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Notes and Additional Reading

Summary and Key Points

Knowledge in Medicine – Defining the Problem

In this age, we aspire to practice *evidence-based medicine*, which has been described as an approach that applies "the best available evidence gained from the scientific method to medical decision making." (Sackett DL, Rosenberg WM, Gray JA et al) Instead, we are more likely to practice *memory-based medicine* meaning that "Current medical practice relies heavily on the unaided mind to recall a great amount of detailed knowledge."(Crane RM)

Our failure to practice evidence based medicine is endemic throughout medical care, as documented by McGlynn et. al. who found that barely 55% of patients get recommended care, and that this could be seen in the management of multiple conditions (Figures 1 & 2). Furthermore, the average time from the discovery of medicine to reach patients is 17 years – because of the slow adoption of practice changes.(Balas EA, Boren SA)

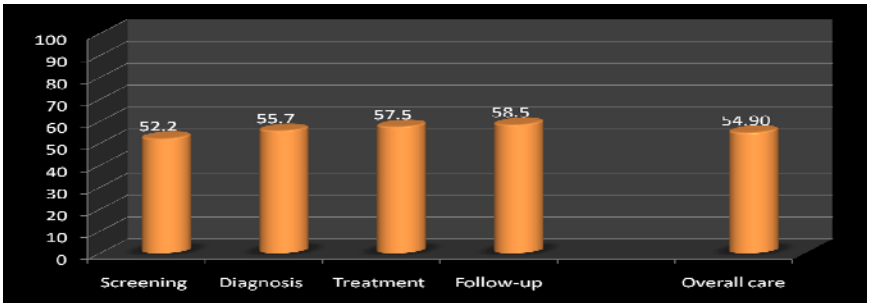

Figure 1: Percentage of patients who receive recommended care (McGlynn EA, Asch SM, Adams J, et al.)

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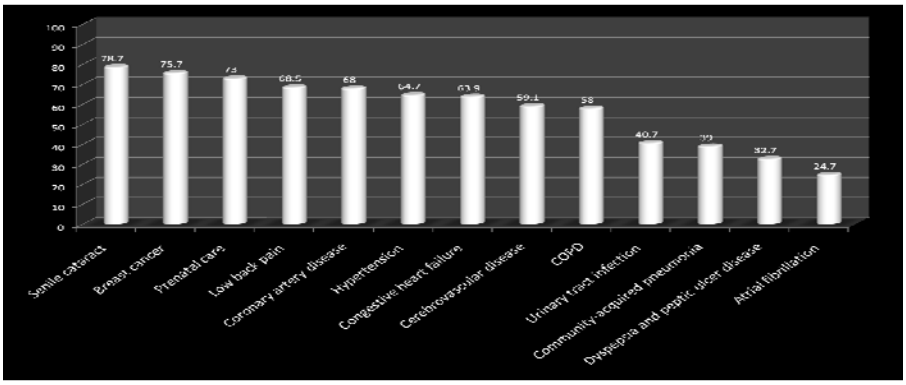

Figure 2: Recommended care by condition (McGlynn EA, Asch SM, Adams J, et al.)

This failure to follow the accepted care regimen is extremely costly. The Rand Corporation estimates that "30 percent of medical costs are avoidable if evidence-based medicine is consistently practiced by providers all of the time." This translates to a potential annual savings $660 billion. (Schmuland D)

It is not surprising that clinicians cannot keep up, given the explosion of medical knowledge. This is evidenced by the number of medical articles indexed by Medline has been growing exponentially since the 1950's (Figure 3).

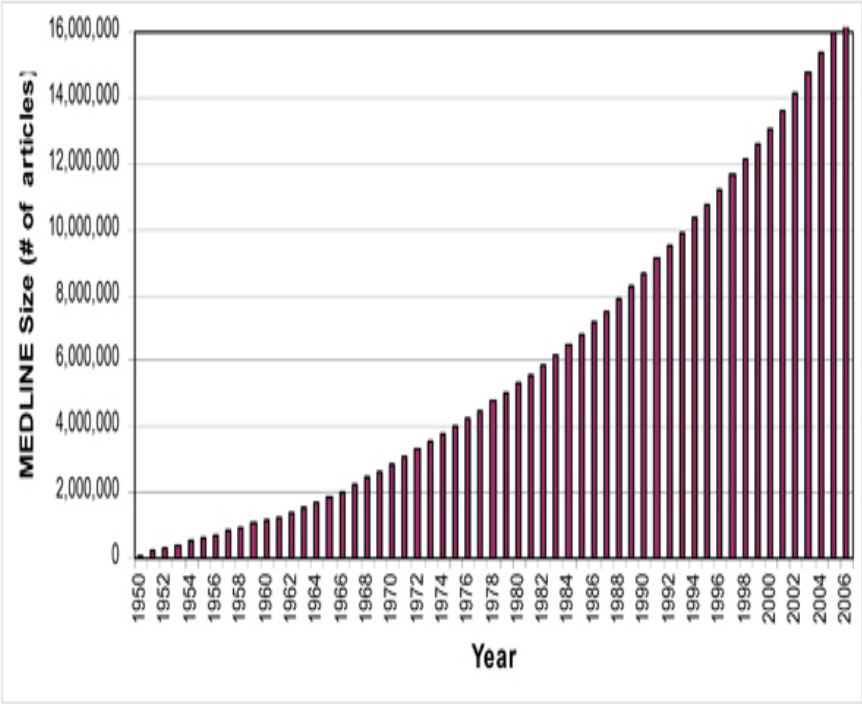

Figure 3: Number of articles indexed on Medline by year (Yoo I, Hu X, Song IY)

Keeping on top of the literature, even for a specialist, can be a full time occupation. Our only hope is computerized Clinical Decision Support.

Clinical Decision Support – A Definition:

At its best, Clinical Decision Support or CDS is the use of computer software to apply knowledge bases, guidelines and algorithms to patient data in order to identify the best course of action, and then present that result to the clinician in a way that helps the clinician understand why that is the best course of action – with an ultimate goal of helping the clinician take the best course of action (Figure 4). In addition, CDS should present information to a patient in a means that helps the patient understand why that is the best course of action – with an ultimate goal of helping the patient comply with the preferred approach.

Knowledge Bases

Most medical knowledge is free text. Journal articles that describe current guidelines use pages of prose to inform the clinician. This prose is not machine readable. Guidelines and other medical knowledge need to be translated into tables of machine readable data, also known as Knowledge Bases. While multiple Knowledge Bases have been created and used by CDS hobbyists, it would be ideal if these Knowledge Bases were created and maintained at the government or specialty society level. One could envision in the future, a cardiology Knowledge Base being maintained by the American College of Cardiology, an Oncology Knowledge Base being maintained by the American Society of Clinical Oncology.

Hopefully, these Knowledge Bases will be developed utilizing formal Levels of Evidence filling in with Expert Opinion panels only when evidence is not available or felt to be unreliable. Large randomized controlled trials, if well designed, are regarded as the gold standard. However, for many clinical questions, only case-controlled studies, or even case observation studies are available. In this situation, expert opinion panels have been used and serve as a the basis in other studies.

Decision Tree/ Algorithms

Clinical decisions require a variety of data points that must be synthesized to determine the best course of action. CDS organizes this mostly by using decision trees or a rules-based approach.

A decision tree walks through a patient scenario, usually using dichotomous branching. In the decision tree shown in Figure 8, the use of Tamoxifen, for chemoprevention, is described.

Levels of evidence, Oxford Centre for Evidenced-Based Medicine

Level	Therapy	Diagnosis
1a	Systematic review with homogeneity * (SRwH) of RCTs	SRwH of level 1 diagnostic studies; CDR with 1b studies from different clinical centres
1b	Individual RCT with a narrow confidence interval	Validating cohort study with good ([dagger]) reference standards, or CDR tested within 1 clinical centre
1c	All or none ([double dagger])	Absolute SpPins and SnNouts
2a	SRwH of cohort studies	SRwH of level 2a-c diagnostic studies
2b	Individual cohort study (including low-quality RCT; e.g., follow-up of <80% of patients)	Exploratory cohort study with good ([dagger]) reference standards; CDR after derivation, or validated only on split sample or databases
2c	"Outcomes" research; ecological studies	
3a	SRwH of case--control studies	SRwH of 3b-and-better studies
3b	Individual case--control study	Non-consecutive study, or one without consistently applied reference standards
4	Case series (and poor-quality cohort and case--control studies)	Case-control study, poor ([section]) or non-independent reference standard
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	

Table 1. Levels of Evidence, Oxford Centre for Evidenced-Based Medicine. Graham AJ, et al. Levels of evidence and grades of recommendations in general thoracic surgery. Can J Surg. 2004;47(6):461. Academic OneFile. Web. 28 December 2010.

CDR = clinical decision rule (an algorithm or scoring system that leads to a prognostic estimation or a diagnostic category); RCT = randomized controlled trial; SnNout = a diagnostic finding with a sensitivity so high that a negative result rules out the diagnosis; SpPin = a diagnostic finding with a specificity so high that a positive result rules in the diagnosis; SRwH = systematic review with homogeneity.

* A systematic review that is free of troubling variations in the directions and degrees of results between individual studies

([dagger]) Reference standards that are independent of the test, and applied blindly/objectively to all patients.
([double dagger]) Met when all patients died before the treatment/

prescription became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it.

([section]) Reference standards that are applied haphazardly, but are still independent of the test.

Table adapted from http://www.cebm.net/levels_of_evidence.asp.
Graham AJ, et al. Levels of evidence and grades of recommendations in general thoracic surgery. Can J Surg. 2004;47(6):461. Academic OneFile. Web. 28 December 2010

Grade	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Table 2. Grades of recommendations, Oxford Centre for Evidence-Based Medicine.

Graham AJ, et al. Levels of evidence and grades of recommendations in general thoracic surgery. Can J Surg. 2004;47(6):461. Academic OneFile. Web. 28 December 2010.

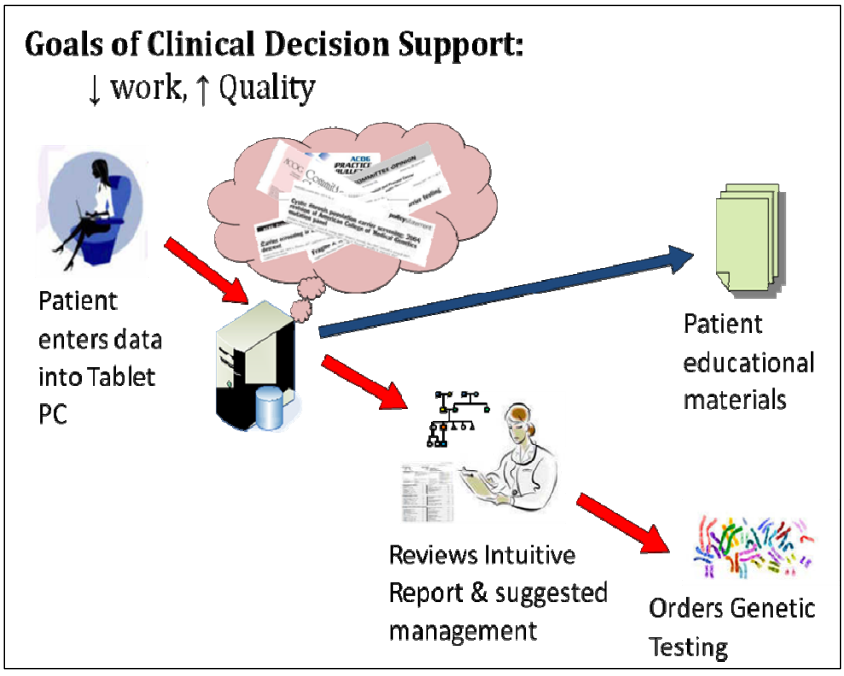

Figure 4: The Overall Goals of Clinical Decision Support

The display of information to patients or clinicians is often best accomplished with visualization, that is, a graphical display of the data that makes the management and implications intuitive. An example chosen from the field of genetics is the pedigree visualization (Figure 5). This touchstone of family history curation has tremendous power in showing patterns of disease within a family. Ultimately, describing a complex family structure in free text is almost uninterpretable, while describing a set of family connections by a pedigree makes the relationships and the diseases obvious

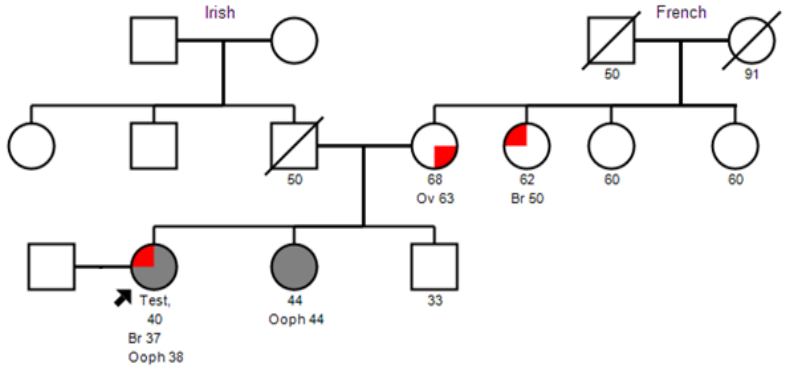

Figure 5: Ethnicity of grandparents shown at the top. Circles are women, squares are men, cutouts are diseases, ages appear below each relative, and diseases or conditions appear below as well (Ooph =Oophorectomy, Br = Breast Cancer, Ov = ovarian cancer)

One Example of the Power of CDS: HughesRiskApps

One robust example of CDS is HughesRiskApps (www.HughesRiskApps.net), a commercial software package that uses CDS to help identify and manage women at high risk for hereditary cancer (Figure 6).

Women with hereditary breast ovarian cancer (HBOC) syndrome are seldom identified until after they have cancer, and when identified, management is time-consuming and inefficient. If we could identify and manage these patients, we could markedly decrease the morbidity and mortality of these diseases.

It is typical to find CDS elements as integrated parts of a larger information workflow. As a system, HughesRiskApps leverages modules for patient data entry, statistical analysis and automatic document generation to help support the CDS algorithms and visualizations. The software shows how using patient data entry can help clinicians focus on analysis and patient care instead of keypunching in data and generating documents. The process starts with the patient completing a tablet-PC based questionnaire. This data is then analyzed using CDS to determine the level of risk of developing HBOC, and patients at risk are flagged for specialized management. The clinician is able to view a pedigree and a printout of the results of the algorithms, and the patient receives a letter explaining the problem and providing contact information for a consultation. The result is a decrease in the labor intensive and costly effort required of clinicians.

These kinds of systems require that the data patients provide be stored in a structured way that is suitable for database interactions and algorithmic analysis. Formalizing decision making processes for genetic testing, enhanced screening protocols, chemoprevention, and prophylactic surgery into a machine readable module is a substantial undertaking. These challenges are met by resources from international standards institutes, academic research, and expert opinion.

The benefits of this approach are that it can (1) increase the quality of care patients receive, (2) decrease the amount of labor required by clinical staff, and (3) increase the volume of patients a typical clinician can care for.

BRCAPRO Lifetime Breast tab

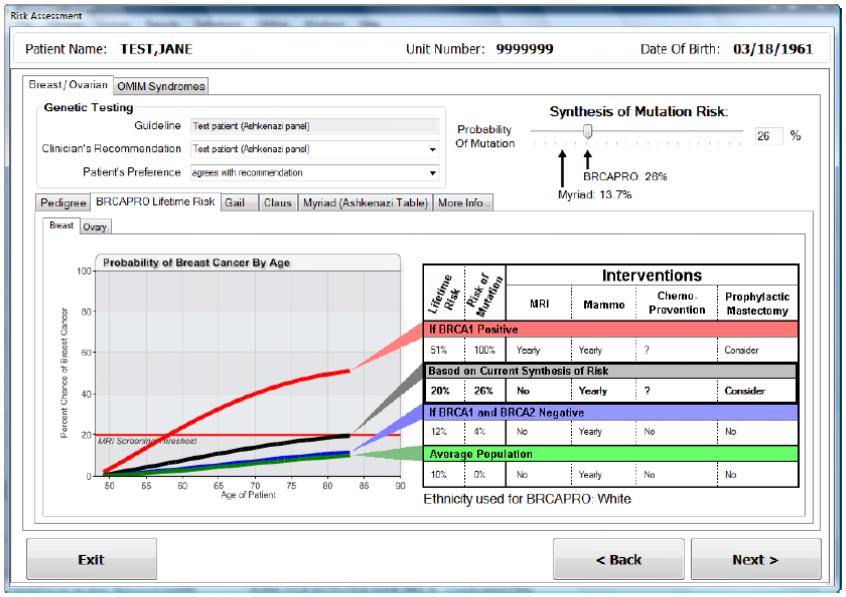

Figure 6: HughesRiskApps Display of Patient's Risk of Developing Breast Cancer (www.hughesriskapps.net)

Requirements for CDS

In order for medical care to take full advantage of CDS, several requirements are necessary, which include but are not limited to:

- Structured patient data in a standard format
- Machine readable Knowledge Base
- Decision tree / algorithm or rules engine to come to a conclusion

Structured Data

Most medical information is recorded as free text, that can be understood by a human with specialized medical knowledge, but which cannot easily or consistently interpreted by a computer. Structured data simply means data that is consistent and has a forced composition. Examples of structured data include numerical data (e.g. age and weight), yes/no checkboxes (e.g. smoker / non-smoker), and drop down menu's that provide a list of items to choose

from. Unstructured free text is difficult and in most cases impossible for CDS systems to process.

Even when clinicians try to structure data free text, they do it with such inconsistency that it is usually not interpretable by a CDS system. For example, the same family history may be represented by a clinician as

MGM Ov 90
M Aunt Ov 49
Patient Breast 53

Maternal GM Ov 90
Maternal Aunt Ov 49
Pt Breast 53

Mother's mother Ovary 90
Mother's sister Ovarian 49
Pt Br 53

Grandmother Mother's side Ovarian 90
Maternal Aunt Ovary 49
Pt Br 53

Maternal Grandmother Ovarian 90
Aunt Mother's side Ovary 49
Pt Br 53

In order to capture patient data in a structured format, most systems require the clinician to input data into a central database using a client pc-based application. Some applications allow data entry via a web-portal. HughesRiskApps allows *patients* to enter their own data from either to a tablet PC, a website, or a desktop PC. The HughesRiskApps offers a tablet PC interface which is simple to use – and allows the patient to complete without assistance from clinical staff. This has been accomplished by creating an interface that assumes no more than a 5th grade reading level and is available in English, Spanish, and Italian. Some examples of the table interface are shown below (Figure 7).

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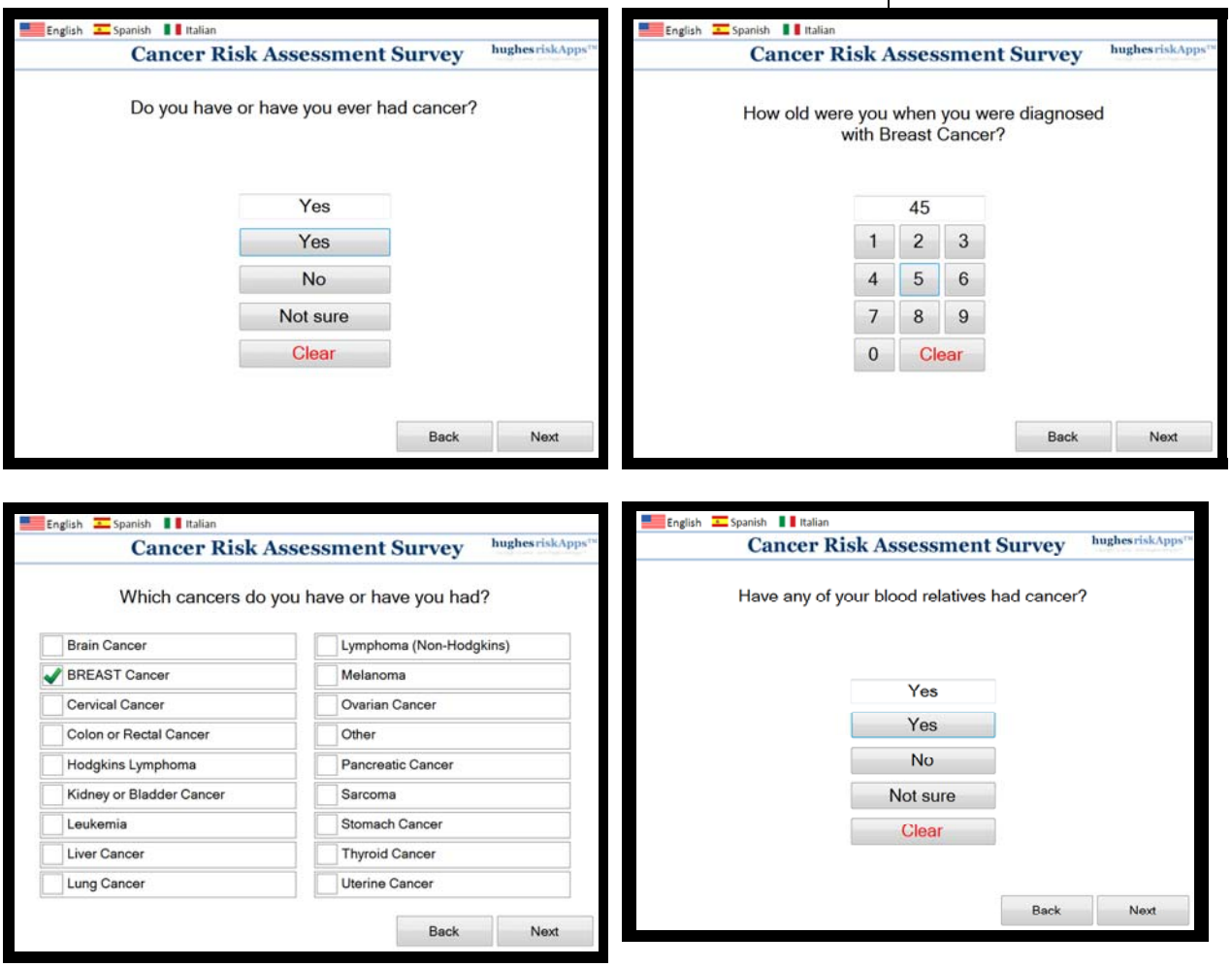

Figure 7: HughesRiskApps Tablet PC Interface for Patient Data Entry (www.hughesriskapps.net)

Once structured data has been entered into a CDS, the system can process the information utilizing pre-defined algorithms to help the clinician interpret the data. In the case of HughesRiskApps, the patient's data undergoes analysis using a variety of risk models (Claus EB, Risch N, Thompson WD; Parmigiani G, Berry D, Aguilar O; Frank TS, Deffenbaugh AM, Reid JE, et al) and a simplified printout is produced for the clinician to utilize which provides (1) the degree of risk and (2) a patient-specific pedigree.

The system has been in use at the Newton Wellesley Hospital since 2007, and in the period 4/1/2007 to 3/31/2008 approximately 25,763 family histories were collected and analyzed, identifying 915 women who would benefit from counseling. The amount of effort it would have taken to identify these high-risk women *manually* is almost incalculable.

It should also be noted that once structured data has been obtained, not only can it be used for CDS, but it can also then be exchanged among and brought into various electronic health record systems using standardized nomenclatures and messaging systems, the most ubiquitous of which is HL7. (Shabo A, Hughes KS)

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use of tamoxifen for chemoprevention is described.

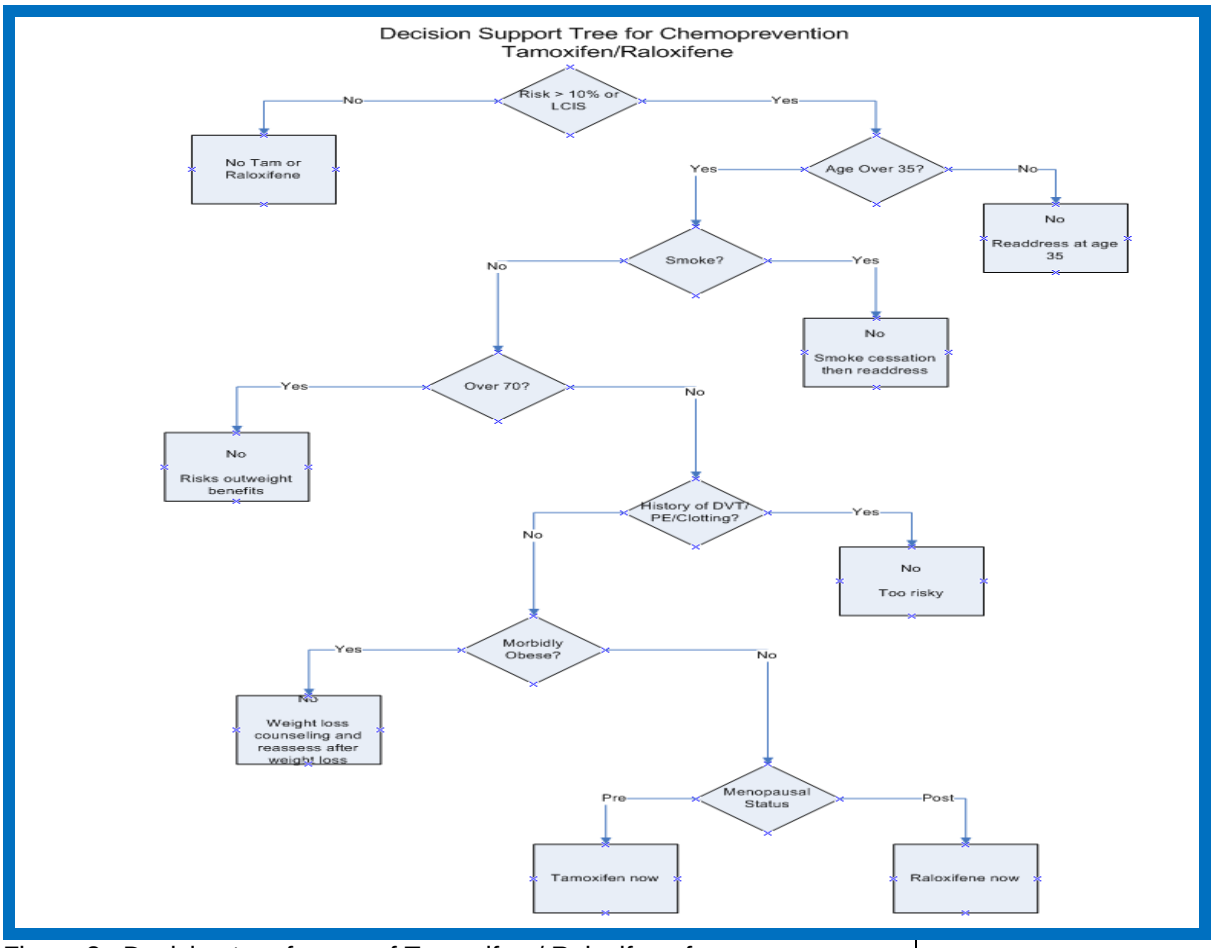

Figure 8: Decision tree for use of Tamoxifen / Raloxifene for chemoprevention

While a decision tree is very powerful, it has the weakness of looking at each problem as a yes/no, and of stopping once an endpoint is reached. For example:

> *If a female patient is a 74 year old smoker, she is told to come back after she stops smoking. If she stops smoking and comes back, she starts down the tree again, but this time is told she can't have tamoxifen because she is over 70.*

An alternative to a decision tree is a *rules based approach*. Here a set of rules would be developed that encompasses every possible combination of factors, with a suggested course of action for each situation.

For the scenario described above, a rules based approach might use a table including the fields age, smoker, level of risk, and recommendation. A 75 year old smoker would be told she is not eligible for tamoxifen because she is over 70, but she should stop smoking anyway. A 45 year old smoker would be told to stop smoking and come back for consideration of tamoxifen at that time.

Limitations of Clinical Decision Support

Poorly implemented CDS is useless at best and dangerous at worst. CDS must include interfaces and visualizations that fit into the clinical workflow and make the quality of care better. Unfortunately, many systems fail in this respect, requiring clinicians to change their workflow in unnatural ways that lead to objections on the part of the end-users. This lack of consideration of the real world environment can lead to rejection of the system, and situations in which the clinician ignores important information.

Isaac et. al. identified that clinicians overrode 90.8% of drug-drug interaction alerts, and 77% of allergy alerts in study of CDS systems.(Isaac T, Weissman JS, Davis RB, et al) In another study Singh et. al. identified that abnormal radiologic imaging alerts were not responded to 18.1% of the time.[13] Clearly, the presentation and timing of alerts does not always stimulate the appropriate response by the clinician. Keep in mind that these shortcomings are problems associated with software design and computer ergonomics, as opposed to a failure on the part of the clinician.

One example where a clinical system failed to take into account the clinical workflow was highlighted in a study by Han et. al. In this study of mortality in a pediatric intensive care unit, the authors found a significantly increased from 2.80% before computerized physician order entry implementation to 6.57% after CPOE implementation.[14] The important point here is that poorly designed software, which does not take workflow and ergonomics into account, can *decrease*

the quality of medicine. This is an unconscionable occurrence and must be avoided.

Research

In order to refine and improve CDS, a great deal of ongoing research is currently underway which involves the intersection of information science, computer science, and health care. This goal of this work, generally referred to as being within the field of medical informatics, is to use structure and algorithms to improve the communication, understanding and management of medical information. The end objective of biomedical informatics is the coalescing of data, knowledge, and the tools necessary to apply that data and knowledge in the decision-making process at the time and place that a decision needs to be made.

Much of this work focuses on refining decision algorithms, creating medical ontologies (or structured lists of information) that can be used by CDS systems, refining both the clinician-machine and patient-machine interfaces, and understanding the overall impact of these kind of systems on patient outcomes. There are still many unanswered questions about how these systems can be optimally employed to benefit clinicians, patients, and the overall health care system in the most cost-effective and efficient manner.

Future of Clinical Decision Support:

In the future advanced algorithms utilizing artificial intelligence and a variety of machine learning techniques will likely be able to process real-time information utilizing contextual patient data, clinical guidelines and expert opinion to provide contextual information processing that allows the end-user (i.e. the clinician) to benefit from information that would otherwise be uninterpretable by the unassisted human mind.

While this happens to some extent with current CDS systems, there are current limitations imposed by the extent of the existing Knowledge Base and the degree to which information can be obtained in a structured format and processed in real-time. However, it is likely that researchers will develop more effective ways of translating unstructured elements into machine readable structured data formats and more effective ways of providing notifications to clinicians in such a manner that the end-user's behavior changes to ultimately affect a better outcome for the patient in question.

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