

# MEDICAL SCIENCE & PRACTICE

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## Wanted: Critical Thinkers

Overconfident doctors can be hazardous to your health. Doctors' capacity to change perspective can be key to optimal health care. So claims an experienced clinician, who believes senior physicians must lead the way in creating an open climate to improve clinical decisions.

On Carl-Gustaf Elinder's desk, at one of the many identical physician offices at Karolinska University Hospital, Huddinge, you will find a book of optical illusions.

– If you look quickly at the images you will see only colored patterns, he explains. But if you fix your eyes on an imaginary point behind the image, suddenly the hidden motif reveals itself.

Bob Eisdale / Getty

## Size matters – in treatment effects

A stereotypical response to someone who questions an unproven treatment is: “Oh, you’re just the type of person who wouldn’t trust your own mother”. Apart from the lack of evidence showing that mothers are more trustworthy than fathers, acceptance of untested interventions on blind faith is not only naïve, but potentially harmful.

Evidence based medicine (EBM) is not about disbelieving everything. And it’s not about demanding randomized trials to confirm the obvious, eg, that blood transfusion benefits those who have lost a lot of blood, that insulin helps diabetics, or that suturing repairs major wounds. Trials, however, may show how to best deliver these treatments.

Dramatic benefits need not be tested. A rational person would never claim that healthcare providers should do nothing until a randomized trial confirms what is already known. That would indeed be a fundamentalist and clearly perilous stance.

Nevertheless, we still find pompous windbags who maintain that EBM demands evidence to demonstrate the obvious, as a kind of perverted nihilism. That’s probably why four leading EBM proponents (BMJ 2007;334:349–51), recently felt the need to reiterate that randomized trials are not always necessary. Glasziou, Chalmers, Rawlins, and McCulloch reassure us that science does not ask us to prove again that the Earth is round.

Instead, they suggest a rule of thumb – if we estimate that a treatment improves patients’ health by, say, 10 times, it is highly unlikely that we can attribute the outcome to confounding alone.

The authors also remind us of Hill’s classic criteria for making causal inferences from observational studies (Proc R Soc Med 1965;58: 295–300). These include: treatment preceding the effect, the existence of a strong relation (eg, a strong correlation or a large relative risk), consistency across settings and methods, coherence with knowledge of related treatments, dose–response relation, specificity, ie, treatment causing the effect, and little else.

As a case in point, SBU is currently testing a new system for grading the evidence, suggested by the GRADE working group. Here, evaluators consider effect size and the strength of a relation when grading the evidence. Just as before, SBU takes a broader view encompassing more than randomized trials alone.

The ultimate value of EBM depends on asking truly relevant questions and seeking the best available evidence to answer them. It’s about minimizing unnecessary uncertainty, acting on the best available knowledge, spotting important knowledge gaps, and filling them in. Why should we argue?



RAGNAR LEVI, EDITOR

To get the ‘whole picture’ you need to look from different of perspectives.

– Well, I like to change perspectives, trying to see things from different points of view, says Dr Elinder, who heads the Department of Renal Medicine at Karolinska.

### CRITICAL CAPACITY

According to a recent article in the *British Medical Journal*, the capacity to see several possible explanations for a given symptom profile can be a critical characteristic in medical decision-making. Weighing all the facts, even when they contradict our expectations, can be key in reaching an accurate diagnosis and prescribing the best treatment.

But this is a challenging art. Clearly, we tend to strive for consistency and try to confirm initial impressions. For example, physicians tend to direct their questions to patients in a way that reinforces their early judgments. But starting off on the wrong track makes it difficult and time consuming to get things right.

### OPPOSING OPINIONS

– We all attempt to justify our own opinions. For instance, a few days ago I overheard how two physicians came to diametrically opposed conclusions about the effects of cortisone treatment in a patient with gouty arthritis. The physician who administered the cortisone believed the treatment had a positive effect. Of course, this interpretation supported his treatment decision. But his colleague, who had not been involved, had the opposite view. For the patient’s sake it is important

to consult colleagues who can help reveal the different shades of gray.

– Myself, I know that when I read scientific journals it’s easier to latch on to studies that support my pet hypotheses and passions. For example, I think that we prescribe entirely too much omeprazol in the field of renal medicine. When I see studies that confirm this, I copy the articles and send them to colleagues. Studies that point in the opposite direction I probably miss.

### CONFIRMATORY BIAS

In psychology, this common human phenomenon is called confirmatory bias. Scientists seem to fall into the trap as easily as others. A study asked medical experts to grade the methodology used in different scientific articles that had employed exactly the same scientific methods, but had arrived at completely different results. The findings showed that experts gave higher grades to the studies that confirmed their opinions than to those that did not.

– Having a one-track mind in medicine is risky. Fortunately, I have people around me who dare to question my thinking, laughs Carl-Gustaf Elinder.

Another problem addressed in the *British Medical Journal* is that decisions are often based on the facts that are easiest to remember and not on the data that are most relevant.

– Several years ago at the Department of Renal Medicine here in Huddinge we had two deaths following renal biopsy. Statistics indicate perhaps once in ten thousand



Dr Carl-Gustaf Elinder

or hundred thousand cases. I believe that we who experienced these dramatic cases are now somewhat more restrictive with the procedure than our colleagues in Solna who were not exposed to this mortality rate.

As Department Head, Carl-Gustaf Elinder sees an obligation to try to create an open and trusting climate at the department, where people feel free to think independently and critically without this being perceived as threatening or problematic.

– Senior physicians must lead the way and show younger ones that it is OK to express contrary opinions, and that it is important for everyone to re-examine their points of view.

#### Additional reading

Klein JG. Five pitfalls in decisions about diagnostics and prescribing. *Brit Med J* 2005;330:781-783.

## AVOID FALLACIES IN REASONING

### DISTINGUISH BETWEEN CORRELATION AND CAUSE

An association, or correlation, between two events does not necessarily infer a cause-and-effect relationship between them. Example: Because a certain gene is more common in people with depression does not necessarily mean that the gene causes depression.

### IF B OCCURS AFTER A THIS DOES NOT MEAN THAT A CAUSES B

A time correlation is often misinterpreted as a causal correlation. In Latin, this classical error in reasoning is expressed: *post hoc ergo propter hoc* (after this, therefore because of this). Example: A patient gets a headache after having a massage. This does not necessarily mean that the massage caused the headache. That a patient improved after having taken a drug does not necessarily mean that the drug caused the patient to improve.

### NECESSARY OR SUFFICIENT CAUSE?

The fact that a certain cause is necessary to produce a certain effect does not automatically mean it is sufficient

to cause the effect. Other concurrent conditions might be necessary. Example: A virus is necessary to cause a particular infection, but a favorable environment and a receptive host are also necessary for the infection to develop.

### LACK OF EVIDENCE OR LACK OF EFFECT?

Because we lack evidence supporting an assertion does not mean that the assertion is false. The fact that we lack evidence against it does not mean that the assertion is true. Example: The absence of reports on side effects does not mean that a treatment is free from side effects. The lack of evidence that a treatment is effective does not necessarily mean that it is ineffective.

### DISTINGUISH BETWEEN GROUP AND INDIVIDUAL CORRELATIONS

Correlations that have been measured only at the group level are not necessarily applicable at the individual level, and vice versa. Example: A negative correlation was observed at the regional level between smoking habits and cardiac diseases. But it would be an ecological fallacy to assume that this applies to individuals. On the contrary; in individuals, smoking increases the risk for heart disease.

### EFFECTS IN SUBGROUPS DO NOT NECESSARILY APPLY TO WHOLE GROUPS, AND VICE VERSA

Correlations that apply to a whole group do not necessarily apply to a subgroup. And correlations that apply to a certain subgroup do not necessarily apply to the whole group. Example: In a clinical trial for a new drug, the stage of the patient's disease is unknown. Even if the drug is shown to be effective for the group as a whole, it is not certain that patients at an early stage respond in the same way as patients who have had the disease longer.

### WHAT IS CAUSE AND WHAT IS EFFECT?

Causal associations can point in one direction or another – or in both directions. Example: Panic anxiety can lead to alcohol problems, and vice versa. Researchers must take into account all possibilities.

### AVOID THE DOMINO FALLACY

The fact that a certain event is followed by a chain of events does not necessarily mean that the first event causes the last one. Example: Divorce can cause psychological problems, that can lead to alcohol problems, that can increase the risk for liver cirrhosis. However, we cannot claim that divorce is the cause of liver cirrhosis.

### WATCH OUT FOR “ALL OR NOTHING”

Black-or-white arguments, or false dichotomy, wrongly rule out all options except two extremes. Example: That smoking cessation methods do not always succeed does not mean that these methods are meaningless.

# How Good Are Diagnostic Methods?

**Accuracy is the keystone in assessing diagnostic methods. But an accurate diagnostic tool does not automatically benefit the patient.**

Ultimately, whether or not a diagnostic method is valuable depends on whether it provides new information that affects the delivery of care – and improves the patients' health.

This assumes that the disorder being targeted actually affects human mortality, morbidity, or quality of life. The health risks associated with the diagnostic procedure itself must be acceptable, and effective treatment must be available.

Only when these basic requirements are met is it appropriate to assess the per-

formance of the diagnostic method.

The ideal diagnostic method not only shows a positive result in every sick patient – in other words, not only does it have 100% sensitivity. The method must also have 100% specificity – it shows a negative result in every healthy individual.

Few diagnostic methods are this accurate. Rather, we are forced to accept tests that occasionally miss cases of disease and can trigger false alarms.

## **PREDICTIVE VALUE**

Predictive value is a concept used to describe the probability that a diagnostic method will yield an accurate result. A positive predictive value expresses the probability that a positive test result is true,

while a negative predictive value expresses the probability that a negative result is true.

The strength of the predictive value depends on more than how well the diagnostic method itself performs. It also depends on the prevalence of a disease in the context where the test result was obtained – an important consideration when applying research on a particular diagnostic method in environments other than the one studied.

## **LIKELIHOOD RATIO**

To avoid problems in describing the probable accuracy of a diagnostic method, we use the "likelihood ratio" concept. This measure concurrently summarizes the sensitivity and specificity of a diagnostic method – and it has the ad-

vantage of not being influenced by the disease's prevalence. But, it is a measure that can be more difficult to understand and keep in mind.

## **PROBABILITIES**

A likelihood ratio describes the probability of obtaining a particular test result in a sick person in relation to the probability of obtaining the same result in a healthy person. A method's positive likelihood ratio is the ratio of the percentage of accurately identified cases and the percentage of false alarms. Hence, it gives the odds that the disease actually exists if the test result is positive.

A method's negative likelihood ratio is the percentage of missed cases divided by the percentage of cases correctly ruled out.

## **FACTS: DIAGNOSTIC ACCURACY**

Diagnostic methods are seldom perfect. Hopefully, most people who are healthy receive negative results (true negatives). But even some people who are actually sick will receive negative results (false negatives). Although many people who have the disease receive positive results (true positives), some people who are healthy will also receive positive results (false positives).

The various combinations of test results and disease prevalence can be illustrated by the four quadrants presented on page 5. Every diagnostic method has its special profile of strengths and weaknesses. For

example, the sensitivity of a method may be so high that it successfully captures all cases of disease in the group tested. Yet, it could be so imprecise that it also shows positive results for several conditions other than the one being investigated. Other methods, however, can be highly sensitive and specific at the same time.

Concepts such as the sensitivity, specificity, and predictive value of a method reflect its balance of true versus false positive and true versus false negative results.

Sensitivity indicates the probability that a method will accurately establish that the

person tested has the disease, while specificity indicates the probability that the methods will accurately rule out the presence of a disease.

The predictive value of a diagnostic method describes either the probability that a positive test result is accurate (positive predictive value), or the probability that a negative test result is accurate (negative predictive value).



		REFERENCE METHOD SHOWS...	
		...disease present	...disease absent
NEW TEST SHOWS...	...positive result	<b>a</b> <b>true positive</b> accurately confirms	<b>b</b> <b>false positive</b> "false alarm"
	...negative result	<b>c</b> <b>false negative</b> "missed case"	<b>d</b> <b>true negative</b> accurately rules out

## SOME COMMON TERMS

**REFERENCE METHOD** (gold standard) – Best available method to establish a diagnosis.

**PREVALENCE** (pre-test probability) – Presence of the disease in a population, as measured by the reference method.

**SENSITIVITY** – Probability that the test accurately identifies disease (compared to the reference method). The percentage of true positive test results found in the group that actually has the disease. See table above:  $a/(a+c)$ .

**SPECIFICITY** – Probability that the test accurately rules out disease (compared to

the reference method). The percentage of true negative test results found in the group that is actually healthy. See table above:  $d/(b+d)$ .

**POSITIVE PREDICTIVE VALUE (PV+)** – Probability that a positive test result is accurate. True positives as a percentage of all positive test results. See table above:  $a/(a+b)$ .

**NEGATIVE PREDICTIVE VALUE (PV-)** – Probability that a negative test result is accurate. True negatives as a percentage of all negative test results. See table above:  $d/(c+d)$ .

**LIKELIHOOD RATIO (LR)** – A figure that indicates the clinical value of a particular diagnostic method. If the LR is close to 1.0 the method is of little value.

**POSITIVE LIKELIHOOD RATIO (LR+)** – The odds of accurately identifying cases versus false alarms, ie,  $\text{sensitivity}/(1 - \text{specificity})$ .

**NEGATIVE LIKELIHOOD RATIO (LR-)** – The odds of missing cases versus accurately ruling out cases, ie,  $(1 - \text{sensitivity})/\text{specificity}$ .

# “Evidence Sells – We All Strive for Excellence”

– I began my professional career by selling typewriters. Selling evidence shouldn't be too much different, quips Måns Rosén, with a broad smile. Måns Rosén is Professor of Epidemiology and SBU's new Executive Director.

– Jokes aside, SBU's mission is exceptionally important, which was probably the main reason why I accepted this position, says Måns Rosén after a few months in the new director's chair.

Many have asked whether he misses his previous work at the National Board of Health and Welfare, where he served

as Director of the Centre for Epidemiology, a department he helped create.

– Of course I was very happy there, he admits, but after carefully considering the offer, I realized what an exciting challenge this job could be.

## WAR TIME HEALTH CARE

Raised in Stockholm and educated in mathematics, statistics, and economics, Måns Rosén – after a brief sojourn as typewriter salesman – arrived at the National Board of Health and Welfare where he planned health services in the event of war.

– But after a time a person feels somewhat detached, planning for something nobody wants to happen.

## RESEARCH PASSION

Måns Rosén went on to improve strategies for planning health services.

– I thought that the approaches used by the county councils in Sweden were inadequate. They needed to be based on the documented health problems and healthcare needs of the population. Shouldn't we be able to use health data registries as a basis for planning?

In the 1980s, Rosén was among the first in Sweden to pursue questions on health-

care quality assurance. Having a passion for research, for many years he conducted his own research alongside other job responsibilities. Måns Rosén has published nearly 100 scientific articles in international medical journals and has been appointed Adjunct Professor in Epidemiology. But now he looks forward to new responsibilities.

## SBU CAN CONTRIBUTE

– I'm convinced that SBU can contribute toward health services being more effective – saving more lives, improving the quality of life for patients, and utilizing healthcare resources better.

But will better evidence actually direct health services?

– Yes, absolutely, since the driving forces for better care are largely the caregivers themselves, says Måns Rosén.

– Basically, everyone working in health services wants to perform well. Also, we all want to draw on the best information available.

– At the same time, he continues, each of us can face obstacles in changing our routines. Habit is a powerful force. Therefore, I also believe that health services – and every one of us – may need an extra push to change.

As an example, Måns Rosén advocates the use of quality indicators in health

## MÅNS ROSÉN

Executive Director, SBU

Born 1949 in Stockholm, Sweden. Bachelor of Science in Mathematics and Mathematical Statistics, 1973. Bachelor Business Admin, 1976. Doctor Med Sci (PhD in epidemiology), 1987. Assoc Prof Social Med; Health Services Research, Karolinska Institute, 1991. Adj Prof Epidem and Public Health, Univ of Umeå, Dept of Epidem and Publ Health, 1994–. About 100 peer-reviewed scientific articles in international journals. Executive Director of SBU since August 2006.



Anders Norderman

care, public statistics that clearly compare the performance of different healthcare providers.

– SBU’s evidence fits in naturally when it comes to identifying the best technologies. It is essential to have real evidence before taking a position on what works well and what doesn’t.

– I’m convinced that local comparisons generate local involvement, which leads to improvement. Therefore, I think that small-area studies of practice variations can be a way for SBU to influence healthcare practices.

Måns Rosén adds that the interest in monitoring practice variations and healthcare quality improvement has increased substantially in recent years.

**LOWER FEAR FACTOR**

– I believe that the ‘fear factor’ associated with this type of data is now substantially lower among healthcare professionals. Many now recognize that improving healthcare quality actually requires us to monitor our outcomes. And as more people engage in this type of monitoring activity they find it less threatening.

Sweden and the other Nordic countries have an excellent foundation to build on.

– The Nordic countries are

– Sweden and the other Nordic countries have outstanding healthcare quality registers to monitor practice changes, says SBU’s new Executive Director, Professor Måns Rosén.

in a class of their own when it comes to healthcare quality registers. The problem is that we do not always feed back the information in a direct and useful way.

– And our registers on the treatments administered, eg, pharmaceuticals, need more data describing the indications.

The evidence also needs to be presented more clearly, suggests Måns Rosén.

**SHARPER MESSAGE**

– I believe that the message in SBU reports can be sharper and more concise, and thereby provide better guidance to those who work in health care and those who plan health services. For example, the reports should focus on a few key results and draw con-

clusions that are more specific.

– Furthermore, the SBU reports should spark more interest among research councils, universities, colleges, and individual researchers, encouraging them to bridge the important knowledge gaps we identify.

As a researcher, Måns Rosén stands out in the sense that he is as impassioned about practical applications as he is about finding new knowledge. These dual interests have been an underlying theme throughout his professional career.

– The data alone are just not enough. I’ve always thought that. Evidence must be applied – otherwise what good does it do?

“I’m convinced that local comparisons generate local involvement, which leads to improvement.”

# Can We Measure the Impact of Evidence?



Practice is influenced by many factors. The extent to which evidence directs healthcare decisions has been questioned at times. But in many instances, it is possible to observe the impact of new evidence, write Nina Rehnqvist and Lars-Åke Marké.

SBU intends for health resources to be utilized as appropriately and efficiently as possible, giving the population access to the best possible care. Toward this end, SBU systematically assesses new and established health technologies from a broad medical, economic, ethical, and social perspective. The assessments provide a foundation of evidence for national and local recommendations, guidelines, and protocols.

## DIFFERENT LEVELS

The effects of SBU's critical assessments can be observed at different levels of health care. For example, the reports can affect patient outcomes as well as the economy, clinical practice, health policies, and research. Although changes in each of these areas can be measured, the impact of the SBU reports cannot be readily isolated from other influences. It is difficult to identify the extent to which a change in practice

can be attributed to SBU versus other factors – SBU does not work in a vacuum. But regardless of whether it is the SBU reports that have triggered changes in clinical practice, it is rewarding to see practice and guidelines move closer toward the scientific evidence. Below, we describe several examples where the findings presented in SBU reports had a likely impact on the practice changes that followed. We also discuss conceivable economic consequences.

## DEPRESSION

As a concrete result of the SBU report on treatment of depression, the drug committees in Sweden reached a consensus concerning pharmacotherapy of mild to moderate depression. The drug committees recommend using citalopram, an SSRI agent, as first-line treatment, and they are monitoring compliance with the recommendation. Sales data from the National Corporation of Swedish Pharmacies (Apoteket) show that sales of citalopram, measured in number of daily doses, increased 4.3% between 2003 and 2004 and another 4.1% during 2005.

## ALCOHOL AND DRUG ABUSE

The SBU report on treatment of alcohol and drug abuse led to an educational program in

collaboration with several social service agencies. The work on national guidelines that is under way by the National Board of Health and Welfare is based on evidence presented in the SBU report. The report shows that several medications have scientific support as treatment methods for dependence. Prescriptions for one of the three medications used increased fourfold between 2000 and 2005. The largest increase occurred in 2002, the year following publication of the SBU report. After 2002, prescriptions increased by 50%.

## BACK PAIN

The SBU report on back pain showed, eg, that sick leave and bed rest are directly harmful in treating back problems. Several years after publication, the sick leave rate attributed specifically to back pain declined substantially. Several factors, eg, changes in the economy, probably contributed to this decline. But one likely factor is SBU's well-publicized conclusion that these patients should continue with normal daily activities to the extent possible.

## PREOPERATIVE ROUTINES

An early SBU assessment addressed routine preoperative testing. A study of 6 hospitals and 3000 patients





Disorder or intervention	Cost of disorder or intervention in billion SEK (2005 valuation)			Number of patients or interventions per year	Potential effects of changed practice based on SBU evidence			
	Direct	Indirect	Total		Patient benefit	Cost		
						↑	↓	?
Depression	2.8	10.5	13.3	500 000	increases		X <sup>1</sup>	
Osteoporosis	3.5	0.5	4.0	70 000 fractures (incl. 18 000 hip)	increases	X <sup>2</sup>		
Obesity	3.2	3.2	6.4	500 000	increases		X <sup>3</sup>	
Alcohol/drugs		30–100		250 000	increases		X <sup>4</sup>	
Back pain	3.5	37.5	40.8	1 400 000	increases	X <sup>5</sup>		
Hypertension	1.7	-	1.7	1 100 000	increases		X <sup>6</sup>	
Mild head injury	0.15	3.5	0.5	17 000	unchanged	X <sup>7</sup>		
Preoperative routines	1.2	-	1.2	500 000 routine procedures	unchanged	X <sup>8</sup>		
Bone density measurement	0.023	-	0.023	35 000 measurements	unchanged	X <sup>9</sup>		

Scientific assessment shows which healthcare interventions provide the greatest benefits to patients and how health services can utilize resources in the best way. Health care should aim to use methods shown to be cost effective. This, however, does not always mean a reduction in the direct costs of health care. Direct costs may often increase, while indirect costs (eg, lost productivity) often decrease. The following footnotes to the above table refer to costs described in the SBU reports.

1. If treatment options are used consistently in accordance with SBU's conclusions, the expenditures for pharmaceuticals could increase as more patients are identified, or could decrease through more rational drug selection. The costs for psychotherapy and other treatment programs increase. However, the increase will probably be outweighed by a decrease in indirect costs.

2. An increase can be expected in the direct costs of treating osteoporosis, while the expected decrease in fractures would not reduce costs to a corresponding degree.

3. Preventive interventions against obesity can be expected to reduce the total costs to society, while treatment interventions have only marginal effects. Surgical treatment, however, is shown to be effective. It is difficult to estimate how prevention and treatment will affect costs in the long term.

4. Costs associated with more effective pharmacotherapy can be expected to increase. This increase may be offset by reduced costs to society from substance abuse.

5. Many methods are shown to be ineffective. Replacing these with more effective methods leads to greater cost effectiveness. Assuming that the new methods reduce the amount of time on sick leave, they could substantially reduce the cost to society.

6. Would probably reduce the pharmaceutical costs per patient, but also increase the number of patients receiving drugs. This would increase the total direct costs. In the long term, the effects of improved control of blood pressure will probably

reduce the number of strokes and other complications. It is difficult to estimate how total costs will change.

7. The direct costs decrease, providing that a strategy is implemented to examine all patients by computed tomography. If CT examination indicates no injury, the patient is sent home rather than being admitted for 24-hour observation.

8. Direct costs decrease since many preoperative exams are shown to be unnecessary.

9. Unnecessary direct costs can be avoided by not implementing screening.

revealed a reduction in the number of routine preoperative examinations, a change in line with SBU's conclusions. This change corresponds to an annual cost reduction of approximately 235 million Swedish kronor (SEK).

#### BONE DENSITY

The SBU report on bone density measurement revealed there was insufficient scientific evidence to recommend bone density measurement for mass screening, targeted screening, or as a component in health checkups. Following the report, the purchase of devices for bone density measurement declined. However, utilization has increased for a new, less-

sophisticated device intended to measure the heel and finger.

#### OBESITY

Efforts to disseminate findings from the SBU report on obesity have been extensive, and have generated broad-based interest. Several implementation programs have been designed based on the report, and special networks have been established to help prevent and treat obesity at the national and regional levels. A study on preventing obesity in school children has been launched.

#### SMOKING CESSATION

The SBU assessment of methods for smoking cessation found that brief, struc-

tured advice, and treatment with nicotine replacement agents, are effective in the context of routine primary care and dental services. Annual sales of nicotine replacement agents have continued to increase, rising by 6 percentage points in 2004 and 2005.

#### HEALTHCARE

##### PRACTICES INFLUENCED

The above examples suggest that evidence influences practice, but also that the changes vary in magnitude and type. A goal of SBU is to improve resource efficiency. This does not always imply lower costs, although at times greater patient benefit can be associated with lower costs. In some cases, this greater level

of benefit can be achieved at an unchanged cost. But even when costs increase, new routines can be cost effective. However, in some areas the economic outcomes are difficult to quantify.

Clearly, better monitoring systems are needed in health care to assess the effects of various interventions, including the impact of evidence.

*Nina Rehnqvist,  
Board Chair, SBU.*

*Lars-Åke Marké,  
Health Economist, SBU.*

#### Additional Reading

Britton M, et al. How SBU affects practice in health care. *Läkartidning* 2002;99:4628-34.

## Lay Advisory Group Checks Expert Messages



Victoria Dyring, Chair of SBU's Lay Advisory Group

Since 1994 a Lay Advisory Group has served SBU under the direction of the executive team. These laypersons advise SBU on patient-oriented matters, complementing the rigorous scientific methods used in SBU projects. The Lay Advisory Group generates advice, viewpoints, and suggestions.

The group's main task is to critically and constructively review SBU's communication with patients, family members, and interested citizens.

The Lay Advisory Group also takes initiatives concerning patient issues they would like to see addressed in SBU's assessments. For

example, the group monitors areas of work by project groups where it is particularly important to incorporate patient and consumer perspectives. The group may also suggest potential topics for assessment by SBU.

Along with suggestions from the Lay Advisory Group, SBU also elicits other types of consumer input. For instance, when an assessment project requires input from particular patient or consumer groups SBU involves these organizations in the project.

SBU's Executive Director appoints the Lay Advisory Group, which includes a Chair and 7 members. Each

of the members has experience in reviewing and appraising how to communicate factual information in a clear, understandable way.

Members are appointed to offer independent and constructive viewpoints. No member should be associated with any interest group that could jeopardize impartiality. Any potential conflict of interest shall be disclosed.

Internationally, many healthcare evaluation projects employ consumer panels, or find other means of involving patients and laypersons in assessment processes.

# Recent SBU Findings

## Early Fetal Diagnosis

Testing a mother's blood plus using ultrasound to scan the neck of the fetus give the best grounds for deciding to investigate for Down syndrome. SBU presents this finding in its systematic review of fetal diagnosis early in pregnancy, up to 22 full weeks. Combined, the two tests are superior to using maternal age as an indicator, which up to now is the most common approach in Sweden.

The most reliable way to decide whether to investigate for Down syndrome is to combine the results of a maternal blood test and a nuchal ultrasound examination of the fetus. This combination detects the highest possible number of cases without giving a high rate of false indications for Down syndrome. The sensitivity of this method, and its ability to provide specific information about the fetus, makes this combined method superior to others in screening for Down syndrome.

Combined screening means analyzing the mother's blood for two proteins formed in the placenta, ie, markers PAPP-A and free beta-hCG, and scanning the width of a fluid column in the fetus' neck at 10 to 14 gestational weeks. Together, the results give an initial indication of

the probability for Down syndrome. Establishing the diagnosis itself requires analyzing fetal chromosomes in a sample of the amniotic fluid or placenta.

Use of the early screening method is not widespread. Rather, the routine approach in Sweden is to offer chromosome analysis based solely on maternal age, usually mothers over 35 years of age. Unfortunately, this approach presents a problem. Taking samples for chromosome analysis increases the risk for miscarriage – the risk that the fetus will not survive increases around one percentage point. Collectively, the research shows that couples considering fetal diagnosis could benefit from maternal blood testing plus nuchal ultrasound scanning of the fetus. This approach exposes fewer fetuses to the risks associated with amniocentesis or sampling of placenta cells for chromosome analysis.

For women who visit maternal health services so late in their pregnancy that nuchal ultrasound examination is no longer an

option, a quadruple blood screen offers the best balance between the percentage of detected cases and the percentage of false positive findings. Four markers in serum are analyzed in this screen.

The safety of the fetus is naturally one of the main considerations in routine ultrasound screening. Since each fetus examined is exposed to ultrasound, it would be extremely serious if the method were harmful. Research, however, has not shown any negative effects

from routine scanning as regards child growth, nervous system development and function, language development, vision, or hearing. Based on analyses of certain subgroups in randomized studies and on registry data in Sweden, left-handedness or no side preference is somewhat more common among children who were examined by routine ultrasound scanning during gestation. But the

available data are insufficient for drawing conclusions.

Fetal diagnosis is a topic that raises difficult and sensitive questions. SBU has not assessed fetal diagnosis *per se*, but highlights a range of ethical problems. For example, the new report calls for a substantial improvement in information to expectant parents so they can make informed choices among the options for fetal diagnosis. By offering the screening tests, maternal health services could help prevent or mitigate suffering. Yet, the test results will bring some expectant parents face-to-face with difficult questions and choices – and this requires good communication with healthcare providers. But most studies point to deficiencies on this front. Expectant parents are not receiving what they need to make well-informed decisions. **DEC 2006**

## Obstructive Sleep Apnea Syndrome

Obstructive sleep apnea syndrome is a condition that covaries with premature death, stroke, and traffic accidents. According to SBU's recent systematic review of diagnostic and treatment methods, the benefit of surgery is uncertain. Instead, evidence supports the use of oral devices and continuous positive airway pressure.

Despite potentially serious side effects and risks, over 700 operations for sleep apnea were performed in Sweden in 2003, reports SBU.

The review shows that continuous positive airway pressure (CPAP) during sleep reduces daytime sleepiness in individuals with obstructive sleep apnea syndrome. A CPAP unit delivers positive pressure to the airways via a face or nasal mask. Treatment reduces the number of pauses

in breathing, regardless of the severity of the condition. The evidence is strong. Most patients tolerate CPAP well, despite some discomfort from the mask and disturbance from the sound of the CPAP unit.

There is also evidence that lower jaw adjustment devices, which are individually formed to draw the lower jaw forward, can reduce pauses in breathing and daytime sleepiness in people with mild to moderate sleep apnea.

Treatment methods having the least evidence and the highest risk are the surgical methods. Scientific evidence is insufficient to draw conclusions about the effectiveness of surgery on daytime sleepiness and quality of life, according to SBU. However, researchers know that a substantial percentage of patients suffer from swallowing problems and other adverse effects from surgery.

Obstructive sleep apnea

syndrome is common. Approximately 4% of all men and 2% of all women have the condition. Common symptoms include daytime sleepiness, snoring, and frequent cessation of breathing during sleep. Pauses in breathing, which last at least 10 seconds in obstructive sleep apnea syndrome, can be complete or partial and occur because air cannot flow freely in the upper airways.

The standard diagnostic method involves an overnight hospital stay for polysomnography. This is a standard test that records respiratory effort, blood oxygen levels, heart rhythm (ECG), and brain waves (EEG) indicating sleep time and stage. Simple, portable sleep apnea diagnostic devices are often used to avoid the cost of an inpatient examination involving EEG.

The SBU review shows that portable devices, which continuously register air flow, respiratory effort, and blood oxygen levels during a night of sleep, are both sensitive and accurate – even when compared to polysomnography. This assumes, however, that the results are interpreted manually, not automatically.

The obstructive sleep apnea project was a collaborative project involving SBU and its Nordic counterparts. A survey from the project showed that 745 operations were performed for snoring or sleep apnea in Sweden in 2003. Norwegian and Finnish physicians were more likely to operate than Swedish physicians. Among the Nordic countries, only Denmark reported a lower rate of surgery than Sweden. **APR 2007**

## Promoting Physical Activity

People with a physically active lifestyle are less likely to develop type 2 diabetes, osteoporosis, cardiovascular diseases, and cancer. In light of such benefits, SBU systematically reviewed the research on methods available to promote various forms of physical activity.

The SBU review reveals the benefits of counseling and advising patients in the course of routine health care. These patients become more physically active, and the effects last at least 6 months. For children and adolescents, development of sports and health subjects in schools is shown to increase activity during physical education classes.

The conclusion – advice given by a healthcare profes-

sional to a patient has important benefits. Strong scientific evidence clearly shows a higher level of physical activity among patients who received such advice, and the effect lasts for at least half a year after the intervention. Advice can take the form of direct recommendations from healthcare professionals to patients, or discussions where the caregiver advises the patient. Some studies are limited to investigating verbal advice, while others measure the effectiveness of including various learning tools. SBU found some scientific evidence that advice complemented with, eg, “prescribing” physical activity, keeping a diary, counting steps, and receiving printed material, could further increase the level of physical activity.

As regards children and adolescents, SBU found strong scientific evidence that

health instruction in schools, study material, and teacher education also increase the level of activity during physical education classes. The effects are greater for boys than for girls.

Special programs in schools are shown to increase physical activity by young people during school days and in some instances even during holidays. Such programs involve multiple approaches, eg, continuing education for teachers, changing the general curriculum, adding extra exercise sessions during classes and breaks, supporting behavioral change, strengthening the health curriculum, and using different ways to involve parents in activities.

SBU’s report points to the lack of health economic studies showing which types of intervention offer the greatest benefits for the resources spent to promote physical activity.

SBU’s findings provide important information to healthcare professionals and decision makers, eg, politicians, administrators, and educators, involved in health services, schools, and health promotion programs.

**NOV 2006**

## Fortifying Flour With Folic Acid

Fortifying flour with folic acid can prevent neural tube



Anders Nordeman

defects (NTD) in the fetus. But the scientific evidence does not clearly show

that the benefits outweigh the risks, according to SBU’s systematic review of relevant research findings.

Supplementing the diet with folic acid early in pregnancy reduces the risk of a newborn with NTD. Mandatory fortification of flour with folic acid would increase the intake across the entire population. Collectively, scientific research suggests this strategy would reduce the incidence of NTD. However, the potential risks have not been scientifically investigated. Scientific support for mandatory fortification of flour is not clear-cut.

Approximately 100 000 children are born in Sweden each year, whereof 20 to 25 newborns have NTD. Around 80 pregnancies per year are terminated after detection of fetal damage. Most of the newborns have severe and complex functional disabilities involving paralysis, skeletal malformation, and bladder and bowel dysfunction.

For several years, Sweden has recommended a daily supplement of 400 micrograms of folic acid for women before and in conjunction with pregnancy. But over half of all pregnancies are more or less unplanned. Hence, many pregnancies are only detected months after conception. At this point, it is often too late to start taking folic acid with the intent to prevent NTD. The spinal cord’s structure is

established during the first gestational weeks, ie, before pregnancy has been confirmed. Consequently, several countries have discussed mandatory fortification of flour. The SBU review found that the scientific literature provides moderately strong evidence that fortification reduces the incidence of NTD. Another issue that has been discussed concerns whether folic acid increases the percentage of twin pregnancies, which per se carries some risk. Research findings are inconsistent as regards the effect of folic acid on the percentage of twin births. A serious risk from mandatory fortification of flour with folic acid could be the potential effects on cancer.

Biologically, it is possible that folates could promote the growth of existing tumors and the transition from precancerous stages to active cancer. There is no conclusive scientific evidence, but some animal trials support the hypothesis, and studies have indicated an association between high folate levels and intestinal cancer. If folic acid actually has such effects on cancer, the negative consequences can be extensive and outweigh the gain of fewer NTD cases.

SBU concludes that no clear-cut scientific evidence supports the mandatory fortification of flour in Sweden. The potential harm of exposing the entire population to a biologically active substance, the effects of which are not fully known, must be weighed against the potential benefits of preventing a limited number of severe fetal disorders. **MAR 2007**

## New Immunomodulating Drugs for Moderate to Severe Psoriasis

An estimated 250 000 people in Sweden have psoriasis, of which there are 5 different forms. Plaque psoriasis is the most common form, accounting for more than 80% of all cases. Severe plaque psoriasis has substantially negative effects on patients' quality of life.

Standard therapy usually consists of a combination of ultraviolet A light waves and psoralen tablets (PUVA)<sup>1</sup> and/or immunosuppressive systemic treatment. Methotrexate and cyclosporine are established systemic drugs that offer effective therapy, and after 12 to 16 weeks of treatment, reduce psoriatic lesions by 75% or more (PASI 75)<sup>2</sup> in 60% to 70% of patients. However, these drugs are associated with a risk for serious side effects. This risk increases as the duration of treatment is increased, and may limit their use. New treatment options are needed since some patients do not tolerate, or do not respond to, the established methods.

Three new immunomodulating drugs – infliximab (Remicade®), etanercept (Enbrel®), and efalizumab (Raptiva®) – were approved in 2004/2005 for treating moderate to severe plaque psoriasis in adults when other systemic therapies have had inadequate effects, or cannot be given for other reasons.

According to SBU's systematic review, there is strong evidence of favorable effects on skin lesions and quality of life in patients with moderate to severe plaque psoriasis after treatment with infliximab, etanercept, and efalizumab for 3 to 6 months. However, the scientific evidence is insufficient to assess the long-term effects of the 3 drugs, as well as the potential, uncommon, and long-term side effects. The mechanisms of action of these drugs carry a potentially increased risk for serious immune-related side effects, including severe infections. No studies have compared the new drugs head-to-head.

Treatment costs per quality-adjusted life-year are high, or very high, even when the drugs are used within the approved indications (patients who respond inadequately to treatment, or who cannot receive established therapy for other reasons). Utilization beyond the scope of the approved indications would generate extremely high costs. **NOV 2006**

Footnotes: <sup>1</sup> PUVA = Psoralen + Ultraviolet A. <sup>2</sup> PASI = Psoriasis Area and Severity Index. <sup>3</sup> DLQI = Dermatology Life Quality Index

## Natriuretic Peptides in Diagnosing Heart Failure

In a systematic review, SBU concludes that moderately strong scientific evidence shows that natriuretic peptides – BNP or N-terminal proBNP – can be used with good reliability to rule out heart failure. However, evidence remains insufficient concerning the cost effectiveness of the method relative to other methods of diagnosing heart failure.

Common symptoms of heart failure are shortness of breath, fatigue, and swollen legs. These symptoms alone, however, are not sufficient to confirm the diagnosis of heart failure. Establishing a diagnosis of heart failure also requires confirmation of impaired cardiac function, usually through echocardiography. This is a labor-intensive and relatively expensive diagnostic procedure.

Measuring the concentration of B-type natriuretic peptides (BNP and N-terminal proBNP) in the blood is intended to help better determine if the symptoms are caused by heart failure, or other conditions. These peptides are produced at a higher rate as the load increases on the ventricular muscles of the heart. BNP and N-terminal proBNP can be analyzed by so-called point-of-care methods that yield results within about 15 minutes. A rapid test result benefits the physician and patient alike, assuming that diagnostic quality is satisfactory.

The high negative predict-

ive value of measuring natriuretic peptides means that one can rule out with considerable certainty that a patient has heart failure. This knowledge can help accelerate the diagnosis of other possible disorders. However, the positive predictive value of the test is not equally as high. Hence, it is necessary to complement the test with an assessment of cardiac function to determine, usually through echocardiography, whether or not the patient has heart failure. Further research is required to determine the optimum decision cut-off points for use in clinical practice.

The cost of taking a sample and analyzing BNP or N-terminal proBNP is approximately 200 to 350 SEK. By comparison, the cost for echocardiography is 1500 to 2500 SEK. Since analysis of natriuretic peptides can identify patients with a low probability for heart failure, further examination by echocardiography in this patient group could be avoided.

**SEPT 2006**

## Implantable Defibrillator

While some cardiac arrhythmias are harmless (eg, extra beats), others such as ventricular tachycardia and ventricular fibrillation are serious disorders that can lead to sudden death. Treatment with an implantable cardioverter defibrillator (ICD), aimed at preventing recurrence of serious arrhythmias, leads to lower mortality. The scientific evidence is strong, according to SBU's systematic literature review. There is moderately strong scientific evidence that ICD treatment aimed at primary prevention leads to lower mortality.

An ICD can continuously monitor the users cardiac rhythm to detect and treat serious arrhythmias in the ventricles of the heart. Treatment involving an ICD may be appropriate in patients who have already experienced a symptomatic ventricular arrhythmia (cardiac arrest) or have life threatening ventricular arrhythmias associated with decreased function in the left ventricle and/or experience fainting. In these cases, the aim of using

an ICD is to prevent recurrence, ie, treatment aims at secondary prevention, which has been the most common area of application for the method in Sweden.

Treatment can also aim at primary prevention. This includes patients at higher risk for life threatening ventricular arrhythmias, eg, following myocardial infarction or cases of heart failure and severely impaired left ventricular function, but who have not yet presented with serious cardiac dysrhythmias. Furthermore, the expected survival with ICD treatment should be at least around 2 years.

The combined results of three RCTs (including nearly 2000 patients) on secondary prevention show a mortality rate of 8.8% in the ICD group compared to 12.3% in the pharmacotherapy group. This indicates that 29 patients would need to be treated with ICD for one year to avoid one additional death.

As regards ICD treatment aimed at primary prevention, 10 randomized trials including slightly over 8600 patients were identified. A meta-analysis synthesized the results from studies on ICD treat-

ment in primary prevention. It showed that mortality was 8% lower in the group that received ICD treatment.

The risks associated with ICD treatment include peri-operative death, infections, thromboembolytic complications, cardiac perforation, and the possibility that the defibrillator could incorrectly interpret the heart rate, leading to delivery of inadequate shocks.

Studies estimate that the cost per life year gained for ICD in secondary prevention is between 500 000 SEK and 1.8 million SEK. Cost-effectiveness analyses have shown that the cost per life year gained for ICD aimed at primary prevention in patients who have had myocardial infarction is between 200 000 and 800 000 SEK.

Regarding primary prevention in heart failure patients, the cost per life year gained is around 400 000 to 800 000 SEK. Due to the capital investment costs associated with implantation, the cost effectiveness of ICD treatment depends on the survival time of patients that respond to treatment. **SEPT 2006**

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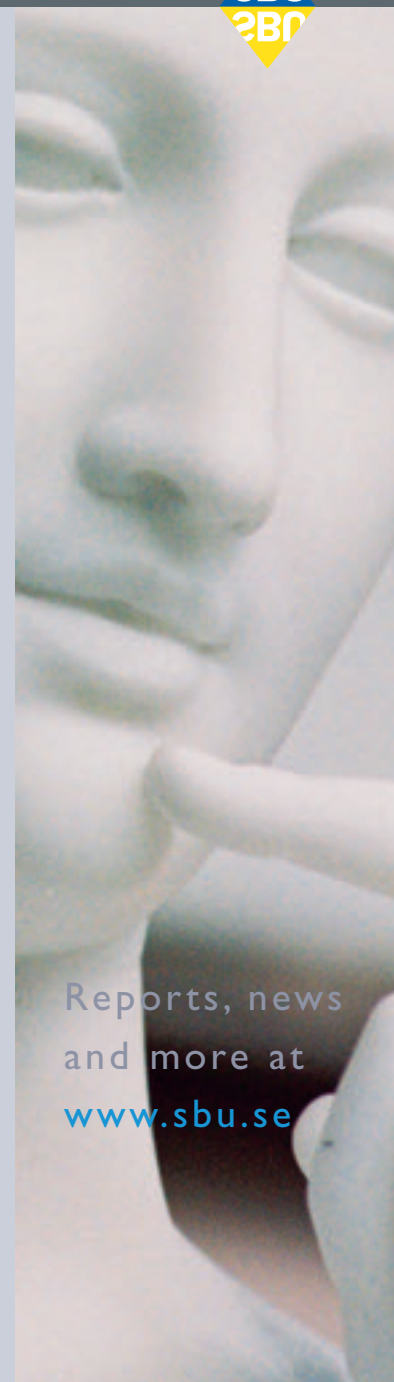
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