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Developing Decision Support Systems in Clinical Bioinformatics

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Summary

There is a growing demand for tools to support clinicians utilize genomic results generated by molecular diagnostic and cytogenetic methods in support of their decision-making. This chapter reviews existing experience and methods for the design, implementation and evaluation of clinical bioinformatics electronic decision support systems (EDSS). It provides a roadmap for identifying decision tasks for automation and selecting optimal tools for building task-specific systems. Key success factors for EDSS implementation and evaluation are also outlined.

Key Words: decision support systems, decision-making, clinical bioinformatics; genomics; artificial intelligence; risk assessment.

Abbreviations: EDSS – electronic decision support systems; LOINC – Logical Observation Identifier Names and Codes; ROC – receiver-operating characteristic curve; SNOMED® — Systematized Nomenclature of Medicine; UMLS – United Medical Language System

1. Introduction

Computerized decision support systems have become an essential part of the vision of evidence-based decision-making, aimed at enhancing the quality and effectiveness of clinical decisions ***(1,2)***. The clinical decision process is challenged by the amount of clinical data now available, and the expanding knowledge base generated by new technologies and clinical trials. For example, there are estimates that in just a few years, primary care practitioners will have to know how to employ as many as 100,000 new genetic screening tests ***(3)***.

From: *Methods in Molecular Medicine, Vol. 141: Clinical Bioinformatics*
Edited by: R. J. A. Trent © Humana Press, Totowa, NJ

Decision aids can significantly reduce human error and have been advocated as a mechanism for the translation of genomics, proteomics, transcriptomics, and metabolomics into new clinical decision models, leading to more personalized medical approaches ***(3)***. Decision aids with a clinical bioinformatics focus have been recently developed including patient-specific risk assessment tools with potential for early warning, risk prediction and assessment, and treatment follow-up ***(5–7)***. They target the range of monogenic inherited disorders, somatic mutations and gene expression profiling as well as complex multifactorial disorders ***(8)***. For example, personalized risk calculators for breast cancer (*see* **Note 1**) and preoperative complications based on genomic data have been developed ***(5,9,10)*** (*see* **Note 2**). They also notify clinicians when their patients might be eligible for a pertinent clinical trial based on either their genotypic or phenotypic patient characteristics ***(3)***.

We define electronic decision support systems (EDSS) as tools that provide access to knowledge stored electronically, and that aid clinicians in making decisions. They encompass a variety of systems and interventions such as computerized alerts and reminders, expert systems, electronic clinical guidelines, practice protocols, pathology order sets, and clinical workflow tools. Software designed to support biomedical research tasks such as sequence similarity and alignment assessment, gene or protein discovery and prediction, and genetic classification and automated sub-typing algorithms have been reviewed elsewhere ***(11,12)*** and will not be considered here (*see* also **Chapter 17**).

EDSS in clinical bioinformatics do differ from traditional decision aids in some ways, usually because they focus either on new clinical tasks or

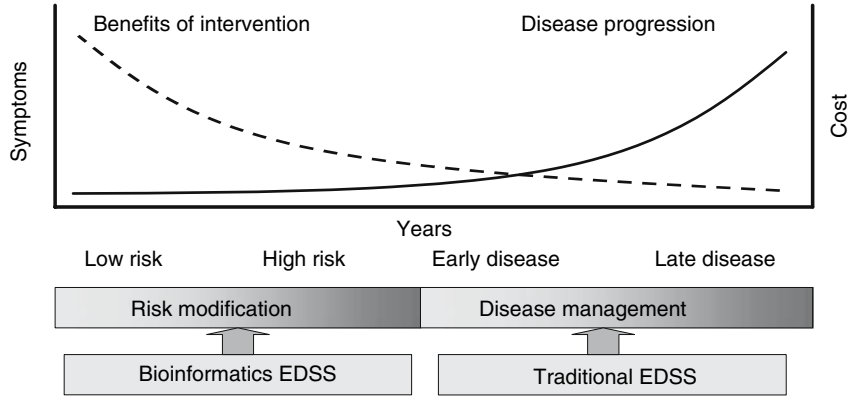

Fig. 1. Risk assessment decision support.

new types of information. Specifically, they may address decisions related to early detection and prognosis of diseases at the pre-symptomatic stage (**Fig. 1**) and utilize risk calculations based on genomic, proteomic or transcriptomic data. Such decisions are often bound by significant uncertainty, they are time-consuming, and clinicians are unlikely to be familiar with these tasks.

Clinical bioinformatics EDSS, in contrast to conventional EDSS, can enhance our capacity for early detection and treatment allowing time for preventative interventions. For example, the assessment of alternatives is assisted by calculation of patient-specific risks of diseases with a large genetic component or outcomes associated with the carriage of genes with high penetrance and processing complex molecular typing patterns and issuing clonal alerts when matching genotypes are detected.

Examples of task-specific clinical decision support systems in use are listed in **Table 1**. Cancer prognostics has been one of the first test cases for bioinformatics EDSS, given the fact that cancer is caused by genomic instability, and

Table 1
Task-specific decision support systems in clinical bioinformatics

Task	Information Support	Examples of Systems
Provision of information relevant to the decision to assess alternatives	Evidence-based information about options and chances of different outcomes occurring with these options Education and decision counseling	Risk Assessment in Genetics (RAG) ***(5)*** Breast cancer management decision aid ***(13)***
Help with the structuring of a decision and preference clarification	Information about diagnostic biomarkers and biomarkers of disease progression Information about personal risk levels	AdjuvantOnline www.adjuvantonline.com
Processing of the information	Calculation and/visualization of patient- or population-specific risks Choice of the 'best' option e.g., the most cost-effective one	HIV genotypic resistance test interpretation systems ***(7)*** Biosurveillance alerts (identification of molecular clusters) ***(14)***

microarrays potentially allow assessment of patients' entire expressed genomes. Analysis of breast cancer patients' expression patterns can already be highly correlated with recurrence risks ***(15)***. Family breast cancer risk assessment tools to estimate patient susceptibility, survivability and recurrence have been employed to identify individuals at high risk of cancer who may benefit from targeted screening or prophylaxis, e.g., tamoxifen chemoprevention for women aged 35 or older with a 1.67% or higher 5-year breast cancer risk cutoff calculated on the Gail model ***(9)***. Evidence suggests that EDSS can successfully support tasks related to clinical decisions associated with genomic medicine by providing relevant information at the point of decision-making ***(13,16)***.

2. System Design

2.1. Choice of Tasks Suitable for Automation

The design of a clinical EDSS begins with the characterization of a decision task, and includes identifying the available data, the available knowledge to guide the decision process, the setting in which the decision is made, the decision maker's specific needs and resources, the task's informational structure and the specific information needs of defined subtasks such as data input. Failure to adequately characterize the task to be supported is a common cause of poor system performance once deployed in a working setting, independent of the quality of the software system itself. Indeed more than half the errors which occur during systems development may be due to requirements errors (where the requirements specification does not match actual user requirements) ***(3)***.

Practitioners with different training and clinical roles may prefer quite different tools to optimize their decisions. For example, a primary care practitioner (also called general practitioner, or family physician—*see* **Chapter 19**) dealing with a patient anxious about her breast cancer family risks will probably need a very different tool compared to that required by a specialist surgeon advising the same patient about her treatment options. The uptake of EDSS is also influenced by the attitudes of decision-makers. There is significant variability in personal beliefs and preferences for evidence seeking and decision support between different clinical professional groups and individual clinicians.

Decision support is especially relevant for tasks that are cognitively demanding, routine and high volume, or are error-prone or infrequent but have important outcomes. Increasing complexity of a decision process is likely to be associated with an increased risk of human error, either because the decision task exceeds inbuilt human cognitive limits such as short term memory, or

because of work-arounds or heuristics which attempt to simplify the task but result in poorer decision outcomes. A corollary is that EDSS are unlikely to be adopted in situations in which they impose additional workload but deliver minimal additional benefit, e.g., for routine clinical decision processes which are well understood, are of minimal complexity and impose little cognitive load. Traditionally areas of high adoption for EDSS include clinical laboratories, where decision volumes are high, or in medication prescription support, where the complexity and risk of drug-drug interactions is such that unassisted prescribing becomes an unacceptable and unsafe clinical practice.

If decision support does not reduce a complex task into a simple one, without loss of decision quality, then the performance of the task is unlikely to benefit from automation. Complexity of a task is thus a central feature in determining EDSS success ***(16,17)***. From the perspective of information theory, task complexity measures the amount and structure of the information that needs to be processed. Complex tasks may have a large number of subtasks, inputs and products with elements that are probabilistic in their behavior and may evolve over time. The process of decision-making and flow of associated data are often represented in functional specifications as Data-Flow Diagrams (*see* **Fig. 2** for an example). Decision complexity can be assessed by one or a combination of approaches, e.g., minimum length of the message ***(18)***, evaluation of cognitive effort ***(19)***, and Clinical Algorithm Score ***(20)***. To decide whether automation will benefit a task, the following stages have been suggested as a good filtering process:

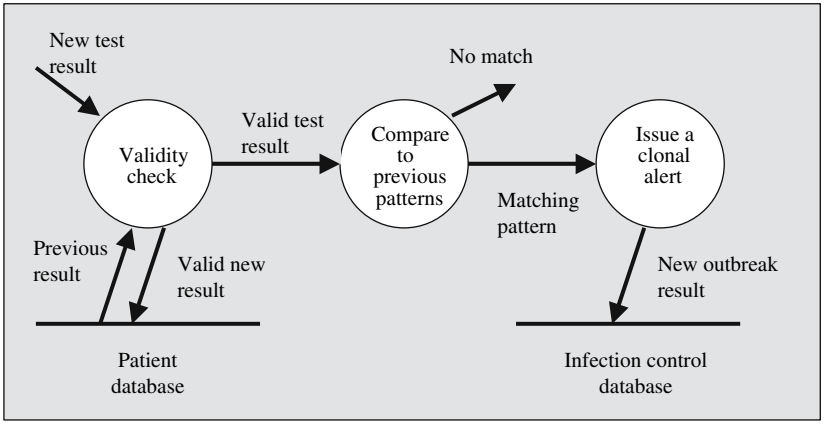

Fig. 2. A data-flow diagram that graphically represents the process and data flows within a biosurveillance system. Bubbles depict processes, vectors depict data flows, and straight lines depict databases.

1. Select the domain and decision tasks
2. Evaluate the complexity of knowledge required for the clinical tasks selected
3. Select the (potentially) most cognitively demanding tasks based upon the comparison of their complexity
4. Assess unaided and EDSS-aided cognitive effort for the selected tasks, to determine if complexity reduction is possible with the use of an EDSS
5. Select computational tools to achieve reduction of task complexity for the user

Sintchenko and Coiera ***(17)*** provide more details on the specific methods for task complexity assessment.

2.2. Building the EDSS

2.2.1. Components of an EDSS

A decision support system at its most abstract encodes one or more *decision procedures* within a *knowledgebase*, and based upon data presented to it by a *database*, draws inferences based upon a predefined set of *decision rules*. The knowledgebase is essentially a store of decision procedures, which is used to generate the EDSS recommendations (**Fig. 3**). For example, a set of if-then rules might be used to encode which diagnosis is most likely based upon the presence or absence of patient data.

The decision rules are the methods used to match the knowledgebase to the database, and are typically either the laws of probability, e.g., when the EDSS is required to make suggestions based upon likelihoods, or the rules of logic as might occur when knowledge is encoded as a set of if-then rules. Other well-known decision methods include neural nets and decision trees (*see **(8)*** for more details). The level of accuracy needed for a prediction rule to be clinically

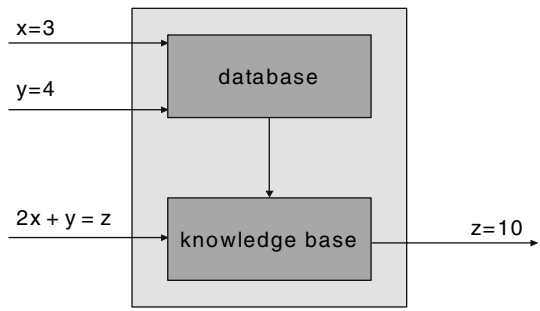

Fig. 3. A decision support system encodes one or more decision procedures within a *knowledge base*, and based upon data presented to it by a *database*, draws inferences based upon a predefined set of *decision rules **(8)***.

useful is more stringent that necessary for determining that gene expression profiles significantly differ between two groups. For example, a predicted 70% recurrence probability should be treated quite differently by clinicians if the associated uncertainty is 30%, than if it were 2%.

The challenge for most EDSS is the process of building the knowledge base. Traditionally there have been two separate processes available. In well-understood domains, where human experts are available to articulate the decision procedures, the knowledge base can be hand crafted using one of several different knowledge elicitation procedures. Perhaps the most widely used and robust approach to hand crafted knowledge based development is the ripple down rule (RDR) approach in which experts provide rules to classify data sets such as laboratory results, and refine the knowledge base only when the initial rule set fails ***(21)***. In domains where knowledge is less explicitly modeled, then automated methods for knowledge base construction are favored.

2.2.2. Automated Knowledge Base Development

Machine learning or data mining methods are of particular interest in clinical bioinformatics, where explicit knowledge is scarce or rapidly evolving, but where there are large data sets which can be processed to discover likely relationships between clinical conditions and biological markers. A wealth of literature describes computational techniques to discover and explore quantitative associations between classes or clusters and to generate semantic descriptions of clinical categories, such as types of disease or prognostic conditions ***(6,22–24)***. Most such methods include a training phase run on samples whose classes are already known, and a testing phase, in which algorithm generalizes from the training data to predict classification of new samples (**Fig. 4**). Because of this directed training phase, prediction methods are referred to as "supervised" classification methods.

For genomic or proteomic data, prediction generally refers to the classification of patients' samples by characteristics such as disease subtype or response to treatment ***(24,25)***. Choosing a prediction method requires selecting from a vast range of techniques. Conventional linear discriminant methods have been extended to include weighted voting ***(26)***, shrunken centroids ***(27)***, and compound covariates ***(28)***. Powerful machine learning approaches are also k-nearest neighbor prediction and neural networks ***(24)***. Two other classes of algorithms are of growing interest for multidimensional learning problems: support vector machines and decision tree classifiers ***(29,30)***. The number of classes in the prediction problem and small sample size may impose additional constraints on the choice of algorithms. Whereas decision trees, neural networks

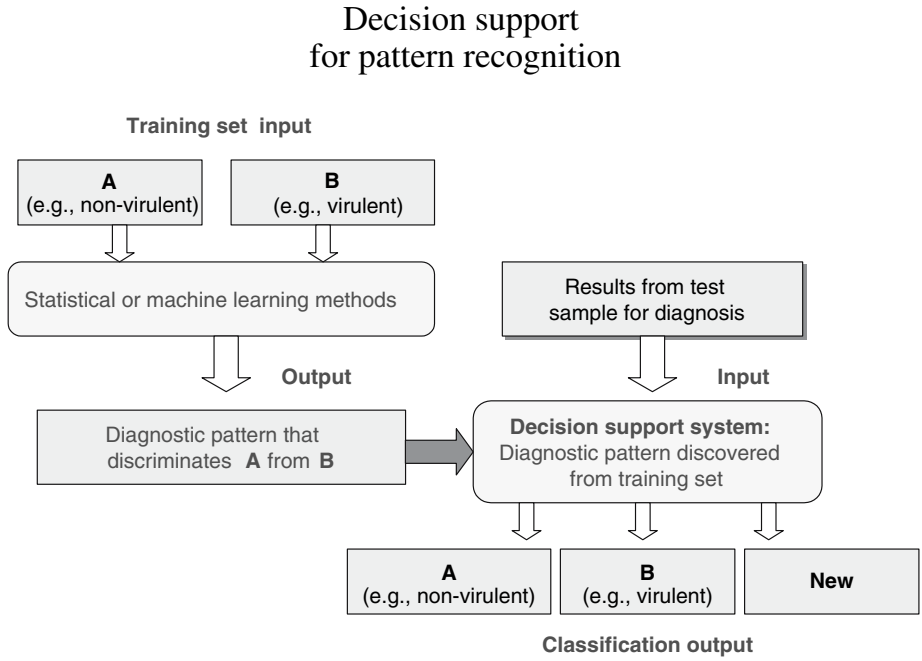

Fig. 4. Classification of data using machine learning approaches.

and k-nearest neighbors can, in principle, separate any number of output classes, support vector machines and linear methods are inherently binary.

There is no universal pattern recognition or classification model to predict molecular profiles across different data sets and medical domains. Many classification and knowledge discovery problems may require the combination of multiple techniques not only to improve the accuracy and efficiency of the analysis task (**Table 2**), but also to support evaluation procedures ***(24)***. There are several tools that integrate open and scalable research platforms, e.g., WEKA—Waikato Environment for Knowledge Analysis ***(40)***.

Table 2 outlines the main stages in preparation of a training data set for use by a machine learning algorithm. Data invariably require some preprocessing to "clean" it of noise, ensure that classification labels are applied consistently to all examples within the data set, and often will require some attempt to identify the features within the data set most likely to be associated with the biological phenomenon of interest. Whilst some algorithms will look for the most useful features, others will benefit from the use of human domain expertise in selecting a useful subset of the full feature set for learning. Simultaneous consideration

Table 2
Machine learning scheme

Step 1. Preprocessing	
Objectives	Removal of irrelevant or redundant data, noise reduction and normalization of the data from different samples
Methods	1. Heuristic noise reduction, e.g., smoothing filters, the wavelet transform 2. Model-based noise reduction
Comments	1. Heuristic noise reduction - Adding irrelevant attributes reduces the performance of decision trees and rules, linear regression and clustering methods (31,32,40). 2. Model-based noise reduction —essential if the task involves numerical attributes but the chosen method can only handle categorical ones ***(33)***
Step 2. Feature Extraction	
Objectives	Extraction of attributes corresponding to distinct pathological states
Methods	1. Attributes from original space ***(31)*** 2. Projecting signals into a lower-dimensional space using linear transformation, e.g., principal component analysis
Comments	1. Projecting signals—Principal component analysis (PCA) identifies the orthogonal directions in which data vary maximally. Very sensitive to the choice of vectors thus criteria for selecting vectors should be determined prior to feature extraction (34,35,40).
Step 3. Feature Selection	
Objectives	Reduction of dimensionality of the data and increase the likelihood of successful classification
Methods	1. Filter method 2. Wrapper method 3. Embedded methods
Comments	1. Filter method —Independent assessment based on general characteristics of data. Determine the subset for classification by ranking individual features based on selection criteria, e.g., t statistics ***(36)***. 2. Wrapper method—The learning algorithm is wrapped into the selection method. Determine the subset for classification by evaluating the relevancy based on metrics of a classifier trained using the subset of features. ROC analysis can be used to measure the relevancy of individual attributes (31,37).

(*Continued*)

Table 2
(Continued)

	3. Embedded method—Implicitly perform feature selection as a part of the classifier training process, e.g., decision trees (35,36).
Step 4 Classifier Training	
Objectives	Distinguish classes based on selected features
Methods	1. Unsupervised machine learning or clustering 2. Supervised machine learning
Comments	1. Unsupervised machine learning or clustering—Natural groupings are identified based without predefined "correct" class membership examples, e.g., hierachical clustering algorithms, self-organizing maps ***(36)***. 2. Supervised machine learning—Classifier is developed using a subset of data with predetermined classes, e.g., artificial neural networks, k nearest neighbor, linear discriminant analysis, support vector machine, Naïve Bayes, rule induction etc (32,38–40).
Step 5 Classifier Evaluation	
Objectives	Assess the performance of a classifier
Comments	Ideally, separate data sets should be used for stages 4 and 5. In practice, however, data partitioning of a single data set, such as 10-fold cross-validation or bootstrap sampling are employed for small size datasets. Over-sampling the minority class and under-sampling the majority class have been common methods to resolve biased classification due to imbalanced data (31,35).

of features, e.g., a composite medical index or panel of markers, may provide more information than individual indicators because the predictability of an outcome is based not on presence or absence of several biomarkers or their linear summation, but on a complex, non-linear relationship between them.

2.2.3. Standards for Data Integration

Information which is relevant to genomic profiling exists in a variety of sources and formats. For EDSS which are "home grown" using local data, and which will only have local institutional use, there may be no compelling reason to adopt a standardized approach to representing data. However, there is an increasing focus on linking disparate databases, disease

Table 3
Standards for data representation and storing

Standards	Examples	URL / Reference
Knowledge engineering standards	CommonKADS	www.commonkads.uva.nl
	OIL	www.ontoknowledge.org
	OML	www.ontologos.org/oml
	Knowledge Query and Manipulation Language	www.cs.umbc.edu/kqml
Software engineering standards	Case Data Interchange Format	(44,45)
	Information Resource Dictionary System	(44)
	Open Information Model	Microsoft
	Unified Modeling Language	(41)
WWW standards	XML	www.w3.org/XML
	Document Content Description	www.w3.org/tr/note-dcd
	Resource Description Framework	
	Web Ontology Language	www.w3.org/2001/sw/WebOnt
Bioinformatics standards	MAGE-ML Microarray and Gene Expression Markup Language	www.geml.org
	Clinical Bioinformatics Ontology	www.clinbioinformatics.org
	BioPathways Consortium	www.biopathways.org
	Gene Ontology Consortium	www.geneontology.org
Medical terminology	SNOMED-CT	www.snomed.org
	UMLS	41

registries, and clinical repositories, and for this to occur the task is substantially simplified if all data are represented in as uniform and standard a way as possible (**Table 3**). For example, databases of microbial genotyping results and clinical observations relating phenotype to genotype form an important part of the genetic variation data landscape. A compilation of microbial reference sequences (RefSeq) specifying gene name and DNA

sequences can be found at http://www.ncbi.nlm.nih.gov/genomes/lproks.cgi (bacterial RefSeq), http://www.ncbi.nlm.nih.gov/genomes/FUNGI/funtab.html (fungal RefSeq) and http://www.ncbi.nlm.nih.gov/genomes/static/vis.html (viral RefSeq).

The ability to capture and share profiling data depends on shared use of a vocabulary (the words), syntax (the "sentence" structure), and messaging protocols. The most developed health care vocabularies are the United Medical Language System (UMLS, National Library of Medicine), LOINC (Logical Observation Identifier Names and Codes; Regenstrief Institute) and SNOMED® (Systematized Nomenclature of Medicine; College of American Pathologists) ***(42)***.

LOINC is an exhaustive catalogue of laboratory tests distinguished by source, e.g., serum or tissue, method, e.g., microscopy, PCR, or immunoassay, and the format in which the result is represented (ordinal, nominal or quantitative). The LOINC number describes a test, but does not provide the result of a specific test ***(42)***. In contrast, SNOMED® is a concept-oriented electronic vocabulary pioneered by the College of American Pathologists. SNOMED-Clinical Terminology (SNOMED-CT) contains around 364,000 concepts, 984,000 terms and 1.45 million defined relationships between concepts ***(43)***. It distinguishes concepts for a condition, e.g., haemochromatosis, the causative mutation, e.g., *BRCA1*, and diagnostic test, e.g., PCR. The UMLS maps the many different source terminologies available, and is a kind of terminological rosetta stone. It models individual systems, identifying for example the information about a laboratory test term, the source terminologies it comes from, which terms it is related to in the hierarchies of those source terminologies, what its synonyms and lexical forms are, and which other terms it is related to in some source terminology ***(43)***. It does not, however, strive to provide definitional information (such as what the test measures are or what its specimen is). However, synergistically, these vocabularies can support the integration of the high-level terms used in decision rules, e.g., "Haemochromatosis," with the relatively low-level terms used in the clinical records, e.g., "Blood test."

2.2.4. Socio-Technical Aspects of EDSS Implementation

The effective introduction and integration of new technology into existing processes requires user participation in design and interdisciplinary collaboration for iterative development. Decision making in healthcare is often more related to agreement with social expectations and the caretakers' perceptions of the clinicians' role than to standard biomedical rules. Therefore, a systematic approach to EDSS implementation, addressing characteristics of users, tasks as well as organizational context is usually fruitful. Specifically, implementation should take into account the differing needs of users with the

variety of experience, training and clinical roles. System context also needs consideration, focusing on the situated conditions of use with explicit organizational goals, missions, control structures and communication modes. It is important to keep in mind potential professional, technical and personal barriers to uptake of EDSS (**Table 4**).

The implementation of EDSS faces the same barriers as the near-term diffusion of genomic medicine. Enthusiasm for the promise of genetic medicine on the part of medical geneticists contrasts markedly with the lack of relevant knowledge on the part of decision makers ***(2)***.

3. Choice of Appropriate Evaluation Methodology

3.1. Evaluation Methodologies

Evaluation is central to any successful EDSS deployment, and should be conducted throughout the system development, starting at the planning and requirements stage and into implementation and the post release stages. Taking an iterative view of information system development, we can conceptually think of all these steps occurring within two different development cycles (**Fig. 5**):

1. Formative development cycle: The form that a system takes is iteratively determined by assessing user needs, designing prototypes, and then getting user feedback on system performance.
2. Summative assessment cycle: Once a system is robust enough for an outcomes assessment, it is put on trial and the summation of system performance results are used to drive the design of the next version of the system.

3.2. Formative Evaluation

At the formative stage of EDSS evaluation, performance of the system is assessed including accuracy of predictions, quality of sources, currency of knowledge and safety of recommendations. Iterative prototyping exposes small samples of prospective users and/or designers to a succession of evaluation protocols using simple models, storyboards, and interactive prototypes. Prototype evaluation uses qualitative methods such as cognitive walkthroughs, questionnaires, structured and informal interviews, focus group analyses, heuristic inspections, and verbal probes. Such evaluation should also include knowledge content evaluation with assessment of accuracy, sensitivity and specificity of classification methods, and estimating the optimum number of clusters to train genomic classifiers and learning parameters, as well as the selection of data sets, relevant features and classification models.

Table 4
Professional, technical, and personal barriers to usage of EDSS

Barriers	Examples	References
Barriers related to characteristics of EDSS		
Rule validity	1. Opinion-based recommendations 2. Insufficient cross-validation 3. Unproven cost-effectiveness	(46,47)
System relevance	1. Limited applicability to clinical practice, e.g., difference in patient mix. 2. Uncertainty about the "shelf-life"of EDSS	(48,49)
System practicality	1. Ambiguous output 2. Disruption to routine practice 3. Low uptake and clinical impact 4. Increase in consultation times	(8,50)
Barriers related to characteristics of EDSS implementation		
IT support	1. Lack of integration into existing systems 2. Lack of IT infrastructure	(47)
Insufficient evaluation	1. Lack of pre-implementation evaluation 2. Lack of post-implementation evaluation	(51)
Medico-legal concerns	No system for EDSS accreditation	(50)
Barriers related to characteristics of EDSS users		
Knowledge	1. Lack of awareness that quality of clinical decisions may be poor 2. Over-estimation of self-reported performance	(8,15)
Skills and abilities	1. Lack of IT skills 2. Belief that he/she cannot perform the task of EDSS use	(47)
Attitudes and beliefs	1. Low outcome expectations 2. Doubts about EDSS credibility 3. Uncertainty about medico-legal implications of EDSS use	(52,53)
Barriers related to characteristics of the organization or decision environment		
Established practices	1. Over-reliance on passive methods 2. Inertia of larger organizations	(47)
Culture	1. Resistance to change 2. Little or no history of EDSS use	(52)
Resources	1. Limited resources	(8)

Knowledge of organizational performance	1. Poor quality of clinical audit 2. Difficulty in measuring of outcomes 3. Short-term outlook rather than appreciation of long-term nature of EDSS impact and sustaining change	(47,51)
Patient factors	1. Preference over choices in clinical management	(51)

3.3. Summative Evaluation

A randomized, controlled trial is the ideal design for clinical impact analysis. Alternatives to a randomized trial include a "before-after" impact analysis (measures outcomes before, during and after using the EDSS) and an "on-off" impact analysis or interrupted time-series (measures outcomes in alternating time periods when the EDSS is or is not available). However, these designs are weaker, subject to temporal and "wash-over" confounding.

Assessment of outcome measures for EDSS should be blinded to patients' risk stratification and the decisions recommended by the EDSS. Ideally, this means that one group of clinicians use the DSS to make clinical decisions and a different group, unaware of the EDSS recommendations, assesses patients' clinical outcomes and impact measures. The potential for bias is significant when outcome events have subjective components.

Although a multi-institutional randomized study is the preferred trial design, the risk of contaminating intervention and control groups is high and the logistic and economic challenges of multicenter studies are formidable, especially without previous strong evidence of impact. Therefore, single-site impact analysis is important because it measures the actual effects of using the EDSS

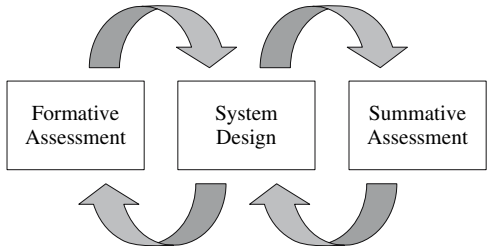

Fig. 5. The process of building an EDSS is an iterative cycle of forming the system around user needs, designing appropriate interactions between the system and users, and then evaluating the true impact of the system using quantitative studies *(8)*.

in clinical practice, which is critical for planning of successful multi-site studies ***(4)***.

An important objective of EDSS evaluation is quantitative assessment of potential impact of EDSS on patient outcomes, work practices and the introduction of new errors. The potential benefits of EDSS can be summarized into three groups:

1. Improved patient safety
    a. Reduction of medical errors
    b. Enhancement of clinical decisions and resource utilization
2. Improved quality of care
    a. Improved compliance with guidelines and clinical protocols
    b. Improved access to and use of evidence
    c. Improvements in the patient satisfaction and the patient consent process
3. Improved efficiency of healthcare delivery
    a. Reductions in costs and in physician time spent on administrative tasks
4. Optimization of resource allocation because of:
    a. The individualized selection of procedure types and post-procedure follow-up
    b. Optimization of personalized therapeutic modalities based on individual molecular risk profiles
    c. Cross-disciplinary treatment paradigm

Outcome measures for DSS should include predictive values, as well as safety and efficiency. For clinicians, negative predictive value and safety are most important because their primary concern is to minimize "missed" patients who have the targeted outcomes. For insurers, positive predictive value and efficiency are the most important because their major concern is cost-effectiveness. Accuracy and other measures (sensitivity, specificity, and area under the receiver-operating characteristic curve (ROC)) may be misleading because they assume equivalent social value for true-positive and true-negative results and may vary with the overall prevalence of outcomes.

Current evidence on the impact of bioinformatics EDSS is limited. It has been documented that they can serve as an educational tool for low-risk patients or can be a useful adjunct to genetic counseling for those at high risk. For example, evidence from randomized controlled trials suggests that an interactive decision support is more effective than standard genetic counseling for increasing knowledge of breast cancer and genetic testing among women at low risk of carrying a mutation ***(13)***. The beneficial impact is more likely

when an EDSS provides specific recommendations, or provides them automatically as part of clinicians' routine workflow. However, beneficial impact in a research study (efficacy) does not guarantee beneficial impact in clinical practice (effectiveness).

4. Conclusions

Successful decision support system design should be task-specific and address situational response requirements and environmental characteristics such as complexity and information overload. Electronic decision aids can reduce decision errors ***(4)*** and also enhance what has become the shared and collaborative process of the use of "omics" technologies for the diagnosis and management of diseases. The dichotomy between the proliferation of evidence such as clinical practice guidelines, and its low uptake, indicates that clinicians are already struggling with information over-supply and concomitant competition for their attention ***(44,49)***. This has lead to the suggestion that the notion of the "best evidence" should be replaced with a more complex notion of the "most effective evidence delivery," which takes into account both the inherent potential of evidence to improve clinical decisions, as well as the likelihood that its mode of delivery will be adopted ***(8)***.

There is a growing demand for tools to support the capture of genomic results as generated by molecular diagnostic and cytogenetic methods, appropriate controlled vocabularies, and applications enabling clinicians to utilize these results to support their decision-making. Success of EDSS in clinical bioinformatics will require planning robust prospective trials, analysis of health care outcome and economic data, and developing new healthcare delivery models. Indeed it is unlikely that the vision for personalized medicine will not be fully realized without workflow integrated, and genomics based, clinical decision support systems.

5. Notes

1. A straightforward electronic risk assessment tool for breast cancer developed by scientists at the US National Cancer Institute and the National Surgical Adjuvant Breast and Bowel Project allows a risk to be calculated for invasive breast cancer www.cancer.gov/bcrisktool/. However, this tool demonstrates some the complexities involved in electronic decision support. For example, the tool is not useful in difficult cases such as ones with a known *BRCA1* or *BRC2* mutation or cases with an earlier cancer or locular carcinoma in situ or ductal carcinoma in situ. One of the seven questions used to assess risk asks for the woman's race/ethnicity. The five ethnic groups given include: White, Black, Hispanic, Asian or Pacific and American Indian. However, responding to any of these groups except for

"White" will provoke a disclaimer indicating that data on non-White ethnicities are uncertain and so may not be accurate until more information is generated.

2. Data provided in reference ***(10)*** indicate that surgery in the USA costs $450 billion per year. On top of this there are additional costs related to complications which total $25 billion. The latter costs will only increase as more surgery is conducted on an increasingly ageing population. Pre-operative risk assessment tools to guide perioperative management of high-risk patients are available but their predictive value is very poor. Hence, a new and alternative approach is "perioperative genomics" which is being used to determine why patients respond so differently to a surgical intervention. The first step is to identify what genes might contribute to post-operative complications, e.g., genes for inflammation, thrombosis, cardiac arrhythmias, wound healing, infection, shock and so on. A genetic "fingerprint" of these genes is then obtained pre-operatively so that an individual's particular risks can be identified early, and appropriate preventative measures put into place. Getting this genetic profile will only the beginning. The assimilation of the results as well as their overall interpretation for the clinician will require informatics-based decision algorithms. A start along the approach described has already been made to predict graft rejection. It is called the AlloMap™ in which the expression of 20 genes is measured by quantitative PCR and then translated into a clinically actionable score that can be used to diagnose cardiac allograft rejection early and non-invasively (10, www.allomap.com/). However, more sophisticated genomics and informatics will be required to predict those at risk of post-operative complications.

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