Chapter 14

Evidence Based Medicine and Clinical Practice Guidelines

ROBERT E. HOYT

WILLIAM R. HERSH

Learning Objectives

After reading this chapter the reader should be able to:

- State the definition and origin of evidence based medicine
- Define the benefits and limitations of evidence based medicine
- Describe the evidence pyramid and levels of evidence
- State the process of using evidence based medicine to answer a medical question
- Compare and contrast the most important online and smartphone evidence based medicine resources
- Describe the interrelationship between clinical practice guidelines, evidence based medicine, and electronic health records
- Define the processes required to create and implement a clinical practice guideline

"The great tragedy of Science - the slaying of a beautiful hypothesis by an ugly fact"
Thomas Huxley (1825-1875)

Introduction

Some might ask why Evidence Based Medicine (EBM) is included in a textbook on health informatics. The reason is that medical decisions and actions should be based on the best available evidence. Clearly, information technology has the potential to improve decision making through online medical resources, electronic clinical practice guidelines, electronic health records (EHRs) with decision support, online literature searches, digital statistical analysis and online continuing medical education (CME). This chapter is devoted to finding the best available evidence and discussing one of its end products, clinical practice guidelines.

Although one could argue that EBM is a buzz word like quality, in reality it means that clinicians should seek and apply the highest level of evidence available through a critical appraisal process. According to the Center for EvidenceBased Medicine, EBM can be defined as:

> "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patient"[1]

Furthermore, in *Crossing the Quality Chasm,* the Institute of Medicine (IOM) states:

> "Patients should receive care based on the best available scientific knowledge. Care

> should not vary illogically from clinician to clinician or from place to place"[2]

What the IOM is saying is that every effort should be made to find the best answers and that these answers should be standardized and shared among clinicians. Such standardization implies that clinical practice should be consistent with the best available evidence that would apply to the majority of patients. This is easier said than done because clinicians are independent practitioners and interpret patient findings and research results differently. It is true that many questions cannot be answered by current evidence so clinicians may have to turn to subject matter experts. In addition, clinicians lack the time and the tools to seek the best evidence. Furthermore, greater than 1,800 citations are added to MEDLINE every day, making it impossible for a practicing clinician to stay up-to-date with the medical literature. Likewise, interpreting this evidence requires expertise and knowledge that not every clinician has. One does not have to look very far to see how evidence changes recommendations, e.g. bed rest is no longer recommended for low back pain[3] or following a spinal tap (lumbar puncture); routine activity is recommended instead.[4]

Until these older recommendations were challenged with high-quality randomized controlled trials (RCTs) the medical profession had to rely on expert opinion, best guess or limited research studies.

Three pioneers are closely linked to the development of EBM. Gordon Guyatt coined the term EBM in 1991 in the American College of Physician (ACP) Journal Club.[5] The initial focus of EBM was on clinical epidemiology, methodology and detection of bias. This created the first fundamental principle of EBM: not all evidence is equal; there is a hierarchy of evidence that exists. In the mid-1990s, it was realized that patients' values and preferences are essential in the process of decision making, and addressing these values has become the second fundamental principle of EBM, after the hierarchy of evidence. Archie Cochrane, a British epidemiologist, was another early proponent of EBM. The Cochrane Collaboration was named after him as a tribute to his early work. The Cochrane Collaboration consists of review groups, centers, fields, methods groups and a consumer network. Review groups, located in 13 countries, perform systematic reviews based on randomized controlled trials. As of 2013 the Cochranee Collaboration has completed over 5000 systematic reviews, even though there have been 300,000 randomized controlled trials published.[6,7] The rigorous reviews are performed by volunteers, so efforts are slow. David Sackett is another EBM pioneer who has been hugely influential at The Centre for Evidence Based Medicine in Oxford, England and at McMaster University, Ontario, Canada. EBM has also been fostered at McMaster University by Dr. Brian Haynes who is the Chairman of the Department of Clinical Epidemiology and Biostatistics and the editor of the American College of Physician's (ACP) Journal Club. Although EBM is popular in the United Kingdom and Canada it has received mixed reviews in the United States. The primary criticisms are that EBM tends to be a very labor intensive process and in spite of the effort, frequently no answer is found.

The first randomized controlled trial was published in 1948.[8] For the first time subjects who received a drug were compared with similar subjects who would receive another drug or placebo and the outcomes were evaluated. Subsequently, studies became "double blinded" meaning that both the investigators and the subjects did not know whether they received an active medication or a placebo. Until the 1980s evidence was summarized in review articles written by experts. However, in the early 1990s, systematic reviews and meta-analyses became known as a more focused, objective, and rigorous way to summarize the evidence and the preferred way to present the best available evidence to clinicians and policy makers. Since the late 1980s more emphasis has been placed on improved study design and true patient outcomes research. It is no longer adequate to show that a drug reduces blood pressure or cholesterol; it should demonstrate an improvement in patient-important outcomes such as reduced strokes or heart attacks.[9]

In spite of some reluctance by the US to embrace EBM universally, the US federal government has established multiple Evidence Based Practice Centers to conduct systematic reviews of topics in clinical medicine, social and behavioral science and economics.[10] More recently, nine US medical societies participated in in a new 2012 initiative known as Choosing Wisely that lists 45 dubious medical tests and therapies that are strongly discouraged, based on best evidence.[11]

Importance of EBM

Learning EBM is like climbing a mountain to gain a better view. One might not make it to the top and find the perfect answer but individuals will undoubtedly have a better vantage point than those who choose to stay at sea level. Reasons for studying EBM resources and tools include:

- Current methods of keeping medically or educationally up-to-date do not work
- Translation of research into practice is often very slow
- Lack of time and the volume of published material results in information overload
- The pharmaceutical industry bombards clinicians and patients every day; often with misleading or biased information
- Much of what is considered the "standard of care" in every day practice has yet to be challenged and could be wrong

Without proper EBM training clinicians will not be able to appraise the best information resulting in poor clinical guidelines and wasted resources.

Traditional Methods for Gaining Medical Knowledge

- Continuing Medical Education (CME). Traditional CME is desired by many clinicians but the evidence shows it to be highly ineffective and does not lead to changes in practice. In general, busy clinicians are looking for a non-stressful evening away from their practice or hospital with food and drink provided.[12-13] Much CME is provided free by pharmaceutical companies with their inherent biases. Better educational methods must be developed. A recent study demonstrated that online CME was at least comparable, if not superior to traditional CME.[14]
- Clinical Practice Guidelines (CPGs). This will be covered in more detail, later in this chapter. Unfortunately, just publishing CPGs does not in and of itself change how medicine is practiced and the quality of CPGs is often variable and inconsistent.
- Expert Advice. Experts often approach a patient in a significantly different way compared to primary care clinicians because they deal with a highly selective patient population. Patients are often referred to specialists because they are not doing well and have failed treatment. For that reason, expert opinion needs to be evaluated with the knowledge that their recommendations may not be relevant to a primary care population. Expert opinion therefore should complement and not replace EBM.
- Reading. It is clear that most clinicians are unable to keep up with medical journals published in their specialty. Most clinicians can only devote a few hours each week to reading. All too often information comes from pharmaceutical representatives visiting the office. Moreover, recent studies may contradict similar prior studies, leaving clinicians confused as to the best course.

EBM Steps to Answering Clinical Questions

The following are the typical steps a clinician might take to answer a patient-related question:

- The physician sees a patient and generate a clinical well-constructed question. Here is the PICO method, developed by the National Library of Medicine:
  - **P**atient or problem: what is the patient group of interest? Elderly? Gender? Diabetic?
  - **I**ntervention: what is being introduced, a new drug or test?

  - **C**omparison: with another drug or placebo? ○ **O**utcome: what needs to be measured? Mortality? Hospitalizations? A webbased PICO tool has been created by the National Library of Medicine to search Medline. This tool can be placed as a short cut on any computer.[15]
  - It has been recently suggested to add a T and S to PICO (i.e., PICOTS) to indicate the Type of study that would best answer the PICO question and the setting where it would take place.
- Seek the best evidence for that question via an EBM resource or PubMed.
- Critically appraise that evidence using tools mentioned in this chapter. Examine internal and external validity and impact of an intervention
- Apply the evidence to your patient considering patient's values, preferences and circumstances [14]

There are many more detailed treatises of EBM; probably the best and oldest is the textbook *Evidence-Based Medicine How to practice and teach* it, by Straus, Glasziou, Richardson and Haynes, now in its fourth edition.[16]

Terminology Used in Answering Clinical Questions

- Evidence appraisal: When evaluating evidence, one needs to assess its validity, results and applicability.
- Validity: Validity means is the study believable? If apparent biases or errors in selecting patients, measuring outcomes, conducting the study, or analysis are present, then the study is less valid.
- Results: Results should be assessed in terms of the magnitude of treatment effect and precision (narrower confidence intervals or statistically significant results indicate higher precision).
- Applicability: Also called external validity, applicability indicates that the results reported in the study can be generalized to the patients of interest.[17]

Most Common Types of Clinical Questions

- Therapy question. This is the most common area for medical questions and the primary one discussed in this chapter
- Prognosis question
- Diagnosis question
- Harm question
- Cost question

The Evidence Pyramid

The pyramid in Figure 14.1 represents the different types of medical studies and their relative ranking. The starting point for research is often animal studies and the pinnacle of evidence is the meta-analysis of randomized trials. With each step up the pyramid our evidence is of higher quality associated with fewer articles published.[18] Although systematic reviews and meta-analyses are the most rigorous means to evaluate a medical question, they are expensive, labor intensive, and their inferences are limited by the quality of the evidence of the original studies.

- Case reports/case series. Consist of collections of reports on the treatment of individual patients without control groups; therefore they have much less scientific significance.
- Case control studies. Study patients with a specific condition (retrospective or after the fact) and compare with people who do not. These types of studies are often less reliable than randomized controlled trials and cohort studies because showing a statistical relationship does not mean that one factor necessarily caused the other.
- Cohort studies. Evaluate (prospectively or followed over time) and follow patients who have a specific exposure or receive a particular treatment over time and compare them with another group that is similar but has not been affected by the exposure being studied. Cohort studies are not as reliable as randomized controlled studies, since the

two groups may differ in ways other than the variable under study.

- Randomized controlled trials (RCTs). Subjects are randomly assigned to a treatment or a control group that received placebo or no treatment. The randomization assures to a great extent that patients in the two groups are balanced in both known and unknown prognostic factors, and that the only difference between the two groups is the intervention being studied. RCTs are often "double blinded" meaning that both the investigators and the subjects do not know whether they received an active medication or a placebo. This assures that patients and clinicians are less likely to become biased during the conduct of a trial, and the randomization effect remains protected throughout the trial. RCTs are considered the gold standard design to test therapeutic interventions.
- Systematic reviews. Defined as protocoldriven comprehensive reproducible searches that aim at answering a focused question; thus, multiple RCTs are evaluated to answer a specific question. Extensive literature searches are conducted (usually by several different researchers to reduce selection bias of references) to identify studies with sound methodology; a very time-consuming process. The benefit is that multiple RCTs are analyzed, not just one study.

Standardized systematic review instruments, such as the Jadad scale can be used to evaluate the quality of individual RCTs.[19] • Meta-analyses. Defined as the quantitative summary of systematic reviews that take the systematic review a step further by using statistical techniques to combine the results of several studies as if they were one large single study.[15] Meta-analyses offer two advantages compared to individual studies. First, they include a larger number of events, leading to more precise (i.e., statistically significant) findings. Second, their results apply to a wider range of patients because the inclusion criteria of systematic reviews are inclusive of criteria of all the included studies.[17]

Table 14.1: Suggested studies for questions asked

Type of Question	Suggested Best Type of Study
Therapy	RCT > cohort > case control > case series
Diagnosis	Prospective, blind comparison to a gold standard
Harm	RCT + cohort > case control > case series
Prognosis	Cohort study > case control > case series
Cost	Economic analysis and modeling

This chapter wil deal primarily with therapy questions so note that RCTs are the suggested study of choice.[20] Studies that don't randomize patients or introduce a therapy along with a control group are referred to as observational studies (case control, case series and cohort) and are usually retrospective in nature.

Evidence of harm should be derived from both RCTs and cohort study designs. Cohort studies have certain advantages over RCTs when it comes to assessing harm: larger sample size, longer follow up duration, and more permissive

Figure 14.1: The Evidence Pyramid

inclusion criteria that allow a wide range of patients representing a real world utilization of the intervention to be included in the study.

Levels of Evidence (LOE)

Several methods have been suggested to grade the quality of evidence, which on occasion, can be confusing. The most up-to-date and acceptable framework is the GRADE (Grading of Recommendations, Assessment, Development and Evaluation).[21] The following is a description of the levels of evidence in this framework:

- Level 1: High quality evidence (usually derived from consistent and methodologically sound RCTs)
- Level 2: Moderate quality evidence (usually derived from inconsistent or less methodologically sound RCTs; or exceptionally strong observational evidence)
- Level 3: Low quality evidence (usually derived from observational studies)
- Level 4: Very low quality evidence (usually derived from flawed observational studies, indirect evidence or expert opinion

In this framework, RCTs start with a level 1 and observational studies start with a level 3. The rationale for this rating reflects the rigor of the RCTs and the strong inference they provide. For example, a recent systematic review and metaanalysis reported that seven observational (nonrandomized) studies demonstrated a beneficial association between chocolate consumption and the risk of cardiometabolic disorders.[22] The highest levels of chocolate consumption were associated with significant reduction in cardiovascular disease and stroke compared with the lowest levels. Although these results seem impressive at face value, it is implausible that the effect of chocolate consumption is that profound (37% and 29% reduction in the risk of cardiovascular disease and stroke). This magnitude of effect rivals the best available drugs and interventions used to prevent these diseases. Observational studies like these, have likely exaggerated the magnitude of benefit due to many factors (i.e., bias and confounding). It is possible that chocolate users are healthier, wealthier, more educated or have other characteristics that make them have lower incidence of disease. The opposite is also possible. Therefore, our confidence in estimates of effects generated from observational studies is lower than that of randomized trials. Hence, one derives evidence with different quality rating. Furthermore, it is important to recognize that the quality of evidence can be upgraded or downgraded if additional criteria based on study methodology and applicability is available.

Risk Measures and Terminologies

Overall, therapy trials are the most common area of research and ask questions such as, is drug A better than drug B or placebo? In order to determine what the true effect of a study is, it is important to understand the concept of risk reduction and the number needed to treat. These concepts are used in studies that have dichotomous outcomes (i.e., only two possible answers such as dead or alive, improved or not improved); which are more commonly utilized outcomes. The chapter will define these concepts and then present an example for illustration.

Risk is defined as the rate of events during a specific period of time. It is calculated by dividing the number of patients suffering events by the total number of patients at risk for events. Odds are defined as the ratio of the number of patients with events to the number of patients without events.

Notice that *Odds=1 / (1 - risk)*

Example

Amazingstatin is a drug that lowers cholesterol. If a physician treats a 100 patients with this drug and five of them suffer a heart attack over a period of 12 months, the risk of having a heart attack in the treated group would be 5/100= 0.050 (or 5%). The odds of having a heart attack would be 5/95= 0.052. In the control group, if he or she treats 100 patients with

placebo and seven suffer heart attacks, the risk in this group is 7/100=0.070 or 7% and the odds are
7/93=0.075.

Notice that the risk in the experimental group is called experimental event rate (EER) and the risk in the control group is called control event rate (CER). To compare risk in two groups, the following terms are used:

- Relative Risk (RR) is the ratio of two risks as defined above. Thus, it is the ratio of the event rate of the outcome in the experimental group (EER) to the event rate in the control group (CER). ○ RR = EER/CER
- Relative Risk Reduction (RRR) is the difference between the experimental event rate (EER) and the control event rate (CER), expressed as a percentage of the control event rate.
  - RRR = (EER-CER)/CER
- Absolute Risk Reduction (ARR) is the difference between the EER and the CER.
  - ARR = EER-CER
  - (Note that "difference" is not the same as subtracting CER from EER. For example if the EER is 1.5 and the CER is 2.0, the difference is .5, not -.5)
- Number Needed to Treat (NNT) is the number of patients who have to receive the intervention to prevent one adverse outcome.[23]
  - NNT = 1/ARR
  - (or 100/ARR, if ARR is expressed as a percentage instead of a fraction)
- Odds Ratio (OR) is the ratio of odds (instead of risk) of the outcome occurring in the intervention group to the odds of the outcome in the control group.

On Amazingstatin, 5% (EER) of patients have a heart attack after 12 months of treatment. On placebo 7% (CER) of patients have a heart attack over 12 months

RR = 5% /7% = 0.71

RRR = (7% - 5%) /7% = 29%

ARR = 7% - 5% = 2%

NNT = 100/2 = 50

In summary, on average, 50 patients must be treated with Amazingstatin over 12 months to prevent one heart attack. As calculated above, the odds for the intervention and control group respectively are 0.052 and 0.075; the odds ratio (*OR*) = 0.52/0.075 = 0.69.

Comments

RR and OR are very similar concepts and as long as the event rate is low, their results are almost identical. These results show that this drug cuts the risk of heart attacks by 29% (almost by a third), which seems like an impressive effect. However, the absolute reduction in risk is only 2% and therefore 50 patients need to be treated to prevent one adverse event. Although this NNT may be acceptable, using RRR seems to exaggerate our impression of risk reduction compared with ARR. Most of what is written in

the medical literature and the lay press will quote the RRR. Unfortunately, very few studies offer NNT data, but it is very easy to calculate if the ARR specific to your patient is known. Nuovo et al. noted that NNT data was infrequently reported by five of the top medical journals in spite of being recommended. [24] In another interesting article, Lacy and co-authors studied the willingness of US and UK physicians to treat a medical condition based on the way data was presented. Ironically, the data was actually the same but presented in three different ways. Table 14.2 suggests that US physicians may need more training in EBM.[25]

Table 14.2: Physician's Likelihood of Prescribing Medication Based on How Research Data is Presented

Physicians From	Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	Number Needed To Treat (NNT)
United States	54%	4%	10%
United Kingdom	24%	11%	22%

Examples of Using RRR, ARR and NNT

A full page article appeared in a December 2005 Washington Post newspaper touting the almost 50% reduction of strokes by a cholesterol lowering drug. This presented an opportunity to take a look at how drug companies usually advertise the benefits of their drugs. Firstly, in small print, the reader notes that patients have to be diabetic with one other risk factor for heart disease to see benefit. Secondly, there are no references. The statistics are derived from the CARDS Study published in the Lancet in Aug 2004.[26] Stroke was reported to occur in 2.8% in patients on a placebo and 1.5% in patients taking the drug Lipitor. The NNT is therefore 100/1.3 or 77. So, a physicians would have to treat 77 patients for an average of 3.9 years (the average length of the trial) to prevent one stroke. This doesn't sound as good as "cuts the risk by nearly half." Now armed with these EBM tools, look further the next time a miraculous drug effect is advertised.

Number Needed to Harm (NNH) is calculated similarly to the NNT. If, for example, Amazingstatin was associated with intestinal bleeding in 6% of patients compared to 3% on placebo, the NNH is calculated by dividing the ARR (%) into 100. For our example the calculation is 100/.03 = 33. In other words, the treatment of 33 patients with Amazingstatin for one year resulted, on average, in one case of intestinal bleeding as a result of the treatment. Unlike NNT, the higher the NNH, the better.

The Case of Continuous Variables and effect size. The results of studies (effect measures) described so far (i.e., RR, OR, ARR) are used when outcomes are dichotomous (such as dead or alive, having a heart attack or not, etc.). However, outcomes can also be continuous (e.g., blood cholesterol level). These outcomes are usually reported as a difference in the means of two study groups. This difference has a unit, which in the cholesterol example, is mg/dL. In addition to the mean difference, results would also include some measure that describes the spread or dispersion of measurements around the mean (i.e., standard deviation, range, interquartile range or a confidence interval).

If the metrics of continuous variables do not have intuitive intrinsic meaning (e.g., a score on a test or a scale), the *effect size* can be standardized (i.e., difference in means is divided by the standard deviation; which makes the data measured in standard deviation units). This process allows the comparison of students taking different tests, or tests taken in different years, or comparing the results of studies that used different scales as their outcomes. This is possible because all these measurements are standardized (have the same unit, which is standard deviation unit). A commonly used effect size is Cohen's d, which is a standardized

difference in means. It is interpreted arbitrarily as a small, moderate or large effect, if d was 0.2, 0.5 or 0.7; respectively. In addition to knowing that a result is statistically significant, calculating the effect size gives one an idea of how big the difference actually is.

Confidence Intervals. Most results published in journals will include confidence intervals that give the reader an idea of the precision of the results. In other words, if the result of interest is a mean of 5.4 kilograms and the 95% confidence intervals are 3.9-6.9, then this means there is a 95% chance the true result lies somewhere between 3.9 and 6.9 (and 5% would fall outside this range). Be leary of results with wide confidence intervals as this frequently means the sample size was too small Also, if the confidence intervals includes zero (example -3.0 to 30) one can't be sure an intervention had a positive or negative effect.[27]

Cost of Preventing an Event (COPE). Many people reviewing a medical article would want to know what the cost of the intervention is. A simple formula exists that sheds some light on the cost: COPE = NNT x number of years treated x 365 days x the daily cost of the treatment. Using our example of Amazingstatin = 50 x 1 x 365 x $2 or $36,500 to treat 50 patients for one year to prevent one heart attack. COPE scores can be compared with other similar treatments.[28]

Limitations of the Medical Literature and EBM

Because evidence is based on information published in the medical literature, it is important to point out some of the limitations researchers and clinicians must deal with on a regular basis:

- There is a low yield of clinically useful articles in general.[29]
- Conclusions from randomized drug trials tend to be more positive if they are from forprofit organizations.[30]
- Up to 16% of well publicized articles are contradicted in subsequent studies.[31] A more recent review of articles published from 2001 to 2010 in just the New England Journal of Medicine concluded that 40% represented reversal of prior recommendations.[32]
- Even systematic reviews have their limitations. An evaluation of over one thousand reviews in the Cochrane Library revealed that 44% of treatments were likely to be beneficial but in only 1% was no further research recommended. Similarly, they found that 49% of interventions were not determined to be either helpful or harmful and only in 1% of cases was no further research recommended.[33]
- Peer reviewers are "unpaid, anonymous and unaccountable" so it is often not known who reviewed an article and how rigorous the review was.[34]
- Many medical studies are poorly designed:[35]
  - The recruitment process was not described.[36]
  - Inadequate power (size) to make accurate conclusions. In other words, not enough subjects were studied.[37]
  - Studies published in high-impact journals attract a lot of attention but are often small randomized trials with results that may not be duplicated in future studies. This may be positive publication bias.[38]
  - Studies with negative results (i.e., results that are not statistically significant) are not always published or take more time to be published, resulting in "publication bias." In an effort to prevent this type of bias the American Medical Association advocates mandatory registration of all clinical trials in public registries. Also, the International Committee of Medical Journal Editors requires registration as a condition to publish in one of their journals. However, they do not require publishing the results in the registry at this time. Registries could be a data warehouse for future mining and some of the well-known registries include: ▪ ClinicalTrials.gov

  - WHO International Clinical Trials Registry
  - Global Trial Bank of the American Medical Informatics Association
  - Trial Bank Project of the University of California, San Francisco[39]

In spite of the fact that EBM is considered a highly academic process towards gaining medical truth, numerous challenges exist:

- Different evidence rating systems by various medical organizations
- Different conclusions by experts evaluating the same study
- Time intensive exercise to evaluate existing evidence
- Systematic reviews are limited in the topics reviewed (over 5,000 in the Cochrane Library in 2013) and are time intensive to complete (6 to 24 months). Often, the conclusion is that current evidence is weak and further high quality studies are necessary
- Randomized controlled trials are expensive. Drug companies tend to fund only studies that help a current non-generic drug they would like to promote
- Results may not be applicable to every patient population; i.e. external validity or generalizability
- Some view EBM as "cookbook medicine"[40]
- There is not good evidence that teaching EBM changes behavior[41]

Other Approaches

EBM has had both strong advocates and skeptics since its inception. One of its strongest proponents Dr. David Sackett published his experience with an "Evidence Cart" on inpatient rounds in 1998. The cart contained numerous EBM references but was so bulky that it could not be taken into patient rooms.[42] Since that article, multiple, more convenient EBM solutions exist. While there are those EBM advocates who would suggest the sole use of EBM resources, many others feel that EBM "may have set standards that are untenable for practicing physicians."[43-44]

Dr. Frank Davidoff believes that most clinicians are too busy to perform literature searches for the best evidence. He believes that healthcare needs "Informationists" who are experts at retrieving information.[45] To date, only clinical medical librarians (CMLs) have the formal training to take on this role. At large academic centers CMLs join the medical team on inpatient rounds and attach pertinent and filtered articles to the chart. As an example, Vanderbilt's Eskind Library has a Clinical Informatics Consult Service.[46-47] The obvious drawback is that CMLs are only available at large medical centers and are unlikely to research outpatient questions.

According to Slawson and Shaughnessy clinicians must become an "information master" to sort through the "information jungle." They define the usefulness of medical information as:

$$\textbf{Usefulness} = \frac{\textit{Validity} \times \textit{Relevance}}{\textit{Work}}$$

Only the clinician can determine if the article is relevant to his/her patient population and if the work to retrieve the information is worthwhile. Slawson and Shaughnessy also developed the notion of looking for "patient oriented evidence that matters" (POEM) and not "disease oriented evidence that matters" (DOEM). POEMS look at mortality, morbidity and quality of life whereas DOEMS tend to look at laboratory or experimental results. They point out that it is more important to know that a drug reduces heart attacks or deaths (POEM), rather than just reducing cholesterol levels (DOEM).[48] This school of thought also recommends that clinicians not read medical articles blindly each week but should instead learn how to search for patient-specific answers using EBM resources.[49] This also implies that physicians are highly motivated to pursue an answer, have adequate time and have the appropriate training. See case study below for example of EBM being applied to a clinical scenario.

Case Study

People with blockage of the carotid artery are at risk of stroke and death. They can be treated via surgery (called endarterectomy) or a less invasive procedure (putting a stent in the blocked area by going through the arteries, i.e., without surgery). The choice of procedure is controversial.

The evidence

A systematic review and meta-analysis appraised the quality of the totality of existing evidence in this area. They found 13 randomized controlled trials that enrolled a total of 7,484 patients. The methodological quality of the trials was moderate to high. Compared with carotid endarterectomy, stenting was associated with increased risk of stroke (relative risk [RR], 1.45; 95% confidence interval [CI], 1.06-1.99) and decreased risk of myocardial infarction (MI) caused by surgery (RR, 0.43; 95% CI, 0.26- 0.71). For every 1,000 patients opting for stenting rather than endarterectomy, 19 more patients would have strokes and 10 fewer would have MIs.

Patients values, preferences and context

Patients vary in their values such as aversion (fear) of stroke vs death and their fear of surgery and surgical complications such as scars in the neck and anesthesia. Patients also vary in their surgical risk (e.g., those with history of heart disease may prefer less invasive procedure to avoid prolonged anesthesia).

Guidelines

Due to the different impact of these procedures on the different outcomes, the guidelines were nuanced and stratified and allowed patients values and preferences, age, surgical and anatomical risk factors to be used in decision making. This example highlights the importance of patients' values and preferences as the second principle of EBM

References

Murad MH, Shahrour A, Shah ND, Montori VM, Ricotta JJ. A systematic review and meta-analysis of randomized trials of carotid endarterectomy vs stenting.J Vasc Surg. 2011 Mar;53(3):792-7. Epub 2011 Jan 8

Ricotta JJ, Aburahma A, Ascher E, et al. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease: executive summary. J Vasc Surg. 2011 Sep;54(3):832-6.

Evidence Based Health Informatics (EBHI)

EBHI is not a separate field, it represents the application of EBM tools to the field of health informatics. Dr. Elske Ammenwerth, a major proponent of EBHI defined this approach in 2006 as the "conscientious, explicit and judicious use of current best evidence when making decisions about information technology in healthcare."[50] While the quality of health informatics research has improved in the past decade, the overall report card for most studies is mixed, regardless of which technology is being

studied.[51] There are at least three reasons why published research studies in health informatics have not been optimally evidence based:

- **Early Hype**. In multiple other chapters the overly optimistic predictions regarding the impact of HIT on healthcare quality, safety, proficiency and cost reduction is pointed out. Many of these predictions were based on expert opinions or modeling and not high quality research. The hype was not isolated to HIT vendors and techno-enthusiasts; it was shared by academia and the federal government. It was aggravated by "technology pressure" or the natural tendency to try to fit new technologies into healthcare, even when the benefits have not been proven. This tends to raise expectations and may cause governments to introduce technology friendly policies, prior to having all of the facts. Early success stories were widely broadcast, even though many of the early innovations came from several medical centers with a track record for home grown successful technology.[52-53]

- **Methodological challenges**. Early research studies frequently suffered from internal validity (quality of study design and execution) and external validity (whether results are generalizable to other locations and patients) issues. Most studies reported on health information technology (HIT) are observational and retrospective in nature. Many are before/after studies.This distinction is important because cause and effect are difficult to prove with observational studies, compared to prospective RCTs. Randomization and blinding are difficult with health information technology. As an example, randomizing physicians to electronic prescribing (vs. paper prescribing) is difficult to implement and often impractical. In an observational study, physicians who volunteer to try electronic prescribing are likely "early adopters" and not representative of average physicians, which could skew the results. Alternate methods of randomization are feasible and desired. For example, "cluster randomization" would be a practical methodology in this situation. With this method, several clinics or hospitals can be randomized as a whole practice to electronic prescribing whereas other clinics or hospitals can be randomized to paper prescribing. HIT interventions are complicated in nature and one could argue represent a technosocioeconomic experience. Early studies tended to have small sample sizes, short term outcomes, inadequate endpoints, inadequate cost data and few comments about negative effects.

  Clearly, there are HIT innovations that are popular and save time such as drug look-up apps for mobile technology, patient portals and voice recognition but they have been poorly studied so there is a lack of good qualitative and quantitative data about their overall effect.

  There are several articles that focus on the methodological challenges of HIT research along with recommendations.[54-56]

  Dr. Ammenwerth has been instrumental in developing guidelines for *evaluating* health informatics (GEP-HI) and *reporting* health informatics studies (STARE-HI).[57-58]

- **The failure to anticipate unintended consequences** related to HIT adoption. Weiner coined the term "e-iatrogenesis" in 2007 to describe adverse events related to technology.[59] Sittig and Singh divided unintended consequences into: technology unavailable; technology malfunctions and technology functions but there is human error (e.g. e-presribing works properly but clinician entered wrong drug dose).[60] Additional aspects of unintended consequences that include patient safety issues are as follows:

  - The Joint Commission issued a Sentinel Event alert in 2008 to alert healthcare workers that 25% of medication errors were related to a technology issue.[61]

- Alert fatigue may cause drug and lab test alerts to be ignored.[62]
- Alarm fatigue is as big an issue as alert fatigue. This is discussed in more detail in the chapter on patient safety and HIT.[63]
- Distraction while using mobile devices and social media and issue while on the job [63]
- Upcoding with EHR use could increase healthcare costs and raise thorny ethical/legal issues.[64]
- HIT may raise, not lower long term healthcare costs.[65]
- Privacy and security issues are on the increase due to widespread HIT adoption. This is addressed in the chapter on Healthcare Privacy and Security.

The end result of this convergence of factors could be widespread negativism towards HIT, increased medical errors and cost and decreased governmental and payer-based funding. Hopefully, with better research over time one will have fewer questions and more answers. Dr. Ammenwerth has been instrumental in promoting EBHI and creating a web based repository (EVALDB) of over 1500 health informatics interventions archived.[66]

EBM Resources

There are many first-rate online medical resources that provide EBM type answers. They are all well referenced, current and written by subject matter experts. Several include the level of evidence (LOE). These resources can be classified as **filtered** (an expert has appraised and selected the best evidence, e.g., up-to-date or **unfiltered** (non-selected evidence, e.g., PubMed). For the EBM purist, the following are considered traditional or classic EBM resources:

- Clinical Evidence[67]
  - British Medical Journal product with two issues per year
  - Sections on EBM tools, links, training and articles
  - Evidence is oriented towards patient outcomes (POEMS)
  - Very evidence based with single page summaries and links to national guidelines
  - Available in paperback (Concise), CDROM, online or PDA format
- Cochrane Library[68] ○ Database of systematic reviews. Each review answers a clinical question
  - Database of review abstracts of effectiveness (DARE)
  - Controlled Trials Register ○ Methodology reviews and register ○ Fee-based
- Cochrane Summaries[69] ○ Part of the Cochrane Collaboration ○ Reviews can be accessed for a fee but abstracts are free. A search for low back pain in 2011, as an example, returned 393 reviews (abstracts)
- EvidenceUpdates[70] ○ Since 2002 BMJ Updates has been filtering all of the major medical literature. Articles are not posted until they has been reviewed for newsworthiness and relevance; not strict EBM guidelines ○ Users can go to their site and do a search or choose to have article abstracts emailed on a regular basis
  - These same updates are available through www.Medscape.com
- ACP Journal Club[71] ○ Bimonthly journal that can be accessed from OVID or free if a member of the American College of Physicians (ACP) ○ Over 100 journals are screened but very few articles end up being reviewed
  - They have a searchable database and email alerting system
- Practical Pointers for Primary Care[72] ○ Free online review of articles from the New England Journal of Medicine, Journal

of the American Medical Journal, British Medical Journal, the Lancet, the Annals of Internal Medicine and the Archives of Internal Medicine
    - Program can be accessed via the web or monthly reports e-mailed to those who subscribe
    - Editor dissects the study and makes summary comments that are very helpful to the average reader
- Essential Evidence Plus[73] ○ Physician oriented content that is feebased
    - Offers daily patient oriented evidence that matters (POEMS) (easy to read synopses) emailed to subscribers
    - Essential evidence plus search tool researches EBM topics, EBM guidelines (CPGs), POEMS, Cochrane Systematic Reviews, National Guideline Clearinghouse CPGs, and decision and diagnostic calculators
- Evidence Based On-Call[74] ○ User friendly site intended for quick look-ups for clinicians on call
    - Has multiple critically appraised topics (CATs) that point out the most important clinical pearls, with level of evidence
- TRIP Database has a search engine that using three different strategies to determine a search score[75]
- OVID has the ability to search the Cochrane Database of Systematic Reviews, DARE, ACP Journal Club and Cochrane Controlled Trials Register at the same time. Also includes Evidence Based Medicine Reviews.[76]
- SUMSearch. Free site that searches Medline, National Guideline Clearing House and DARE [77]
- Bandolier. Free online EBM journal; used mainly by primary care doctors in England. Provides simple summaries with NNTs. Resource also includes multiple monographs and books on EBM that are easy to read and understand.[78]
- Centre for Evidence Based Medicine is a comprehensive EBM site presented by Oxford University.[79]
- Best Bets (best evidence topics) lists topics of interest to primary care and emergency department clinicians. Hosted by the Emergency Department at the Manchester Royal Infirmary, UK.[80]
- Evidence Based Health Care is a very good EBM resource repository from the Health Sciences Library at the University of Colorado.[81]
- Google. Inserting "evidence based" with any search question will yield multiple results.[82]
- The NNT web site provides NNT and NNH for multiple medical conditions. In addition to therapy reviews they provide probabilities for diagnosis related conditions.[83]
- MDCalc is a web based calculator site based on EBM. Helpful for those looking for examples of common clinical calculations.[84]
- EBM for Mobile Technology:
    - MedCalc 3000 calculators are both web based and available for smartphones. EBM Stats includes approximately 50 EBM calculators to include NNT, NNH, etc. Fee-based app for iPhone and Android operating systems.[85]

Clinical Practice Guidelines

The Institute of Medicine in 1990 defined clinical practice guidelines (CPGs) as:

> "systematically developed statements to assist practitioner and patient decisions about health care for specific clinical circumstances"[86]

CPGs take the very best evidence based medical information and formulate an approach to treat a specific disease or condition. If one considers evidence as a continuum that starts by data generated from a single study, appraised and synthesized in a systematic review, CPGs would represent the next logical step in which evidence is transformed into a recommendation. Many medical organizations use CPGs with the intent

to improve quality of care, patient safety and/or reduce costs. Information technology assists CPGs by expediting the search for the best evidence and linking the results to EHRs and smartphones for easy access. Two areas in which CPGs may be potentially beneficial include disease management and quality improvement strategies, covered in other chapters. As 83% of Medicare beneficiaries have at least one chronic condition and 68% of Medicare's budget is devoted to the 23% who have five or more chronic conditions, CPGs can play an important role in improving care and lowering costs.[87] There is some evidence that guidelines that address *multiple comorbidities* (concurrent chronic diseases) actually do work. As an example, in one study of diabetics, there was a 50% decrease in cardiovascular and microvascular complications with intensive treatment of multiple risk factors.[88]

In spite of evidence to suggest benefit, several studies have shown poor CPG compliance by patients and physicians. The well publicized 2003 RAND study in the New England Journal of Medicine demonstrated that "overall, patients received 54% of recommended care."[89-90] In another study of guidelines at a major teaching hospital there was overuse of statin therapy (cholesterol lowering drugs). Overuse occurred in 69% of primary prevention (to prevent a disease) and 47% of secondary prevention (to prevent disease recurrence or progression), compared to national recommendations.[91]

It should be emphasized that creating or importing a guideline is the easy part because hundreds have already been created by a variety of national and international organizations. Implementing CPGs and achieving buy-in by all healthcare workers, particularly physicians, is the hard part.

Developing Clinical Practice Guidelines

Ideally, the process starts with a panel of content and methodology experts commissioned by a professional organization. As an example, if the guideline is about preventing venous thrombosis and pulmonary embolism, multi-disciplinary content experts would be pulmonologists, hematologists, pharmacists and hospitalists.

Methodology experts are experts in evidence based medicine, epidemiology, statistics, cost analysis, etc. The panel refines the questions, usually in PICO format, that was discussed in the previous chapter. A systematic literature search and evidence synthesis takes place. Evidence is graded and recommendations are negotiated. Panel members have their own biases and conflicts of interest that should be declared to CPG users. Voting is often needed to build consensus since disagreement is a natural phenomenon in this context.

The Strength of Recommendations

Guideline panels usually associate their recommendations by a grading that describes how confident they are in their statement. Ideally, panels should separately describe their confidence in the evidence (the quality of evidence, described in previous chapter) from the strength of the recommendation. The reason for this separation is that there are factors other than evidence that may affect the strength of recommendation. These factors are: (1) how closely balanced are the benefits and harms of the recommended intervention, (2) patients' values and preferences, and (3) resource allocation.

For example, even if there is very high quality evidence from randomized trials showing that warfarin (a blood thinner) decreases the risk of stroke in some patients, the panel may issue a weak recommendation considering that the harms associated with this medicine are substantial. Similarly, if high quality evidence suggests that a treatment is very beneficial, but this treatment is very expensive and only available in very few large academic centers in the US, the panel may issue a weak recommendation because this treatment is not easily available or accessible.

Application to Individuals

A physician should consider a strong recommendation to be applicable to all patients who are able to receive it. Therefore, physicians should spend his/her time and effort on explaining to patients how to use the recommended intervention and integrate it in their daily routine.

On the other hand, a weak recommendation may only apply to certain patients. Physicians should spend more time discussing pros and cons of the intervention with patients, use risk calculators and tools designed to stratify patients' risk to better determine the balance of harms and benefit for the individual. Weak recommendations are the optimal condition to use decision aids, which are available in written, videographic and electronic formats and may help in the decisionmaking process by increasing knowledge acquisition by patients and reduce their anxiety and decisional conflicts.

Appraisal and Validity of Guidelines

There are several tools suggested to appraise CPGs and determine their validity. These tools assess the process of conducting CPGs, the quality and rigor of the recommendations and the clarity of their presentation. The following list includes some of the attributes that guidelines users (clinicians, patients, policy makers) should seek to determine if a particular CPG is valid and has acceptable quality:

- Evidence based, preferably linked to systematic reviews of the literature
- Considers all relevant patients groups and management options
- Considers patient-important outcomes (as opposed to surrogate outcomes)
- Updated frequently
- Clarity and transparency in describing the process of CPGs development (e.g., voting, etc.)
- Clarity and transparency in describing the conflicts of interests of the guideline panel
- Addresses patients' values and preferences
- Level of evidence and strength of recommendation are given
- Simple summary or algorithm that is easy to understand
- Available in multiple formats (print, online, PDA, etc.) and in multiple locations
- Compatibility with existing practices
- Simplifies, not complicates decision making[92]

Barriers to Clinical Practice Guidelines

Attempts to standardize medicine by applying evidence based medicine and clinical practice guidelines have been surprisingly difficult due to multiple barriers:

- Practice setting: inadequate incentives, inadequate time and fear of liability. A 2003 study estimated that it would require 7.4 hours/working day just to comply with all of the US Preventive Services Task Force recommendations for the average clinician's practice! [93]
- Contrary opinions: local experts do not always agree with CPG or clinicians hear different messages from drug detail representatives
- Sparse data: there are several medical areas in which the evidence is of lower quality or sparse. Guideline panels in these areas would heavily depend on their expertise and should issue weak recommendations (e.g. suggestions) or no recommendations if they did not reach a consensus. These areas are problematic to patients and physicians and are clearly not ready for quality improvement projects or pay-forperformance incentives. For years, diabetologists advocated tight glycemic control of patients with type 2 diabetes; however, it turned out from results of recent large randomized trials that this strategy does not result in improved outcomes.[94]

- More information is needed why clinicians don't follow CPGs. Persell et al. reported in a 2010 study that 94% of the time when clinicians chose an exception to the CPG it was appropriate. Three percent were inappropriate and 3% were unclear.[95]
- Knowledge and attitudes: there is a lack of confidence to either not perform a test (malpractice concern) or to order a new treatment (don't know enough yet).

Information overload is always a problem.[96-97]

- CPGs can be too long, impractical or confusing. One study of Family Physicians stated CPGs should be no longer than two pages.[98-100] Most national CPGs are 50 to 150 pages long and don't always include a summary of recommendations or flow diagram
- Where and how should CPGs be posted? What should be the format? Should the format be standardized?
- Less buy-in if data reported is not local since physicians tend to respond to data reported from their hospital or clinic.
- No uniform level of evidence (LOE) rating system
- Too many CPGs posted on the National Guideline Clearinghouse. For instance, a non-filtered search in June 2013 by one author for "type 2 diabetes" yielded 608 CPGs. The detailed search option helps filter the search significantly.[100]
- Lack of available local champions to promote CPGs
- Excessive influence by drug companies: A survey of 192 authors of 44 CPGs in the 1991 to 1999 time frame showed: ○ 87% had some tie to drug companies ○ 58% received financial support ○ 59% represented drugs mentioned in the

  CPG ○ 55% of respondents with ties to drug companies said they did not believe they had to disclose involvement[101]
- Quality of national guidelines: National guidelines are not necessarily of high quality. A 2009 review of CPGs from the American Heart Association and the American College of Cardiology (1984 to Sept 2008) concluded that many of the recommendations were based on a lower level of evidence or expert opinion, not high quality studies.[102]
- No patient input. At this point patients are not normally involved in any aspect of CPGs, even though they receive recommendations based on CPGs. In an interesting 2008 study, patients who received an electronic message about guidelines experienced a 12.8% increase in compliance. This study utilized claims data as well as a robust rules engine to analyze patient data. Patients received alerts (usually mail) about the need for screening, diagnostic and monitoring tests. The most common alerts were for adding a cholesterol lowering drug, screening women over age 65 for osteoporosis, doing eye exams in diabetics, adding an ACE inhibitor drug for diabetes and testing diabetics for urine microalbumin.[103] It makes good sense that patients should be knowledgeable about national recommendations and should have these guidelines written in plain language and available in multiple formats. Also, because many patients are highly "connected" they could receive text messages via cell phones, social networking software, etc., to improve monitoring and treatment.

Initiating Clinical Practice Guidelines

Examples of Starting Points:

- High cost conditions: heart failure
- High volume conditions: diabetes
- Preventable admissions: asthma
- There is variation in care compared to national recommendations: deep vein thrombophlebitis (DVT) prevention
- High litigation areas: failure to diagnose or treat
- Patient safety areas: intravenous (IV) drug monitoring

The Strategy

- Leadership support is crucial
- Use process improvement tools such as the Plan-Do-Study-Act (PDSA) model Identify gaps in knowledge between national recommendations and local practice
- Locate a guideline champion who is a wellrespected clinical expert.[104] A champion

acts as an advocate for implementation based on his/her support of a new guideline

- Other potential team members:
  - Clinician selection based on the nature of the CPG
  - Administrative or support staff
  - Quality Management staff
- Develop action plans
- Educate all staff involved with CPGs, not just clinicians
- Pilot implementation
- Provide frequent feedback to clinicians and other staff regarding results
- Consider using the checklist for reporting clinical practice guidelines developed by the 2002 Conference on Guideline Standardization (COGS).[105]

Electronic Clinical Practice Guidelines

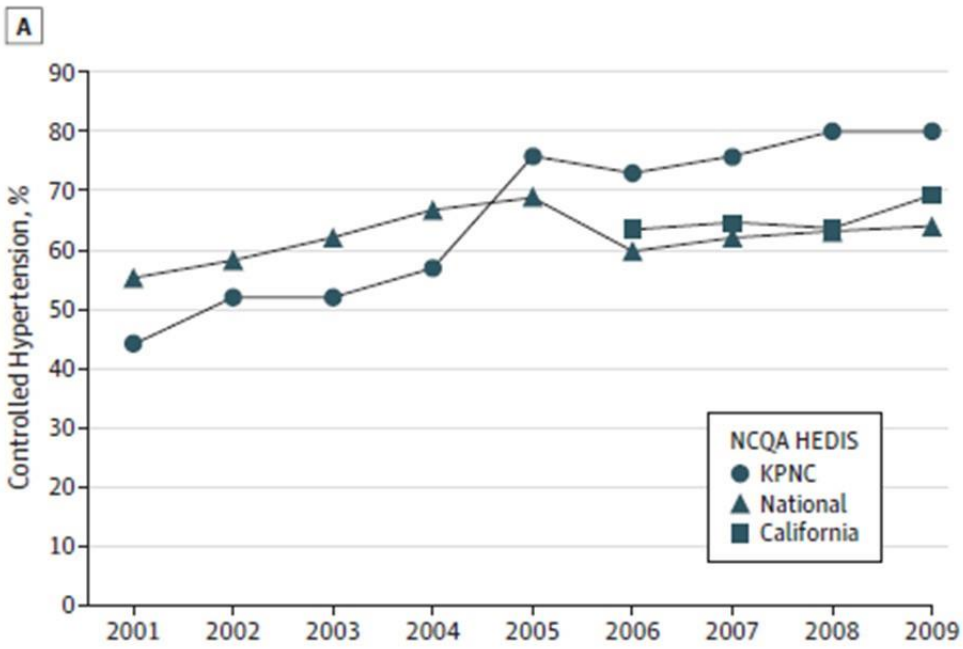
CPGs have been traditionally paper-based and often accompanied by a flow diagram or algorithm. With time, more are being created in an electronic format and posted on the internet or Intranet for easy access. Zielstorff outlined the issues, obstacles and future prospects of online practice guidelines in an early review.[107] What has changed since then is the ability to integrate CPGs with smartphones and electronic health records.

CPGs on smartphones: These mobile platforms function well in this area as each step in an algorithm is simply a tap or touch of the screen.

Clinical Practice Guideline Example

There have been thousands of CPGs created anddisseminated but far fewer have been studied, in terms of impact and even fewer have been significantly successful. Figure 14.2 represents a 2013 study reported from Kaiser Permanente Northern California (KPNC) for hypertensive control. Note that control of hypertension increased from a baseline of 43% in 2001 to 80% in 2009. The national averages are also presented. It is important to realize that Kaiser has had a sytem wide EHR since 2005 and that they have developed multiple evidence based CPGs. Furthermore, because everyone has the same leaderhip and information technology system, it is easier to get everyone on the team on the same page. This study is presented later in this chapter under "current knowledge."[106]

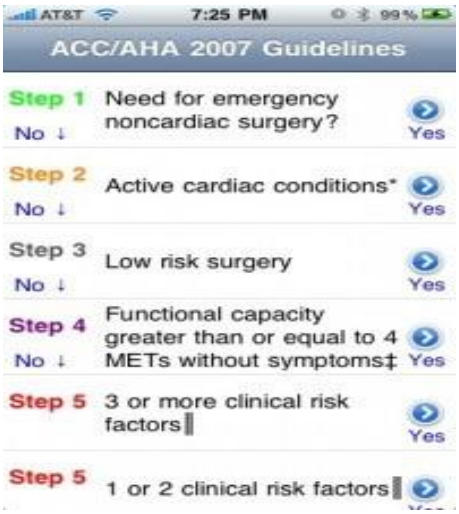
Figure 14.2: Results from 2013 Study using hypertension CPG



In Figures 14.3 and 14.4 programs are shown that are based on national guidelines for cardiac risk and cardiac clearance. Figure 14.3 depicts a calculator that determines the 10 year risk of heart disease based on serum cholesterol and other risk factors. A cardiac clearance program determines whether a patient needs further cardiac testing prior to an operation (Figure 14.4).[108] Many excellent guidelines for the smartphone exist that will be listed later in this chapter.

Figure 14.3: 10 Year Risk of Heart Disease

Figure 14.4: Cardiac Clearance



Web-Based Risk Calculators: Many of these are available on a mobile platform and are also available online. While these are not CPGs exactly, they are based on population studies and are felt to be part of EBM and can give direction to the clinician. As an example, some experts feel that aspirin has little benefit in preventing a heart attack unless your 10 year risk of one exceeds 20%. The following is a short list of some of the more popular online calculators:

- ATP III Cardiac risk calculator: estimates the 10 year risk of a heart attack or death based on your cholesterol, age, gender, etc.[109]
- FRAX fracture risk calculator: estimates the 10 year risk of a hip or other fracture based on all of the common risk factors for osteoporosis. Takes into account a patient's bone mineral density score, gender and ethnicity.[110]
- GAIL breast cancer risk assessment tool: estimates a patient's risk of breast cancer, again, based on known and accepted risk factors.[111]

  Stroke risk calculator: based on the Framingham study it predicts 10 year risk of a stroke based on known risk factors.[112]
- Risk of stroke or death for new onset atrial fibrillation: also based on the Framingham

study, it calculates five year risk of stroke or death.[113]

Electronic Health Record CPGs

Although not all electronic health records have embedded CPGs, there is definite interest in providing local or national CPGs at the point of care. CPGs embedded in the EHR are clearly a form of decision support. They can be linked to the diagnosis or the order entry process. In addition, they can be standalone resources available by clicking, for example, an "infobutton." Clinical decision support provides treatment reminders for disease states that may include the use of more cost effective drugs. Institutions such as Vanderbilt University have integrated more than 750 CPGs into their EHR by linking the CPGs to ICD-9 codes.[114] The results of embedded CPGs appears to be mixed. In a study by Durieux using computerized decision support reminders, orthopedic surgeons showed improved compliance to guidelines to prevent deep vein thrombophlebitis.[115] On the other hand, three studies by Tierney, failed to demonstrate improved compliance to guidelines using computer reminders for hypertension, heart disease and asthma.[116-118] Clinical decision support, to include order sets is discussed in more detail in the chapters on electronic health records and patient safety.

There are other ways to use electronic tools to promulgate CPGs. In an interesting paper by Javitt, primary care clinicians were sent reminders on outpatient treatment guidelines based only on claims data. Outliers were located by using a rules engine (Care Engine) to compare a patient's care with national guidelines. They were able to show a decrease in hospitalizations and cost as a result of alerts that notified physicians by phone, fax or letter. This demonstrates one additional means of changing physician behavior using CPGs and information technology not linked to the electronic health record.[119] Critics might argue that claims data are not as accurate, robust or current as actual clinical results.

Software is now available (EBM Connect) that can compute compliance with guidelines automatically using administrative data. The program translates guidelines from text to algorithms for 20 disease conditions and therefore would be much more efficient than chart reviews. Keep in mind it will tell users if, for example, LDL cholesterol was ordered, not the actual results.[120]

Clinical Practice Guideline Resources

Web-based CPGs

- **National Guideline Clearinghouse.** This program is an initiative of the Department of Health and Human Services and is the largest and most comprehensive of all CPG resources. Features offered: ○ Includes about 2664 guidelines ○ There is extensive search engine filtering i.e. one can search by year, language, gender, specialty, level of evidence, etc. ○ Abstracts are available as well as links to full text guidelines where available ○ CPG comparison tool ○ Forum for discussion of guidelines ○ Annotated bibliography ○ They link to 17 international CPG resource sites[100]
- **National Institute for Health and Clinical Excellence (NICE)** ○ Service of the British National Health Service ○ Approximately 100 CPGs are posted and dated ○ A user-friendly short summary is available as well as a lengthy guideline, both in downloadable pdf format ○ Podcasts are available[121]
- **Agency for Health Care Research and Quality (AHRQ)** ○ 1 of 12 agencies within the Department of Health and Human Services (HHS) ○ AHRQ supports health services research initiatives that seek to improve the quality of health care in America ○ AHRQ's funds evidence practice centers that conduct evidence appraisal and

reviews to support the development of clinical practice guidelines[122]

- **Health Team Works (formerly Colorado Clinical Guidelines Collaborative)** ○ Free downloads available for Colorado physicians and members of CCGC
  - ○ As of October 2011 they have 14 CPGs available
  - ○ Guidelines are in easy to read tables, written in a pdf format
  - ○ References, resources and patient handouts are available[123]
- **Institute for Clinical Systems Improvement (ICSI)** ○ Collaboration of three major health plans in Minnesota to improve healthcare quality
  - ○ Their web site includes about 40 CPGs with adoption by 180 countries
  - ○ Each CPG has a main algorithm with hyperlinked steps
  - ○ They also have order sets and patient resources. Some are for members only
  - ○ Evidence based and rated CPGs ○ Executive summary with date of publication[124]
  - ○ Smartphone-based CPGs

Most CPGs can be downloaded for the iPhone or iPad through the iTunes Store or the Android Market. For further information about medical apps, readers are referred to the chapter on mobile technology. The following are a sample of CPGs available for smartphones:

- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are available for iPhone and Android.
- Skyscape has multiple free CPGs available for download and also has 150+ fee-based CPGs. For example, Pediatric Clinical Practice Guidelines & Policies provides access to more than 30 clinical practice guidelines and more than 380 policy statements, clinical reports and technical reports.[125]
- mTBI Pocket Guide provides evidence based information about traumatic brain injury (TBI) and is available on the Android Market.
- ePSS is an app available for all operating systems, developed by the US Preventive Services Task Force. Preventive medicine guidelines are presented based on age, gender, smoking status, etc.[126]

Recommended Reading

Several recent articles are posted that address EBM and CPGs

- *Improving Adherence To Otitis Media Guidelines With Clinical Decision Support And Physician Feedback* is a 2013 clusterrandomized study of adherence to CPGs for acute otitis media (AOM) and otitis media with effusion (OME), using EHR-CDS and monthly physician feedback. Researchers found that clinical decision support (CDS) and feedback both improved CPG compliance but they were not additive.[127]
- *Childhood Obesity: Can Electronic Medical Records Customized With Clinical Practice Guidelines Improve Screening And Diagnosis?* Researchers wanted to know if CPGs that are part of an EHR improve recording of BMI, growth chart completion, risk score questionnaire completion and coding for obesity. In this before/after study there was an increase in all parameters, but the number of children reported with obesity was still below the known rates of obesity for this community.[128]
- *Use Of Health IT For Higher-Value Critical Care.* Authors advocated using CPGs in EHRs to risk stratify partients, particularly with non-cardiac illnesses, for admission to the critical care unit.[129]

  A "Smart Heart Failure Sheet: Using Electronic Medical Records To Guide Clinical Decision Making. The authors report their experience with an embedded CPG Developed at the Beth Israel Deaconess Medical Center. The resource is highly educational for both the physician and patient. The smart sheet automatically

uploads lab and imaging pertinent to heart failure diagnosis and treatment. It appears in the EHR after adding heart failure to the problem summary list or demonstrating a low ejection fraction by echocardiography. The program also allows a clinician to see all of his/her patients with heart failure, along with flow charts, etc. No outcome data has been published.[130]

- *Improved Blood Pressure Control Associated with a Large Scale Hypertension Program.* This Kaiser-Permanente Northern California (KPNC) study looked at blood pressure control based on reported HEDIS measures from 2001-2009 in California. After implementing a hypertension CPG and creating a hypertension registry for the entire region they also instituted a polypill (single pill containing several blood pressure medications). Follow-up visits were by medical assistants. The end result was to see control rise from 43% to 80%; a percentage considerably higher than the national average (55% in 2001, 64% in 2009). Also, see Figure 14.2.[106]

- *Why Randomized Controlled Trials are Needed to Accept New Practices: 2 World Views* and *The Necessity for Clinical Reasoning in the Era of Evidence Based Medicine.* Both of these articles appeared in a late 2013 issue of the Mayo Clinic Proceedings. They highlight the healthly controversy between those who believe clinicians must have evidence before they proceed and those who accept that the evidence is lacking or mixed so one must employ a good clinical reasoning.[131-132]

Future Trends

The field of EBM continues to evolve. Methodologists continue to identify opportunities to improve our understanding and interpretation of research findings. It is anticipated that more standardization of reporting and more transparency. The Appraisal of Guidelines for Research & Evaluation (AGREE II) is a web based tool that rates the quality of CPGs with 23 items covering 6 quality domains. Two studies published in 2010 help refine our knowledge base:

- Trials are often stopped early when extreme benefits are noted in the intervention group. The rationale for stopping enrollments of participants is that it is "unethical" to continue randomizing patients to the placebo arm because researchers are depriving them from the benefits of the intervention. However, it was found that stopping trials early for benefit exaggerates treatment effect by more than 30%; simply because the trial is stopped at a point of extreme benefit that is clearly made extreme by chance. Such exaggeration leads to the wrong conclusions by patients and physicians embarking on comparing the pros and cons of a treatment and also leads to the wrong decisions by policymakers. In fact, stopping early may be unethical from a societal and individual point of view.[133]

- The second recent advancement in methodology relates to the finding that authors who have financial affiliation with the industry are three times more likely to make statements that are favorable to the sponsored interventions. It is very plausible that this bias is subconscious and unintentional; nevertheless, as readers of the literature, one should recognize the potential and implications of this bias.[134]

Advances with CPGs will be related to better integration with a variety of HIT and more research into those factors that improve CPG compliance. It is not known if embedded CPGs will become part of stage 3 meaningful use.

Conclusion

Knowledge of EBM is important for those involved with patient care, quality of care issues or research. Rapid access to a variety of online EBM resources has changed how clinicians practice medicine. In spite of its shortcomings, an evidence based approach helps healthcare workers find the best possible answers. Busy clinicians are likely to choose commercial high quality resources, while academic clinicians are likely to select true EBM resources. Ultimately, EBM tools and resources will be integrated with electronic health records as part of clinical decision support.

The jury is out regarding the impact of CPGs on physician behavior or patient outcomes. Busy clinicians are slow to accept new information, including CPGs. Whether embedding CPGs into EHRs will result in significant changes in behavior that will consistently result in improved quality, patient safety or cost savings remains to be seen. It is also unknown if linking CPGs to better reimbursement (pay-forperformance) will result in a higher level of acceptance. While it is being determined how to optimally improve healthcare with CPGs, most authorities agree that CPGs need to be concise, practical and accessible at the point of care. Every attempt should be made to make them electronic and integrated into the workflow of clinicians.

Acknowledgement

We thank Dr. M. Hassan Murad and Dr. Brian Haynes for their contributions to this chapter.

Key Points

- Evidence Based Medicine (EBM) is the academic pursuit of the best available answer to a clinical question
- The two fundamental principles of EBM are: (1) a hierarchy of evidence exists (i.e., not all evidence is equal) and (2) evidence alone is insufficient for medical decision making. It should rather be complemented by patient's values, preferences and circumstances.
- Health information technology will hopefully improve medical quality, which is primarily based on EBM.
- There are multiple limitations of both EBM and the medical literature.
- The average clinician should have a basic understanding of EBM and know how to find answers using EBM resources.
- Clinical Practice Guidelines (CPGs), based on evidence based medicine, are the roadmap to standardize medical care.
- CPGs are valuable for chronic disease management or as a means to measure quality of care.

References

1. Evidence Based Medicine: What it is, what it isn't. http://www.cebm.net/ebm_is_isnt.asp (Accessed September 3, 2005)
2. Crossing the Quality Chasm: A new health system for the 21th century (2001) The National Academies Press http://www.nap.edu/books/0309072808/html/ (Accessed September 3, 2005)
3. MedlinePlus http://www.nlm.nih.gov/medlineplus/ency/article/003108.htm (Accessed September 3, 2006)
4. Teece I, Crawford I. Bed rest after spinal puncture. BMJ http://emj.bmjjournals.com/cgi/content/full/19/5/432 (Accessed Aug 24, 2006)
5. Guyatt GH. Evidence based medicine. ACP J Club 1991;114:A16
6. Evidence Based Medicine. Wikipedia. http://en.wikipedia.org/wiki/Evidence_based-medicine (Accessed September 5,

2005)

7. Levin A. The Cochrane Collaboration Ann of Int Med 2001;135:309-312
8. Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. BMJ 1948;2:769-82
9. Gandhi GY, Murad MH, Fujiyoshi A, et al. Patient-important outcomes in registered diabetes trials. JAMA. Jun 4 2008;299 (21):2543-2549
10. Agency for Healthcare Quality and Research. Effective Healthcare Program. www.effectivehealthcare.ahrq.gov (Accessed June 18, 2013)
11. Choosing Wisely. www.choosing wisely.org (Accessed June 18, 2013)
12. Davis DA et al. Changing physician performance. A systematic review of the effect of continuing medical education strategies. JAMA 1995; 274: 700-1.
13. Sibley JC. A randomized trial of continuing medical education. N Engl J Med 1982; 306: 511-5.
14. Fordis M et al. Comparison of the Instructional Efficacy of Internet-Based CME with Live Interactive CME Workshops. JAMA 2005;294:1043-1051
15. National Library of Medicine PICO http://askmedline.nlm.nih.gov/ask/pico.php (Accessed September 7, 2005)
16. *Evidence-Based Medicine How to practice and teach* it, by Straus, Glasziou, Richardson and Haynes. Fourth Edition. Churchill Livingstone, Elsevier. 2011. Toronto, CA.
17. Centre for Evidence Based Medicine http://www.cebm.net (Accessed September 7, 2013)
18. Haynes RB. Of studies, syntheses, synopses and systems: the "4S evolution of services for finding the best evidence." ACP J Club 2001;134: A11-13
19. Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trails. 1996;17:1-12
20. The well built clinical question. University of North Carolina Library http://www.hsl .unc.edu/Services/Tutorials/EBM/Supplements/QuestionSupplement.htm (Accessed September 20, 2005)
21. Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. The GRADE Working Group. Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommenddations. BMJ 2008;336:924-926
22. Buitrago-Lopez A, Sanderson J, Johnson L, Warnakula S, Wood A, Di Angelantonio E, Franco OH. Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis. BMJ. 2011 Aug 26;343:d4488. doi: 10.1136/bmj.d4488.
23. Henley E. Understanding the Risks of Medical Interventions Fam Pract Man May 2000;59-60
24. Nouvo J, Melnikow J, Chang D. Reporting the Number Needed to Treat and Absolute Risk Reduction in Randomized Controlled Trials JAMA 2002;287:2813-2814
25. Lacy CR et al. Impact of Presentation of Research Results on Likelihood of Prescribing Medications to Patients with Left Ventricular Dysfunction. Am J Card 2001;87:203-207
26. Collaborative Atorvastatin Diabetes Study (CARDS) Lancet 2004;364:685-96
27. Confidence Intervals. www.onlinestatbook.com (Accessed June 18, 2013)
28. Maharaj R. Adding cost to number needed to treat: the COPE statistic. Evidence Based Medicine 2007;12:101-102
29. Haynes RB. Where's the Meat in Clinical Journals? ACP Journal Club Nov/Dec 1993: A-22-23
30. Als-Neilsen B, Chen W, Gluud C, Kjaergard LL. Association of Funding and Conclusions in Randomized Drug Trials. JAMA 2003; 290:921-928

31. Ioannidis JPA. Contradicted and Initially Stronger Effects in Highly Cited Clinical Research JAMA 2005;294:218-228

32. Prasad V, Vandross A, Toomey C et al. A Decade of Reversal: An Analysis of 146 Contradicted Medical Practices. Mayo Clin Proc 3013; 88(8):790-798

33. El Dib RP, Attallah AN, Andriolo RB. Mapping the Cochrane evidence for decision making in health care. J Eval Clin Pract 2007;13(4):689-692

34. Kranish M. Flaws are found in validating medical studies The Boston Globe August 15, 2005 http://www.boston.com/news/nation/articles/2005/08/15/flaws_are_found_in_validating_medical_studies/ (Accessed June 12, 2007)

35. Altman DG. Poor Quality Medical Research: What can journals do? JAMA 2002;287:2765-2767

36. Gross CP et al. Reporting the Recruitment Process in Clinical Trials: Who are these Patients and how did they get there? Ann of Int Med 2002;137:10-16

37. Moher D, Dulgerg CS, Wells GA. Statistical Power, sample size and their reporting in randomized controlled trials JAMA 1994;22:1220-1224

38. Siontis KC, Evangelou E, Ionnidis JP. Magnitude of effects in clinical trials published in high impact general medical journals. Int J Epidemiol 2011;40(5):1280-1291

39. Evidence Based Medicine. Clinfowiki. www.informatics-review.com/wiki/index.php/EBM (Accessed June 19, 2007)

40. Straus SE, McAlister FA Evidence Based Medicine: a commentary on common criticisms Can Med Assoc J 2000;163:837-841

41. Dobbie AE et al. What Evidence Supports Teaching Evidence Based Medicine? Acad Med 2000;75:1184-1185

42. Sackett DL, Staus SE. Finding and Applying Evidence During Clinical Rounds: The "Evidence Cart" JAMA 1998;280:1336-1338

43. Grandage K et al. When less is more: a practical approach to searching for evidence based answers. J Med Libr Assoc 90(3) July 2002

44. Schilling LM et al. Resident's Patient Specific Clinical Questions: Opportunities for Evidence Based Learning Acad Med 2005;80:51-56

45. Davidoff F, Florance V.The Informationist: A New Health Profession? Ann of Int Med 2000;132:996-999

46. Giuse NB et al. Clinical medical librarianship: the Vanderbilt experience Bull Med Libr Assoc 1998;86:412-416

47. Westberg EE, Randolph AM. The Basis for Using the Internet to Support the Information Needs of Primary Care JAMIA 1999;6:6-25

48. Slawson DC, Shaughnessy AF, Bennett JH. Becoming a Medical Information Master: Feeling Good About Not Knowing Everything J of Fam Pract 1994;38:505-513

49. Shaughnessy AF, Slawson DC and Bennett JH. Becoming an Information Master: A Guidebook to the Medical Information Jungle J of Fam Pract 1994;39:489-499

50. Ammenwerth E. Is there sufficient evidence for evidence-based informatics? 2006. www.gmds2006.de/Abstracts/49.pdf (Accessed September 25, 2013)

51. Keizer NF, Ammenwerth E. The quality of evidence in health informatics: how did the quality of health care IT evaluation publications develop from 1982 to 2005? IJMI. 2008;77:41-39

52. Chaudry B. Systematic review: impact of health information technology on quality, efficiency and cost of medical care. Ann Int Med 2006;144(10):742-752

53. Orszag Pl. Evidence on the costs and benefits of health information technology. CBO. July 24, 2008. www.cbo.gov (Accessed July 31, 2008)

54. Shcherbatykh I, Holbrook A, Thabane L, et. al. Methodologic issues in health informatics trials: the complexities of

complex interventions. J Am Inform Med Assoc 2008;15:575-580

55. Ammenwerth E, Schnell-Inderst, Siebert U. Vision and challenges of EvidenceBased Health Informatics: A case study of a CPOE meta-analysis. IJMI 2010;79:e83e88
56. Liu JL, Wyatt JC. The case for randomized controlled trials to assess the impact of clinical information systems. J Am Med Inform Assoc. 2011;18:173-180
57. Nykanen P, Brender J, Ammenwerth E et al. Guideline for good evaluation practice in health informatics (GEP-HI). IJMI 2011;80:815-827
58. Talmon J, Ammenwerth E, Brender J et.al. STARE-HI---Statement on reporting of evaluation studies in Health Informatics. IJMI 2009;78:1-9
59. Weiner J. "e-iatrogenesis": The most critical unintended consequence of CPOE and other HIT. J Am Med Inform Assoc. 2007;14:387-388
60. Sittig D, Singh H. Defining health information errors: new developments since to Err is Human. Arch Int Med. 2011;171(14):1279-1282
61. The Joint Commission. Sentinel Alert Series. No.42. December 11, 2008. http://www.jointcommission.org/assets/1/18/SEA_42.pdf (Accessed September 25, 2013)
62. Singh H, Spitzmueller C, Petersen N, et.al. Information overload and missed test results in electronic health record-based settings. JAMA. 2013. March 4. Online first. (Accessed April 4, 2013)
63. Top 10 Health technology hazards for 2013. Health Devices. Vol. 41(11). November 2012. www.ecri.org (Accessed December 1, 2012)
64. Schulte F. How doctors and hospitals have collected billions in questionable Medicare fees. www.publicintegrity.org . September 15, 2012. (Accessed January ,6 2013)
65. Adler-Milstein J, Gree CE, Bates DW. A survey analysis suggests that electronic health records will yield revenue gains for some practices and losses for many Health Affairs. 2013;32(3):562-570
66. Evaluation Database (EVALDB) http://evaldb.umit.at (Accessed January 3, 2013)
67. Clinical Evidence www.clinicalevidence.com (Accessed September 25, 2013)
68. Cochrane Library http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HELP Cochrane.html (Accessed September 25, 2013)
69. Cochrane Review http://www.cochrane.org/reviews/index.htm (Accessed September 25, 2013)
70. EvidenceUpdates http://plus.mcmaster.ca/evidenceupdates (Accessed September 25 ,2013)
71. ACP Journal Club. http://plus.mcmaster.ca/acpjc (Accessed September 25, 2013)
72. Practical Pointers for Primary Care www.practicalpointers.org (Accessed September 25, 2013)
73. Essential Evidence Plus www.essentialevidenceplus.com (Accessed June 19, 2013)
74. Evidence Based On-call. www.eboncall.org (Accessed November 12, 2011)
75. Trip Database www.tripdatabase.com (Accessed September 25, 2013)
76. OVID http://gateway.ovid.com (Accessed November 12, 2011)
77. SUMSearch http://sumsearch.uthscsa.edu (Accessed November 12, 2011)
78. Bandolier http://www.medicine.ox.ac.uk/bandolier/ (Accessed September 25, 2013)
79. Centre for Evidence Based Medicine www.cebm.net (Accessed September 25, 2013)
80. Best Bets. www.bestbets.org (Accessed June 18, 2013)
81. Evidence Based Healthcare http://hslibraryguides.ucdenver.edu (Accessed June 18, 2013)
82. Google Search. www.google.com

(Accessed September 25, 2013)

83. The NNT www.thennt.com (Accessed June 18, 2013)
84. MDCalc. www.mdcalc.com (Accessed June 18, 2013)
85. MEDCalc 3000. http://medcalc3000.com/index.htm (Accessed September 25, 2013)
86. Institute of Medicine (1990). Clinical Practice Guidelines: Directions for a New Program. Field MJ and Lohr KN (eds). Washington DC. National Academy Press. Page 38
87. O'Connor P. Adding Value to Evidence Based Clinical Guidelines JAMA 2005;294:741-743
88. Gaede P. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes NEJM 2003;348:383-393
89. McGlynn E . Quality of Health Care Delivered to Adults in the US RAND Health Study NEJM Jun 26, 2003
90. Crossing the Quality Chasm: A new Health System for the 21th century 2001. IOM. http://darwin.nap.edu/books/0309072808/html/227.html (Accessed March 5, 2006)
91. Abookire SA, Karson AS, Fiskio J, Bates DW. Use and monitoring of "statin" lipidlowering drugs compared with guidelines Arch Int Med 2001;161:2626-7
92. Oxman A, Flottorp S. An overview of strategies to promote implementation of evidence based health care. In: Silagy C, Haines A, eds Evidence based practice in primary care, 2nd ed. London: BMJ books 2001
93. Yarnall KSH, Pollak KL, Østbye T et al. Primary Care: Is There Enough Time for Prevention? Am J Pub Health 2003;93 (4):635-641
94. Montori VM, Fernandez-Balsells M. Glycemic control in type 2 diabetes: time for an evidence based about face? Ann Intern Med 2009;150 (11):803-808
95. Persell SD, Dolan NC, Friesema EM et al. Frequency of Inappropriate Medical Exceptions to Quality Measures. Ann Intern Med 2010;152:225-231
96. Grol R, Grimshaw J. From Best evidence to best practice: effective implementation of change in patient's care Lancet 2003;362:1225-30
97. Legare F, O'Connor AM, Graham ID. et. al. Primary health care professionals' views on barriers and facilitators to the implementation of the Ottawa Decision Support Framework in practice. Pat Ed Couns. 2006;63:380-390
98. Wolff M, Bower DJ, Marabella AM, Casanova JE. US Family Physicians experiences with practice guidelines. Fam Med 1998;30:117-121
99. Zielstorff RD. Online Practice Guidelines JAMIA 1998;5:227-236
100. National Guideline Clearinghouse www.guideline.gov (Accessed September 26, 2013)
101. Choudry NK et al. Relationships between authors of clinical practice guidelines and the pharmaceutical industry JAMA 2002;287:612-7
102. Tricoci P, Allen JM, Kramer JM et al. Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines JAMA 2009;301(8):831-841
103. Rosenberg SN, Shnaiden TL, Wegh AA et al. Supporting the Patient's Role in Guideline Compliance: A Controlled Study. Am J Manag Care 2008;14 (11):737-744
104. Stross JK. The educationally influential physician – Journal of Continuing Education Health Professionals 1996; 16: 167-172)
105. Shiffman RN, Shekelle P, Overhage JM et al. Standardized Reporting of Clinical Practice Guidelines: A Proposal form the Conference on Guideline Standardization. Ann Intern Med 2003;139:493-498
106. Jaffe MG, Lee GA, Young JD et al. Improved Blood Pressure Control Associatied with A Large Scale Hypertension Program. JAMA 2013;310(7):699-705

107. Zielstorff, RD. Online Practice Guidelines. Issues, Obstacles, and Future Prospects. JAMIA 1998;5:227-236

108. Cardiac Clearance www.statcoder.com (Accessed September 25, 2013)

109. ATP III Risk http://cvdrisk.nhlbi.nih.gov/calculator. asp (Accessed September 25, 2013)

110. Frax Calculator http://www.shef.ac.uk/FRAX/ (Accessed September 25, 2013)

111. Gail Breast Cancer Risk http://www.cancer.gov/bcrisktool/ (Accessed September 25, 2013)

112. Stroke Risk Calculator. Cleveland Clinic. http://my.clevelandclinic.org/health/tools-quizzes/calculators/stroke-risk-calculator.aspx (Accessed September 26, 2013)

113. Stroke or death due to atrial fibrillation http://www.zunis.org/FHS%20Afib%20Risk%20Calculator.htm (Accessed September 26, 2013)

114. Giuse N et al. Evolution of a Mature Clinical Informationist Model JAIMA 2005;12:249-255

115. Durieux P et al. A Clinical Decision Support System for Prevention of Venous Thromboembolism: Effect on Physician Behavior JAMA 2000;283:2816-2821

116. Tierney WM et al. Effects of Computerized Guidelines for Managing Heart Disease in Primary Care J Gen Int Med 2003;18:967-976

117. Murray et al. Failure of computerized treatment suggestions to improve health outcomes of outpatients with uncomplicated hypertension: results of a randomized controlled trial Pharmacotherapy 2004;3:324-37

118. Tierney et al. Can Computer Generated Evidence Based Care Suggestions Enhance Evidence Based Management of Asthma and Chronic Obstructive Pulmonary Disease? A Randomized Controlled Trial Health Serv Res 2005;40:477-97

119. Javitt JC et al. Using a Claims Data Based Sentinel System to Improve Compliance with Clinical Guidelines: Results of a Randomized Prospective Study Amer J of Man Care 2005;11:93-102

120. Welch, PW et al. Electronic Health Records in Four Community Physician Practices: Impact on Quality and Cost of Care. JAMIA 2007;14:320-328

121. National Institute for Health and Clinical Excellence www.nice.org.uk (Accessed September 26, 2013)

122. Agency for Health Care Research and Quality (AHRQ) http://www.effectivehealthcare.ahrq.gov/ (Accessed September 26, 2013)

123. Health Team Works www.healthteamworks.org (Accessed September 26, 2013)

124. Institute for Clinical Systems Improvement. www.icsi.org (Accessed June 18, 2013)

125. Skyscape www.skyscape.com (Accessed September 26, 2013)

126. Electronic Preventive Sevices Selector http://epss.ahrq.gov/PDA/index.jsp (Accessed October 20, 2013)

127. Forrest CB, Fiks AG, Bailey LC et.al. Improving adherence to otitis media guidelines with clinical decision support and physician feedback. Pediatrics. 2013;131(4):e1071-1081

128. Savinon, C, Taylor JS, Canty-Mitchell J et.al. Childhood obesity: Can electronic medical records customized with clinical practice guidelines improve screening and diagnosis? J Am Acad Nurse Pract. 2012;24(8):463-471

129. Chen LM, Kennedy EH, Sales A et. al. Use of health IT for higher-value critical care. NEJM 2013;368(7):594-597

130. Battaglia L, Aronson MD, Neeman N et al. A "Smart" heart failure sheet: Using electronic medical records to guide clinical decision making. Am J Med 2011;124(2):118-120

131. Prasad V. Why Randomized Controlled Trials Are Needed to Accept New Practices: 2 Medical Word Views. Mayo Clin Proc 2013;88(10):1046-1050

132. Sniderman AD, LaChapelle KJ, Rachon NA, Furberg CD. The Necessity for Clinical Reasoning in the Era of Evidence Based Medicine. Mayo Clin Proc 2013;88(10):1108-1114

133. Bassler RD, Briel M, Murad MH et al. Stopping Randomized Trials Early for Benefit and Estimation of Treatment Effects: Systematic Review and MetaRegression Analysis. JAMA 2010;303 (12):1180-7

134. Wang AT, McCoy CP, Murad MH. Association Between Affiliation and Position on Cardiovascular Risk with Rosiglitazone: Cross Sectional Systematic Review. BMJ 2010. March 18:340.c1344. doi:10.1136/bmj.c1344 (Accessed April 10, 2010)