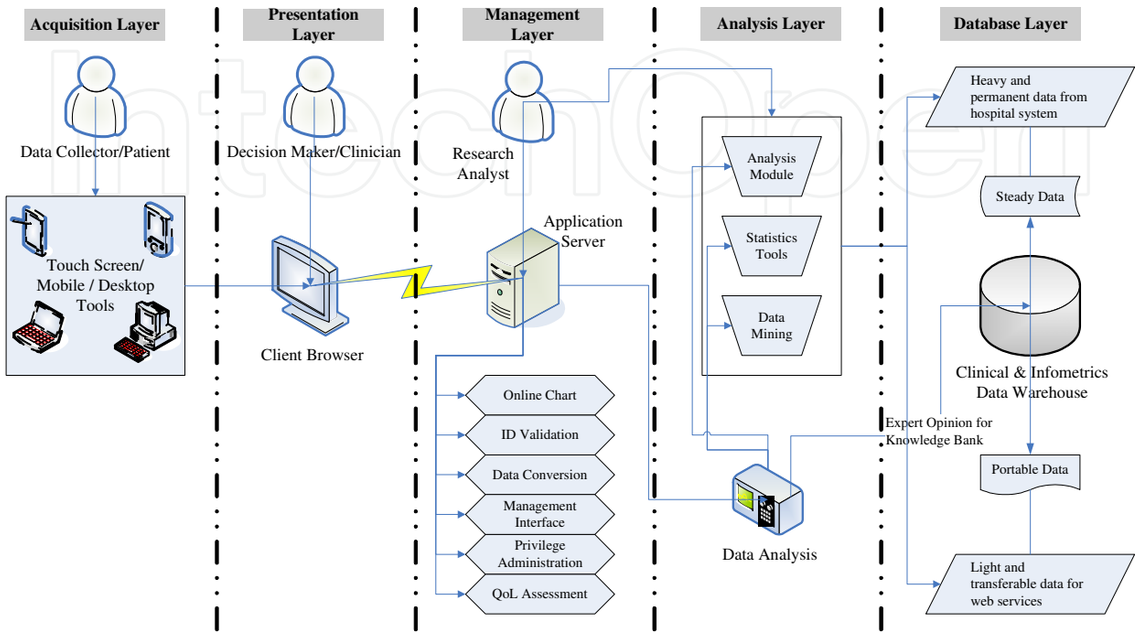

Fig. 5. Five-layer development of RTCDSS infrastructure (Lin et al., 2010).

1. The database layer is the foundation of the system for building clinical data warehouse. Fig 6 illustrates the primary object relationship diagram and schema simplified by entity relationship diagram (ERD), where the attributes denote correlation between QOL domains and treatment effects. The schema combined two sets of fact tables for infometrix and clinical records so that "Answer_Full" and "Answer_Domain" tables store and transform assessment data to QOL domain score, while "Patient_Info" and "Prostate_Cancer" tables retrieve data from PCR. "Answer_Index" is an index table to bridge "Answer" and "Question" tables, which request and arrange assessment data, and derive cube dimensions of PSA, treatment, clinical stages and Gleason scores.
2. The analysis layer assists researchers analyzing data and feeds back statistical results as resource of knowledge bank. In the practice, several types of data file formats converted from database were generated to satisfy different progresses supported by analysis tools. The layer incorporates database and application servers with remote computation or offline data mining and feed expert opinions back to knowledge bank of RTCDSS.
3. The management layer plays the role of control center for managing data flow within the entire system. A management interface is designed to enhance capability of data access functions for health care people and researchers to plot online charts, identify single sign-on, process data conversion, administrate user privilege, and acquire QOL assessment. All modules are built as objects of models for sharing functionality but secured with privilege roles of health care people, clinicians and researchers.

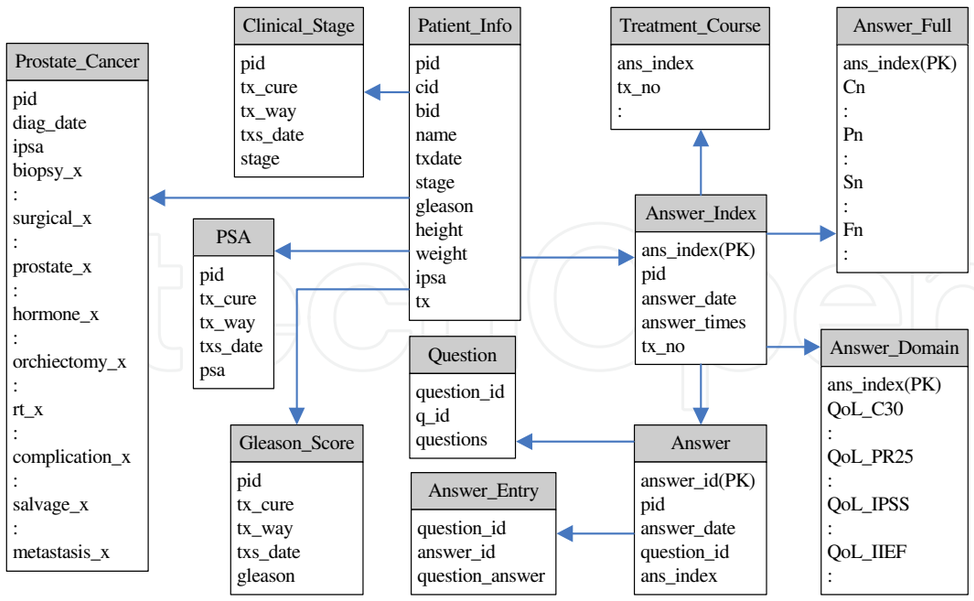

Fig. 6. Object relationship diagram and schema (Lin et al., 2010).

4. The presentation layer is the interface of real time decision support for communication of patients and clinicians. The system presented instantaneous statistical diagrams by referencing expert opinions from knowledge bank for clinicians. In the CIPC, it performs the real time QOL evaluation with respect to mean value of other patients, initial PSA, Gleason score, treatment stage, etc. Clinicians are able to indicate treatment indexes online through graphical interface for decision support.
5. The acquisition layer becomes the data receiver of the system to execute QLQ online behind accessibility interface design. Perhaps most of patients fell uncomfortable, either in physical or mental status, and avoid writing paper sheet by themselves as answering the assessment questions. In the practice, the touched screen, the sizeable large fonts, and the audio media with ear phones are functioned for more accessibilities of patients.

Based on the system design, clinicians and researchers are available to access infometrix data after patients finished assessments through patient-oriented interface. For securing patients' privacy, the clinical records must be forbidden from internet users except of particular clinical people; therefore, the primary database server for instant infometrix becomes the data center in clinic site; meanwhile, a backup database server in research site allows restore data automatically through specified protocol.

4. Practice of patient-to-clinician strategy

The mechanism of innovative CIPC is compiled with online assessments of QOL and PRO modules and the interactive interface is functioned for clinical requirement to efficiently automate the clinical procedure. Beyond the patient- and clinician- oriented interfaces, the P2C communication becomes the strategy through interactive guideline with treatment risk evaluation to provide real time references for decision making. For adapting the CIPC with the P2C strategy into hospital, quasi-real time data transportation is adopted for flexibly arranging administration schedules due to the hospital management policy.

4.1 Interactive guideline

The proposed framework was practiced in the urological cancer department of CMUH. Both of the campus and hospital networks were incorporated with heterogeneous database management. The necessary prostate cancer data resources were extracted and filtered from the cancer data center of CMUH. The interactive guidance design for clinician-oriented interface is evaluated with regard to how well it helps clinicians interact with patients and provide efficient clinical care. With practice of the CIPC system, PROs with QOL can be collected through clinical infometrics and be referred by interactive guidelines for clinical decision support. Herein, the guideline with QOL domains, risk evaluation table, interactive treatment chart, and automated prescription will be discussed. Through the RTCDSS, the approaches regarding clinical infometrics for patient outcome collection of QOL and interactive guideline for clinical decision support will be highlighted below.

i. Statistics of QOL domains – The diagram on Fig 7 lists details of the last assessment results involving the questionnaires, range and scale in each domain, effect and missing items while answering questions. All QOL domains reflect the functions and symptoms of a patient in physical and mental conditions during the treatment cycle. Clinicians can realize statistic results of patient's disease conditions at the beginning of clinic. The historical QOL scores with PSA values shown in Fig 8 provide an overall chart for clinician and patient. It helps the patient describe their real health condition to avoid ambiguous conversation.

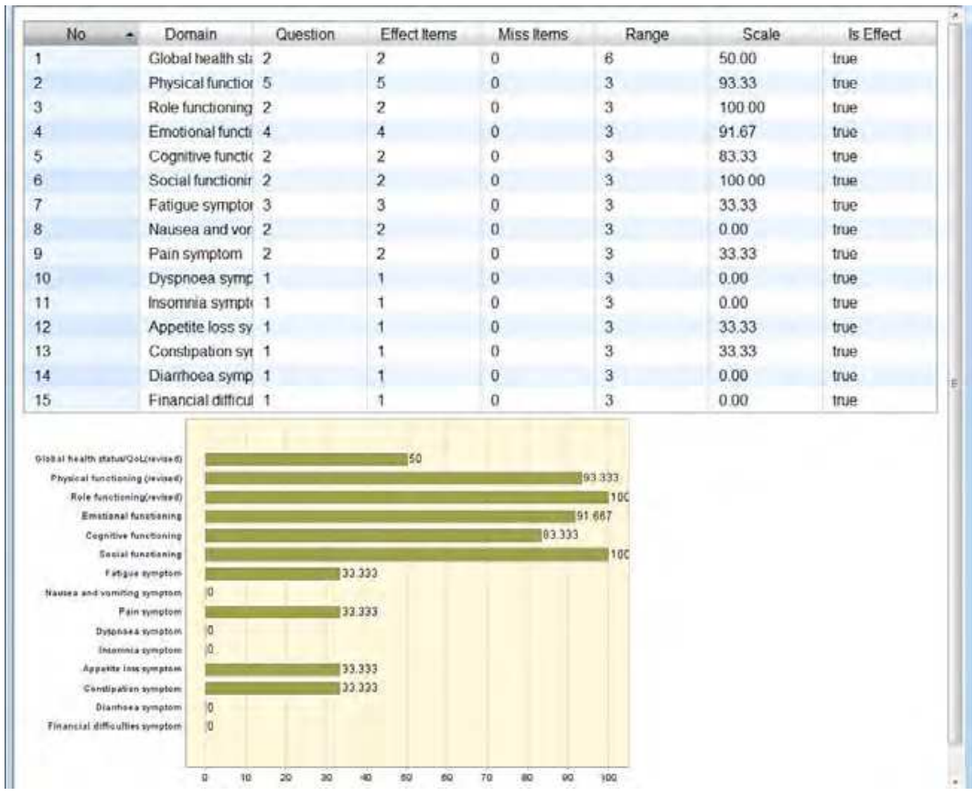

Fig. 7. Statistics of QOL domains (Lin et al., 2010).

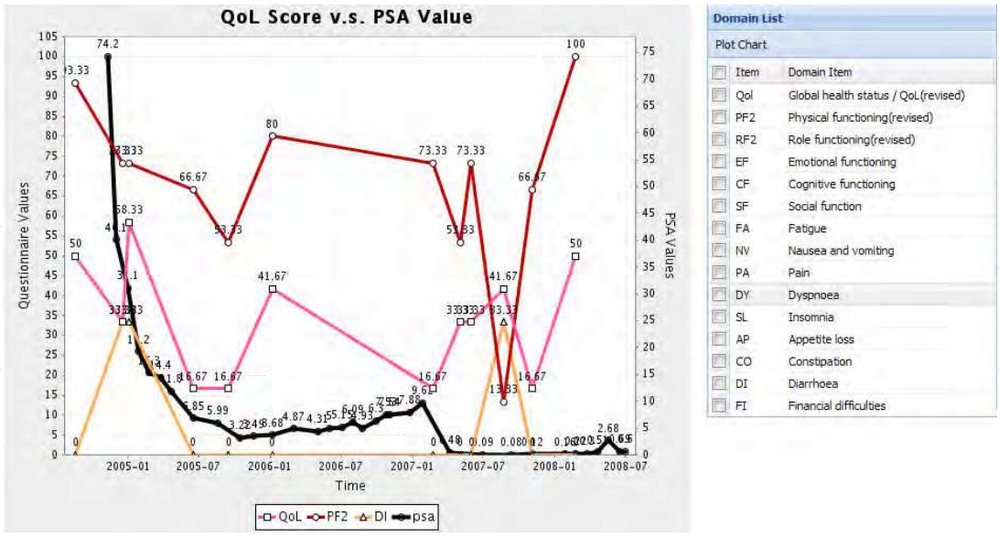

Fig. 8. Graphical QOL diagram with clinical marker - QOL vs. PSA baseline (Lin et al., 2010).

ii. Disease evaluation of the PSA level – Fig. 9 shows the PSAV and PSADT values with PSA baseline while the clinician enters the patient's ID and selects an arbitrary time interval. The real-time diagram shows the disease information of the patient's PSA level throughout different treatments. It can be seen that the system retrieved the patient's data from PCRs and listed related pretreatment parameters for an overview of the patient's disease history. The baseline of PSA is completely plotted during different treatment cycles with significant points (such as the initial PSA) of note.

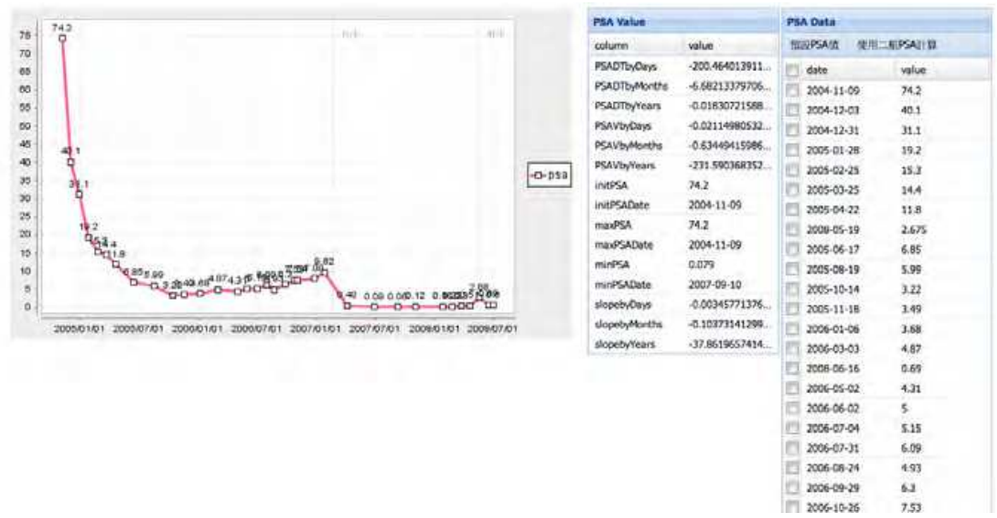

Fig. 9. Interactive guidance to help computing PSA-related data online (Lin et al., 2011).

iii. Risk guidance with the Partin table – Using the Partin table module in the system, the clinician can easily find and input pretreatment parameters such as PSA, Gleason score, and a clinical stage to determine the risk percentage shown in Fig 10. The clinician can find and input pretreatment parameters like PSA, Gleason score and clinical stage for determining the risk percentage. In this case, the clinician input T1c, 32.4, and 5-6 for

TNM stage, PSA value and Gleason grade, respectively; the system immediately estimated risk percentage in high risk group due to Table 1 that shows more than 50% for 5 years of post-therapy PSA failure as well as 30% and 29% for 5-year and 10-year PSA failure-free survival, respectively.

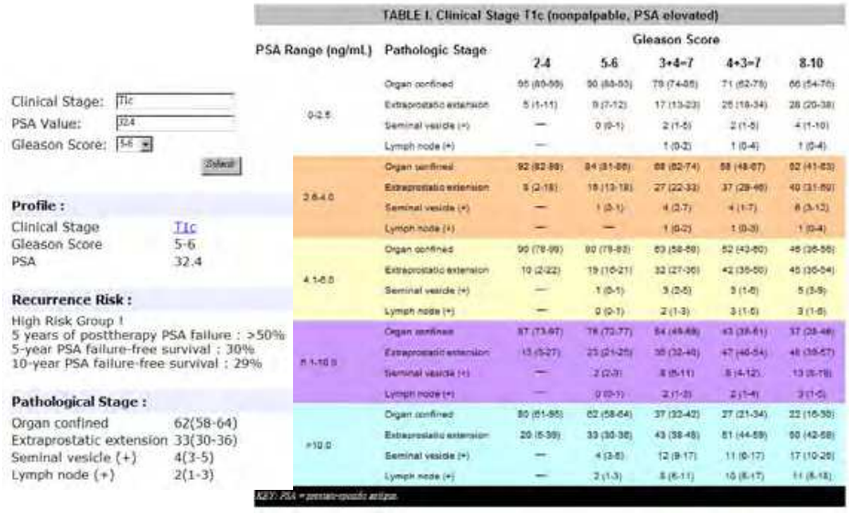

Fig. 10. A screen shot of real-time decision support that the clinician can use to evaluate the recurrence risk and the Partin table online by flexibly adjusting clinical data (Lin et al., 2011).

iv. Interactive guidelines for treatment reference – Clinicians can interact with the guideline thus the phase of treatment procedure based on the criteria are carried out for decision making as PCRs are input. For example on Fig 11, if the PSA was 25.5ng/ml, the clinical stage was T3, Gleason score was 8, life expectancy was more than 5 years,

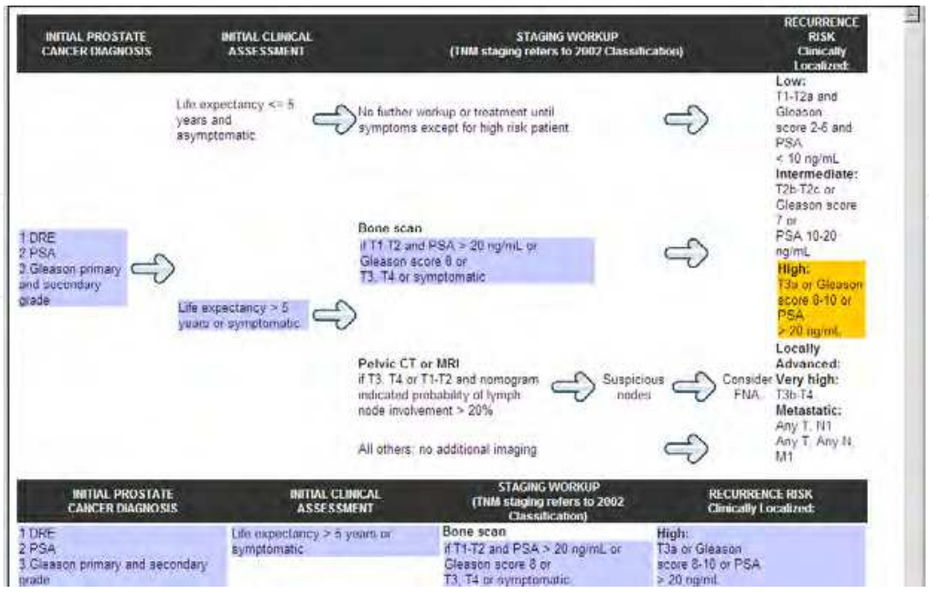

Fig. 11. Interactive guideline of CIPC system for overview guidance that can highlight a suitable prostate cancer treatment flow based on a patient's clinical data.

with symptomatic therapy as bone scan; the blue region will pop up for overview and be duplicated to the bottom area of the screen to signify the cure steps for reference. Meanwhile, the risk evaluation will be highlighted by yellow mark at the right side. By providing a comparison with the non-highlighted steps on the overview of guideline flow, the flowchart allows the clinicians to identify the current stage and see what the next step is.

v. Special diagnostic chart for automated prescription – To prevent typing error by clinicians as input electronic PCRs, the design of special diagnostic chart lists primary clinical markers for selection. Fig 12 displays an interface that the clinician can select required item to immediately produce unified statement of automated prescription as concurrently inputting data into the database for related hospital information systems.

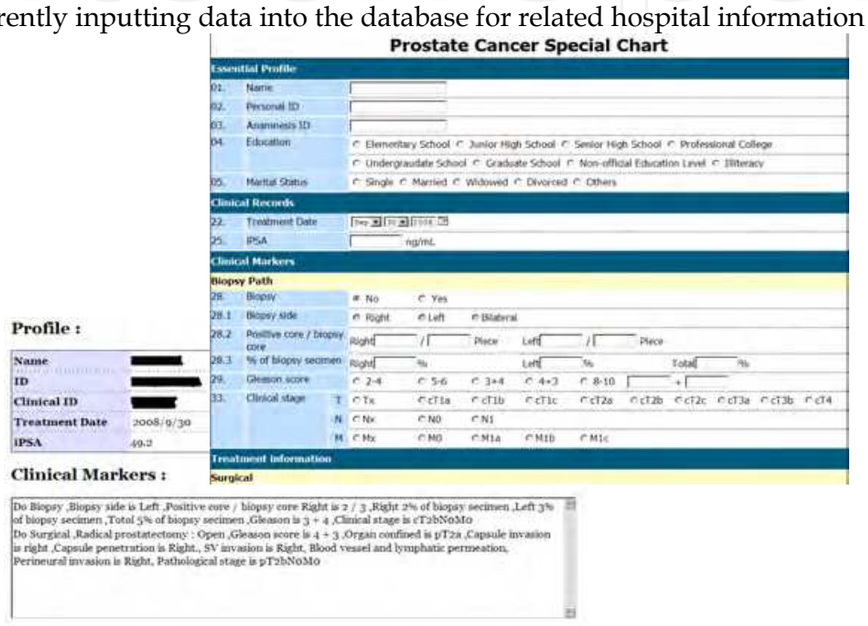

Fig. 12. Clinical interfaces of special chart and automatic prescription.

4.2 P2C communication

Before development of the CIPC, prostate cancer patients were tracked by handwriting QOL assessments during cure period but lacks of automatic electronic progress. Because of physical or mental suffering, patients used to complete paper works through conversation with health care people. Meanwhile, doctors took many efforts to explain PROs at clinic time by printing out PCRs for advices. Therefore, the RTCDSS was established by practical requirements on increasing interaction with patients to consolidate relationship as well as reducing official burden of health care people. Following the CIPC procedure mentioned in Fig 3, moreover, all personal data were encrypted as being written into the database to avoid being falsified and stolen. Hence patients have enough confidence under risk avoidance to comply with clinicians' guidance. In the practice, patients read the introduction and login with personal ID to start the QOL assessment. As shown in Fig 13, there's only one question per browser page and the patient can adjust suitable font size on the touched screen in addition to consider the voice control button for assistance. On the

other hand, the clinician is able to compare patient's record with others who meet similar markers and evaluate assessment results by figures or charts for advanced consultation.

Fig. 13. Screenshot of QOL questionnaire page of CIPC system for prostate cancer patients.

i. *Cross comparison* – the example chart shown in Fig 14 supports the clinician and patient to take an overview for discussing the variation of QOL compared with the mean value of other patients in similar conditions. It enhanced the patient with confidence to follow doctor's comments for advanced treatment. In the pilot study, patients reflected motivation with more interaction to clinicians as recognizing QOL history with clinical markers.

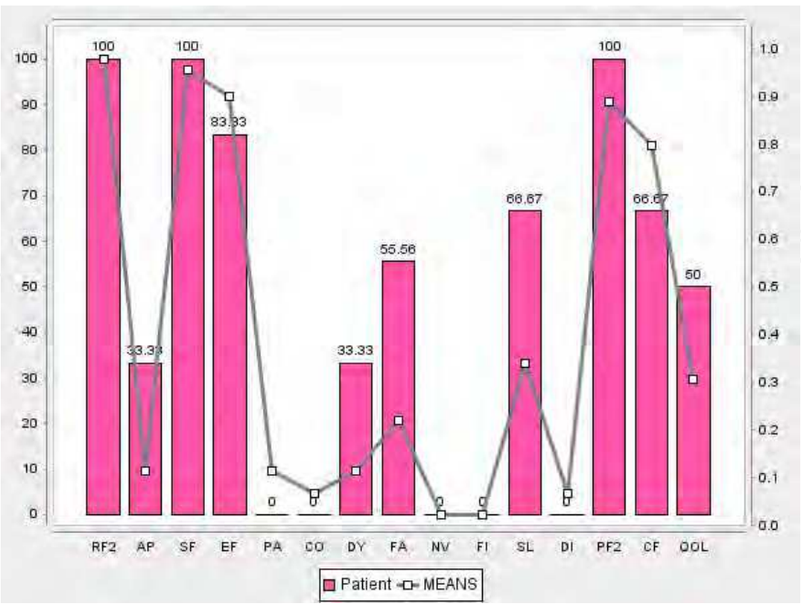

Fig. 14. Cross comparison after assessment (Lin et al., 2010).

ii. *Overall evaluation* – Fig 8 displays the change of QOL, which became better after some particular time because of the successful prostate surgery. Referring the PSA history compared with selected QOL domains, patient's PSA was improved after accepting surgery operation in early 2007. However, a suspected point was observed in the period around July in 2007 under stable PSA baseline, the patient felt uncomfortable since the physical function was suddenly getting worse while the diarrhoea symptom became significant. It assisted the clinician recognizing whether the problem was caused by the prostate disease.
iii. *Real time informetrix categories for patients* – The best practice of the developed system should be applied for patients whose disease can be chronically and periodically tracked by specified clinical markers. Therefore the design of real time infometrix for prostate cancer patients displays their PSA values associated with QOL domains to provide categories of physical, role, cognitive, emotional, and social functions in addition to that of fatigue, pain, nausea and vomiting symptoms. Particularly, it reflects urinary, bowel, treatment-related symptoms and male-related sexual functioning. Patients can recognize personal health condition immediately with respect to others through the instant graphical chart in the clinic.

From aspect of participant clinicians, they use the system mainly for functional assessment as well as for highlighting patients' most bothersome symptoms. The most common benefits would include enhancing communication with patients, identifying under-reported symptoms for clinicians and increasing efficiency in clinics. To assess the advantage of the developed system for users, some interesting problems are observed and discussed below.

i. *Online informatics for clinicians* – The greatest advantage conferred by this system is its ability to assist in the treatment of chronic diseases that can be periodically tracked using the specific clinical variables as shown in Fig 9. The online informatics displays PSA-related data to provide categories of diagnostic information. Clinicians can identify patients' health conditions directly with respect to treatments through the instant diagrams. The participants reported that the RTCDSS saved hours, even several days, of analysis for them by providing instant computation of the relevant parameters.
ii. *Improvement in clinician-patients relationships* – Several studies in chronic diseases suggested that feedback of health status data may facilitate communication between patients and clinicians to enhance patients' care (Kazis et al., 1990; Wagner et al., 1997). Accordingly, incorporating QOL assessments in routine clinical oncology practice can heighten physicians' awareness of their patients' (Detmar et al., 2002). In the CIPC, clinicians predicted potential disease risk as shown in Fig 10. Thus, the clinician could refer to the interactive guideline in Fig 11 while offering the suggestions, ordering the proper treatment, and tracking the follow-up conditions. Correspondingly, the system assists clinicians to discover reliable QOL information of patients since they would like to confess more factual illness status. The auto-data transportation procedure minimizes manual mistakes to ensure data quality and confirm the RTCDSS has capacity to improve clinician-patient relationships.
iii. *Enhancement in P2C communication* – Both of online infometrics and interactive guideline in routine clinical practice can enhance clinicians' awareness of their patients'. Herein, clinicians use the developed system to discover reliable predictive information for prostate cancer patients through real time statistics and computation. Therefore, manual mistakes can be eliminated by the automatic transportation procedure to ensure

data quality. It confirms that the framework of the real time CIPC system is possible and feasible to improve communication between patients and clinicians.

4.3 Advantage and difficulty

The biggest benefits of CIPC system would likely enhance clinical care for patients, support optimal treatment options for clinicians, and increase efficiency in clinics. The advantages of the developed system can be summarized: (a) ensuring quality of clinical care, (b) providing the clinicians real-time online clinical informatics, (c) enhancing P2C communication, and (d) improving clinician-patients relationships. Behind the successes above, however, the past studies also experienced difficulties as practicing the new system restricted by management policies and a flexible strategy is considered to satisfy the actual condition. The hospital management and security policy limited the CIPC system only work partially for proposed clinic beyond the hospital network. As adapting the system to the legacy HIS, noises of diverse systems are always counted for integration. The structural reformation on original HIS should be avoidant but through gradual data immigration under administration rules.

Herein, the CIPC system was installed in the server at the urology clinics in which an individual patient used to make appointment on a specific day of week. In compliance with hospital management for safety policy, the power of clinic room was turned off after clinics and the CIPC server must be shutdown. To avoid conflicting with the HIS but ensure data transformation can synchronize between inconsistent systems, a process scheduling module was employed for data importation between the HIS and CIPC system. The module was embedded in both systems to retrieve required data from the backup log of CIPC system at a specified time point and transform data into the HIS database. As a result, clinicians could obtain the last patient outcomes if their data were imported into the HIS just before clinic time. Fig 15 illustrates three data-update jobs in a cycle as considering two scheduling points

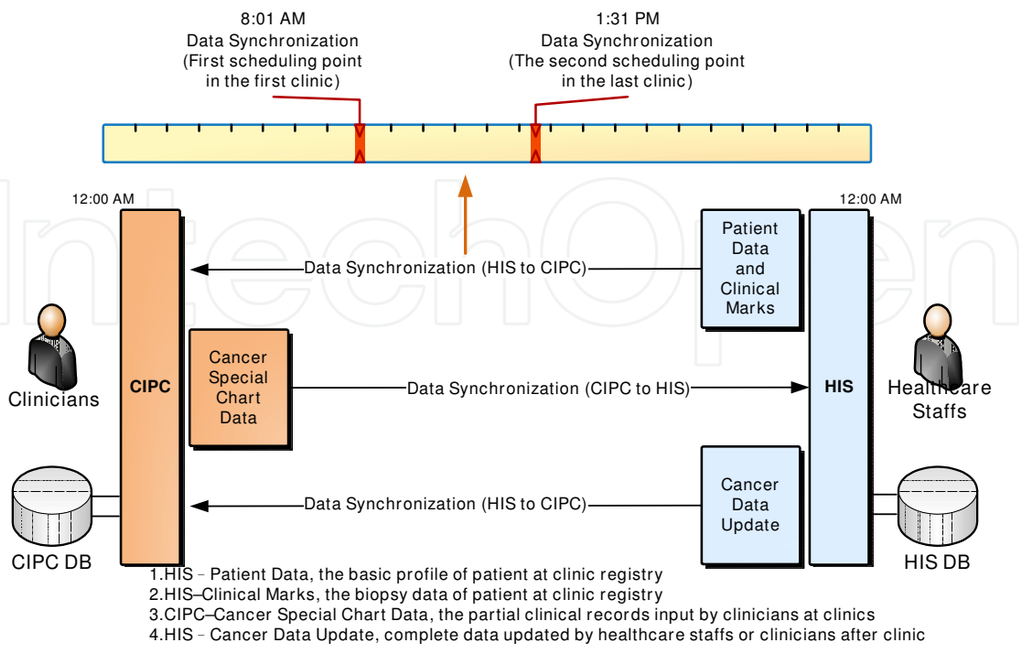

Fig. 15. Processes scheduling of data transformation for heterogeneous system integration.

before and after the clinics. At the first point in the first clinic, the required data are replicated into the backup log. In the cycle, clinicians activate the start button to load PCRs and clinical markers from the log into CIPC database; and then, the new outcomes will be input during clinic time. After the clinic, clinicians can update complete remarks of PCR to CIPC database and all data will be restored to the backup log concurrently. At the second point in the last clinic, the log will be retrieved in schedule and be transformed into the HIS. Once the CIPC server is activated, the scheduling will be automatically started. In the study, the process scheduling was executed twice per week by urological clinics. The "quasi real time" strategy above can help solving the difficulty while implementing a new development into the legacy system under management restriction.

4.4 Practice discussions

The system confers the following benefits: (1) clinicians can explain health conditions clearly to patients by visualized clinical variables and pretreatment parameters; (2) patients are more easily convinced by evidence-based diagrams before accepting the risk evaluation of treatments and the treatment quality can be confirmed; (3) the design presents real-time disease and risk evaluation while the interactive guidelines with treatment suggestions offer the clinician efficient online tools for instant decision making; (4) the proposed framework is constructed upon the Web-based MVC architecture that consists of reusable models, making it flexible and adaptable with many hospital information systems. In the pilot study, more than 90% of users approved the innovative design. Clinicians learned more reliable information regarding patient's private QOL. The efficient diagnosis and communication certainly encourages the advanced study. With RTCDSS for predicting treatment assistance, diverse functionalities can be expectant for advance clinical decision, context-specific access, automatic risk assessment, personal digital assistant screens, as well as practitioner performance and cost-effectiveness on patient outcomes (Aaronson et al., 1993). In the future, the real-time decision support functions can be expanded flexibly by involving other diagnostic variables and modern technologies like RNA and DNA studies. It can also incorporate with advanced prediction models such as nomograms, which may help patients and their treating physicians make informed decisions based on the probability of a pathologic stage, the patient's risk tolerance, and the values they place on the various potential outcomes (Stephenson et al., 2005). The system will aid the rational selection of patients to undergo definitive therapy.

5. Conclusion remarks

This study reveals clinical and infometrics progress with information technology to establish fundamentals of the RTCDSS. Methodologies include MVC architecture, Web services, online analytical process, clinical data warehouse, object relation mapping, and AJAX while the practical CIPC system is implemented for approval. The infrastructure integrates five layers to establish expandable models with flexibility for providing accessible functions in clinic applications of prostate cancer. Heterogeneous database systems distributed in hospital, clinic and campus networks were integrated for an expert bank with remote data backup and disaster recovery. A patient- and clinician-oriented interface is considered as a major subject to assist P2C communication. In advance, the patient outcome is available to offer instant statistical charts for decision making as well as improved communication and relationship

between clinicians and patients. Furthermore, the RTCDSS enables interactive guideline for knowledge feedback, facilitate decision-making, and to improve quality of care.

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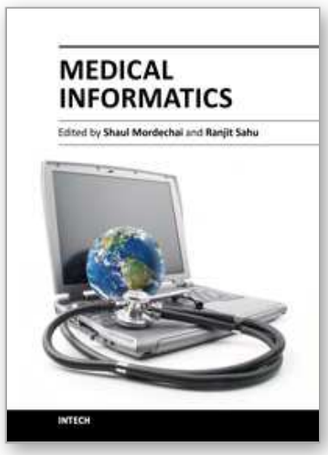

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Information technology has been revolutionizing the everyday life of the common man, while medical science has been making rapid strides in understanding disease mechanisms, developing diagnostic techniques and effecting successful treatment regimen, even for those cases which would have been classified as a poor prognosis a decade earlier. The confluence of information technology and biomedicine has brought into its ambit additional dimensions of computerized databases for patient conditions, revolutionizing the way health care and patient information is recorded, processed, interpreted and utilized for improving the quality of life. This book consists of seven chapters dealing with the three primary issues of medical information acquisition from a patient's and health care professional's perspective, translational approaches from a researcher's point of view, and finally the application potential as required by the clinicians/physician. The book covers modern issues in Information Technology, Bioinformatics Methods and Clinical Applications. The chapters describe the basic process of acquisition of information in a health system, recent technological developments in biomedicine and the realistic evaluation of medical informatics.

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