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Dazzled by DNA

Many hope that testing patients' DNA will lead to personalised, more effective, treatment. But clinical studies must first show that genetic testing can improve medical decisions.

Expectations are sky high. In the past decade, new genetic tests have emerged at a rapid pace, and today more than 1000 tests address 1200 diseases. Tests target not only rare disorders in individual genes. Increasingly, researchers are finding complex associations between human DNA and widespread public health diseases.

Although the field is largely perceived as scientifically pioneering and promising, health services and patients must ask critical questions about the benefits. Contrary to many corporations around the world that market DNA testing as the "all-seeing eye", a recent article in *Science* takes a considerably less enthusiastic stance.

The authors assert that even combin-

Pills and Knives, Poor Consolation

This issue of our newsletter is being released as SBU celebrates 25 years of assessing health technologies. It seems timely to mention the method that is perhaps most neglected – listening to our fellow humans.

We often hear that realistic goals in health care are: "occasionally cure, often relieve, always console." But in modern health care, comfort appears to receive far too little attention. As expressed by Swedish surgeon Johannes Järhult: "Genuine solace has, to some extent, been replaced by implied promises about medical possibilities to vanquish death. But this is only poor theatre."

Consolation is partly a question of time. Not necessarily a lot of time, but one must be available to listen. It is also about empathy – a skill that many possess naturally, and one that can probably be acquired with practice. And not least, it is about stamina. Currently, healthcare staff have high rates of prolonged sick leave due to mental diagnoses. When in such a state of exhaustion, the amount of empathy one can give is very limited.

I am convinced that consolation is needed alongside of cure and relief – and not as a substitute, as can be the case when some practitioners deliver poorly documented, complementary medicine. In conventional health care, the problem appears to be the opposite – offering treatment instead of comfort – and my point is that this, too, is unreasonable. Nevertheless, many questionnaire surveys show this to be rather common (e.g. Fässler et al, 2010).

For instance, a study from 2003 reported that every second general practitioner in Denmark had used some form of placebo more than 10 times during the past year. In another study, half of a sample of American internal medicine specialists and rheumatologists reported that they often recommend vitamins, over-the-counter painkillers, and antibiotics (!) to treat viral infections so patients would have a positive expectancy effect (not for the treatment's pharmacological effects).

In practice, clinicians seldom give sugar pills to console, but provide real examinations and active treatment. The purpose, however, might be unspecific and suggestive – perhaps to create a sense of security, or perhaps to show "I care." We do not know how often carers provide examinations and treatments purely for comfort, relying on methods that ultimately net more harm than benefit due to their cost and the risk of adverse effects.

Research addressing comfort suggests very different approaches. But instead of offering examinations and treatments that are probably ineffective, practitioners should offer comfort by being present and open, showing they are willing to talk about difficult issues and prepared to listen to the inner dialogue that the suffering patient needs to share.

Consolation must be re-established as one of the primary objectives of health services, a goal alongside of relief and cure. Comfort should be re-discovered in mainstream medical care – rather than pseudo-treatments that keep patients in the dark.

RAGNAR LEVI, EDITOR

Helena Halvarsson

ing dozens of genetic risk markers for disease does not yield any real clinical guidance. This is because common diseases – such as most types of cancer and cardiovascular disease – are often caused by multiple factors concurrently. The risks associated with lifestyle far overshadow the genetic markers discovered to date.

MANY AFFECTED

By definition, the risk of contracting a common disease is high, i.e. they affect community health. Consequently, the distinctive features of individuals' genetic material only marginally influence the risk of disease. To start screening programmes for genetic risk markers in entire population groups, e.g. to determine which people should undergo further examination for breast or colon cancer, would do more harm than good.

– A decade after publication of the initial findings from the HUGO Project, expectations remain extremely exaggerated concerning the clinical benefit of testing human genetic material, comments Professor Hans-Olov Adami from the Harvard School of Public Health.

Professor Adami has a long association with Karolinska Institutet and previously served on SBU's Scientific Advisory Board.

WANT TO SELL TESTS

– In my opinion it's like a gigantic bubble. It has been inflated by researchers trying to attract resources, achieve recognition from others, and market commercial applications of their discoveries.

– They receive willing support from uncritical journalists hungry for news items and from corporations that want to be first to sell genetic tests to as many as possible, hopefully followed by lifelong preventive medication for anxious people with various risk markers.

Adami himself has published studies of risk markers for prostate cancer, but is careful to point out that the patients do not benefit from the tests, even though the results are of scientific interest.

– In many ways the hype surrounding personalised medicine is reminiscent of the "war on cancer" declared by USA's President Nixon in 1971. Now, 40 years later, we can hardly claim that the battle against cancer has been won, he says laconically.

TOO NARROW

When the expectations are driven up, there is a risk that resource inputs can become too narrow, according to Hans-Olov Adami. This can delay other interventions that might provide more immediate benefits.

– In fact, we already have considerable knowledge of effective interventions that prevent disease. The greatest problem is that we don't use it.

The authors of the *Science* article express the same line of thought. Much would suggest that well-known interventions that can reduce risk often provide benefits to everyone regardless of genetic risk level. Examples include smoking cessation, avoiding overconsumption of alcohol, eating better, and exercising more.

In Sweden, DNA tests have been marketed directly to the public for several years. Those prepared to pay thousands of Swedish kronor (SEK) can buy an entire packet of DNA information showing, for instance, small differences in the risk of hypertension, myocardial infarction, diabetes, and prostate cancer. The question is: Where do the test results lead?

BEHAVIOURAL CHANGE

Effectively preventing disease often requires behavioural change. Many find it difficult to change their lifestyle. But no evidence confirms that information alone concerning genetic predisposition, e.g. for heart disease, inspires people to eat better or exercise more in the long term, writes James Evans et al in *Science*. Even if it did, the message to those lacking these genetic risk markers might have exactly the opposite effect – giving them false security and choosing a riskier lifestyle.

But some knowledge in this area is closely related to clinical practice. One example concerns metabolism and the effects of drugs, i.e. pharmacogenomics. Genetic variations, for instance, where a person has either too much or too little of an enzyme, or none at all, can render treatment ineffective or cause adverse effects. In some situations, genetic tests could be beneficial. DNA typing of tumour cells is another, more established, area of application.

Regarding disease markers in DNA, many evaluators agree that the clinical successes have yet to match our expectations.

As proposals for genetic testing arise, they must be accompanied by evidence showing that the benefits outweigh the harm, and that they are worth their price. [RL]

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IS GENETIC TESTING CLINICALLY BENEFICIAL?
EVIDENCE THAT SHOULD BE DEMANDED

Proposed use	Confirmed association	Documentation that should be demanded
Diagnosis (of people needing investigation)	A genetic marker is more common in those who already have symptoms.	Is there evidence for faster/safer diagnostics? Will treatment outcomes be better documented in terms of survival, symptom relief, or quality of life? Is the information important in making decisions about care?
Screening (of people lacking symptoms)	A genetic marker is more common in those who will later have symptoms.	Does the test help improve health in those screened? Does the test plus previous treatment help improve survival, symptom relief, or quality of life? Is the method sufficiently sensitive and accurate? Can it accurately identify disease without giving false alarms?
Assessing disease risk	A genetic marker is more common in those who might develop symptoms later.	Can disease be prevented more effectively in those where markers suggest higher predisposition? Does the test plus associated preventive interventions reduce the number of people that become ill?
Assessing disease prognosis	An association is shown between markers and a particular disease course.	Does the information lead to other decisions or other management that improves patient survival, symptom relief, or quality of life?
Individualised treatment	An association is shown between markers and benefits of different treatment methods.	Does the information lead to more effective treatment and thereby improve survival, symptom relief, and quality of life in those examined?

Source: e.g. Teutsch et al, 2009

Defined By Diagnosis

Diagnoses affect our perceptions of being healthy or sick, what we should treat, and which treatments to consider. New diagnoses and definitions must be scrutinised and scientifically assessed before they become part of health services.

An unnamed disease is a homeless disease. In health care and society, unnamed diseases tend to be invisible. People with symptoms, but with no diagnosis, can face double suffering. Once from their problem, and again because they receive little support from society, their environment, and health services. Only when patients receive a diagnosis is their disease confirmed in their own eyes and in the eyes of others.

The importance of diagnosis is a special interest of Maria Gardsäter, member of SBU's lay panel and project leader at Rare Diseases Sweden. She has also co-authored a recent book on diagnosis and identity.

– A clear, well-recognised diagnosis can be the key to receiving help and resources from health services and society. When it involves a chronic condition it could even be part of your self-image.

TOUGH TASK

– But if you have an uncertain diagnosis, or a rare condition that health professionals have barely heard about, it is often up to you as an individual patient to describe your situation and needs, and coordinate the help that you can get from different sources. It's a tough task that many of our members have wrestled with before they were helped, says Maria Gardsäter.

Diagnoses raise expectations on interventions from health services, manufacturers, researchers, and the community at large. Hence, an important question is which health problems should remain anonymous and which ones deserve to be distinguished with their own name – as a separate category, or as one among a group of other disorders.

The battle for a place on the diagnostic map involves all medical conditions, but has become particularly apparent in psychiatry. Presented to the public in 2010 was a preliminary, 5th edition of the American Psychiatric Association's widely used DSM classification (i.e. *Diagnostic and Statistical Manual of Mental Disorders,* DSM-5). This influential manual has focused attention on the debate concerning

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NAMING DISEASES AND CONDITIONS

• Throughout medical history, disease concepts and names have often appeared unsystematically and without empirical support. Collections of more or less similar symptoms and problems have been arbitrarily grouped together under a common heading to serve the needs of the times.

• The first actual classifications of diseases appeared in the mid 1700s. In 1763 a forerunner of Swedish scientist Carl Linnaeus published *Genera Morborum* – a system based on FB de Sauvage's classification from several decades earlier.

• In 1874, Sweden adopted a disease nomenclature developed by the Swedish Society of Medicine. In 1914 a new nomenclature appeared for "preparing medical proposals and reports".

• *The International Statistical Classification of Diseases and Related Health Problems* (ICD) is WHO's classification system of diagnoses. The most recent Swedish version, ICD-10-SE, was published in 2010 by the National Board of Health and Welfare, which emphasises that in addition to diseases it contains "many different types of related health problems" and is not a clinical glossary. ICD contains no definitions and is not binding as regards the diagnoses presented in patient records. The aim focuses primarily on statistics, but ICD has gained increasing importance in computerised patient records and is used by some county councils as a basis for allocating healthcare resources and reimbursing hospitals (via the DRG system, based on ICD).

• *The Diagnostic and Statistical Manual of Mental Disorders* (DSM) is a manual of psychiatric diagnoses that also presents criteria for each diagnosis. It is published by the American Psychiatric Association and has a broad impact internationally. A new version, DSM-5, will be completed in 2013.

views on mental health and ill health.

"The proposals in the first draft of DSM-5 could potentially set off at least eight new false-positive epidemics of psychiatric disorder", writes American psychiatrist Allen Frances in an editorial in the *British Medical Journal*.

MEDICALISATION

Frances, who was appointed to lead the work on the previous edition of DSM, fears that some of the wider diagnostic criteria now proposed will result in naive medicalisation and overtreatment of new, large groups of people.

He also points to five new diagnoses in DSM-5 concerning temper dysregulation, eating patterns, tendency for anxiety/depression, mild cognitive disorders, and risk of psychosis. Allen Frances warns against elevating common and unspecific symptoms to new diagnoses. "Once the diagnostic system is in general use even small changes can be amplified and twisted, with harmful and unintended consequences," he writes.

Others assert that the same type of scrutiny is needed when it comes to physical diagnoses. Fiona Godlee, editor of the *British Medical Journal*, mentions the example of experts recently lowering the threshold value for blood glucose in gestational diabetes to the point that the diagnosis currently applies to nearly one pregnancy in five. And according to an analysis from 2007, the criteria for common conditions have been expanded so much that nearly every elderly adult suffers from at least one chronic disease.

PROVIDE MARKETS

Revising the definitions of diseases is important when it comes to new research findings.

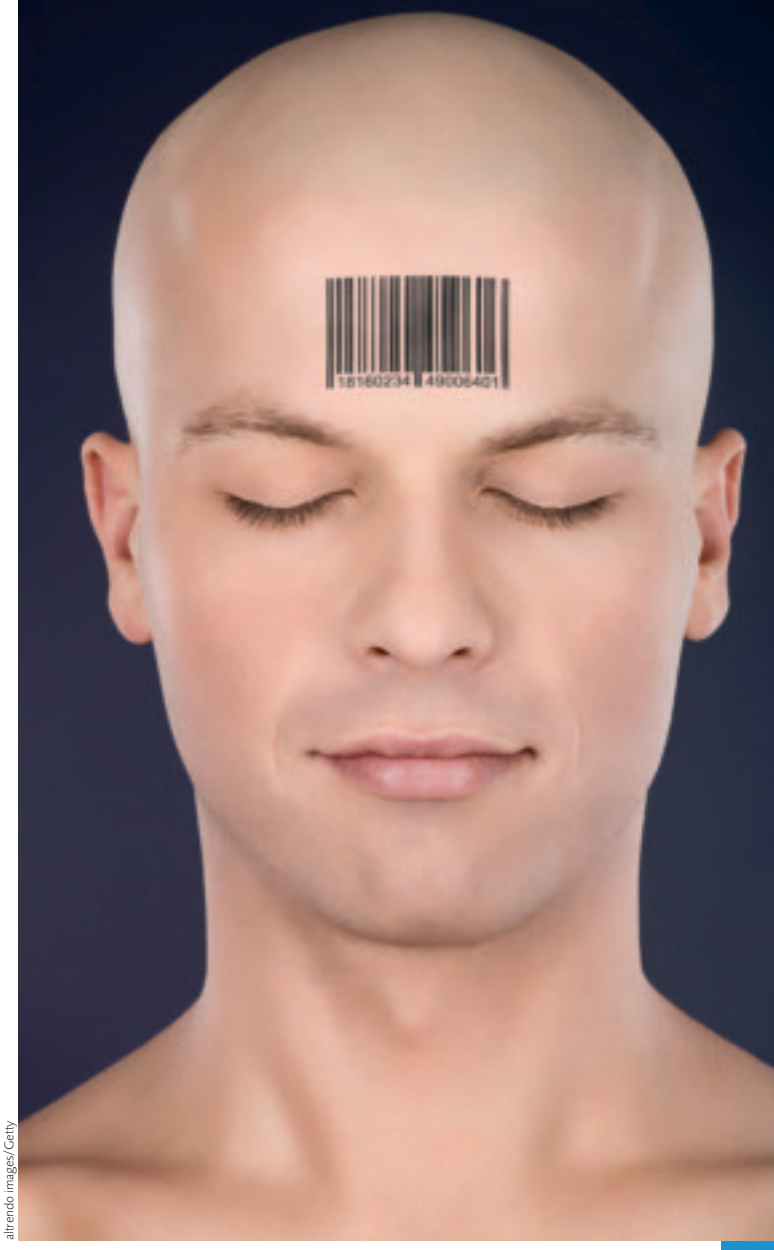
But the critics assert that many new diagnoses have appeared for reasons other than scientific, often to provide industry with markets for their products.

Instead of simply seeking "a cure for every disorder", industry wants to create "a disorder for every cure" and utilise the mass media to present new diagnoses as common and serious.

TRANSFORMS

Medical reporter Ray Moynihan, for example, writes that such a strategy was used to promote female menopause as a hormonal deficiency that should be treated by replacing female sex hormones. Shyness has become a social phobia that can be cured by SSRI agents. Low sexual desire in women translates to a diagnosis of sexual dysfunction to be cured by sildenafil, while male baldness is considered a hair loss problem that requires finasteride.

The rhetoric surrounding new diagnoses transforms aches and pains, individual characteristics, and risk factors into medical problems.



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The diagnoses advocated today are also a result of our current way of thinking and cultural attitudes. Diagnoses are born, have a career, and die in pace with society's changing values. Medical historian, Karin Johannisson, expresses this as follows:

"A diagnosis can disappear when it is no longer perceived as a disease, is swallowed by other diagnoses, or is no longer culturally sanctioned (e.g. chlorosis, hysteria, neurasthenia, hypochondria, nostalgia). In contrast, phenomena that were not previously considered a disease can suddenly become such (premenstrual syndrome, menopause, overweight, childlessness, dwarfism, ageing, low sexual desire, tiredness, hyperactivity)."

Diagnoses appear and disappear in the interplay of patients, doctors, researchers, the pharmaceutical and biotechnical industry, employers, healthcare insurance system, and the image conveyed by the mass media. Most important in this complex dynamic should be the conditions for which medical discoveries and interventions can offer patients the greatest benefit. [RL]

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Surgery: Time for Tough Trial

At last, surgeons have proposed a model to introduce new methods in an orderly fashion while concurrently studying them scientifically, writes Professor Emeritus David Bergqvist.

Assessing drugs is simple – at least in principle. A randomised, double-blind trial compares the new agent with placebo or another active substance, and the results are then assessed.

Equally as important, but often more difficult, is studying the effects of non-pharmacological methods, e.g. surgical procedures.[1]

A particular difficulty is that the outcome often depends on the surgeon's technical skill, experience, and ability to manage unexpected situations that arise during the procedure, e.g. surprising anatomical or pathological discoveries. Know-how and the ability to improvise can play a major role, but can be difficult to standardise. Variations in the craftsmanship of surgeons can also play a role.

SOON MODIFIED

Another challenge is that methods are often soon modified after they come into use. An example in the medical device sector is the early development of vascular prostheses for endovascular aneurysm repair (EVAR).

A vascular prosthesis is placed in the dilated section of the aorta and attached with a stent. When the method was new, stents were used only at the upper end of the prosthesis. But problems with blood leaking into the aneurysm via the lower part of the prosthesis led surgeons to use another stent to fasten the lower end. Since the upper stents occasionally loosened, they were modified so they could be attached to the aortic wall. When the prosthesis showed a tendency to kink in the middle, where no stent was present, then stents were used throughout the entire length of the prosthesis.

NEGLECTED ISSUE

Also, the method's area of application gradually expanded: initially surgeons thought that aneurysms had to be a certain distance from the renal arteries to be treated with this method, an approach that was later abandoned. The example raises the question: At what point in a method's development should researchers start a randomised trial?

Systematic, scientific testing of surgical methods has long been a neglected issue. But three articles published in *The Lancet*,[2,3,4] and commented on in the *Journal of the Swedish Medical Association*,[5] proposed a model to introduce and clinically test surgical meth-

ods. This work was the result of the Balliol Collaboration (named for three colloquia held at Balliol College, Oxford University, on the initiative of Jonathon Meakins, Professor of Surgery).

The first article describes the different stages of a surgical innovation. The second article discusses the special challenges of assessing surgical methods, while the third article presents recommendations. The authors advocate a model that they entitled IDEAL (see Facts).

INTRODUCED EARLY

According to this model, randomised trials should already start during the exploration phase, which seems appropriate for several reasons. Concurrently, certain difficulties might need to be addressed.

For instance, surgeons and patients alike might be hesitant to try an untested method, and if many decline, this can skew the results.

The trial could also have problems from an ethical standpoint – are so-called "sham operations" ethically defensible as placebo? Other difficulties concern the research methodology, e.g. if double blinding is not possible this leads to a risk for expectancy effects. Independent reviewers are essential – and safety committees should be required.

INTRODUCING SURGICAL INNOVATIONS
THE "IDEAL" WAY

Idea | Safety has been tested in animal studies and simulations, and the method is tested under controlled forms on a few carefully selected patients by a few surgeons that report clearly on the results. The surgeon has informed the hospital and departmental managers and the patient of the intent to test a new intervention. Informed consent from the patient is required. The results are reported in detailed, structured, case reports published in a special registry. This registry reports openly and continually on the documented benefits and harms of the new method.

Development | Planned and limited use in an initially small and strictly selected group of patients (seldom more than 30, often fewer than 10) within the framework of a prospective development study of the method. This replaces the traditional type of reporting, i.e. retrospective case series, and aims to document the initial experiences under controlled forms and the effects of refining the method. The method is used only within the study framework and if possible with the help of mentors. No patients are recruited before the study protocol has been registered publicly (outside of the department) and approved (as quickly as possible) by the ethics committee. Only a few surgeons participate. The method is described in detail. Actions are taken to minimise risks and to clearly establish who is responsible for which aspects of patient safety. There is detailed and continual reporting of the principles used to select patients for the study and the outcomes for all trial participants. Potential associations between modified methods and outcomes are carefully documented and analysed.

Exploration | The aim in this phase is to learn more about how the new method could potentially work. After the technical features of the method have been tested in a development study, its use can begin to expand (more surgeons and perhaps up to a few hundred patients) – but still within the framework of systematic follow-up of all patients in prospective research registries, with systematic documentation of important patient-related endpoints, both beneficial and adverse. The databases should contain technical, clinical, and patient-reported data. The first randomised trials should be conducted concurrently, or start from registry data. Now the focus must be on goals/objectives, utility, and mechanisms of action, as well as to prepare for large randomised studies.

Assessment | Here the aim is to study the method's benefits, risks, and costs when used for well-defined indications. At this stage, the method should have developed and matured sufficiently for conducting thorough clinical trials, assessments, and scientific comparisons with other interventions, e.g. current standard practice. Classical randomised controlled trials should be the rule, but modifications or other designs may be necessary in exceptional cases (e.g. for ethical reasons, or when it is impossible to recruit research participants). A medium- to long-term follow-up period is necessary. Health economics should be assessed to analyse the benefits in relation to costs.

Long-term study | The aim is to show rare adverse effects/complications, problems that appear in the longer term, and individual variations in treatment outcomes when the methods are in clinical use. Quality registers and a system for reporting adverse effects should be established. Studies that compare different outcomes in sub-groups can also be conducted, assuming that adequate control of risk profiles has been established.

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As mentioned above, it may be difficult to standardise treatment, e.g. because of differences among surgeons and technical advancements during the course of the trial. Variations can affect care before, during, and after intervention and involve different professions and skills.

Moreover, the results of trials in limited patient groups can be difficult to transfer to a broader population.

PUBLIC FUNDING

Last but not least, it may be difficult to find financial support for trials of surgical methods that cannot be funded by a financially strong business sector. Here, public research funding bodies have a major responsibility.

A recently published report from the Royal College of Surgeons[6] addresses the problem of research involving surgery. The report suggests that the surgical culture is conservative and therefore relatively resistant to change. Hence, the early introduction of research methodology and scientific assessment of new methods is an important element in the education of surgeons and the future of surgical research.

STRICTER RULES

Up to now, the introduction of new surgical methods has required less documentation than, e.g. the introduction of pharmaceuticals. Several reasons speak in favour of stricter rules and better control regarding the performance of trials. Ethical review is one step along the way, but that is not enough.

An increasingly older population means that more people need treatments that must be correctly assessed. Technology is developing more quickly, and new knowledge must be analysed to draw the right conclusions. Patients are often well-informed and justifiably demand optimum technology in treatment. And since our society does not have unlimited resources, it is also important to assess the health economics of new methodologies.

In summary, non-pharmacological treatments – including surgical methods – must be assessed much more systematically than they have been. Although randomised trials of surgical methods are particularly difficult to perform, that is no reason to avoid conducting them. These trials should be registered centrally and flagged in existing quality registers so that researchers can assess long-term effects and identify rare complications. Financial issues must also be addressed.

This is a difficult, but not impossible, undertaking. And there are no shortcuts. In fact, when the benefits and risks of any new method are uncertain it is unethical not to perform well-designed randomised trials.

A reasonable requirement on today's physicians, including surgeons, is that they should be fully aware of how to scientifically assess their methods and how to critically review the information upon which treatments are based.

David Bergqvist
Professor Emeritus
Former Chair, SBU Scientific Advisory Committee

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Do Findings Apply Here and Now?

Rigorous clinical trials can show the benefits of a treatment – under trial conditions. But how universal are the findings? Assessing transferability requires detailed knowledge and critical thinking.

The collective research, the evidence, shows the likelihood of benefiting from different treatments. When the evidence shows a method to be effective, the likelihood is high that many who receive treatment will benefit from it.

Systematic literature reviews, such as those from SBU or the Cochrane Collaboration, indicate how much better the odds are with a certain treatment as opposed to a different one. This is often expressed as an odds ratio: the odds of patients in the treatment group becoming ill divided by the respective odds in the control group.

TRANSFERABILITY

However, it is not only the correctness, i.e. internal validity, which determines whether we can apply the results as guidelines in routine practice. It is also important to assess the external validity, i.e. whether these results apply within the setting where the treatment will be used. Here, the question of transferability arises.

The selection of study participants is one factor that determines the transferability of findings. Few research findings cover all patients under all circumstances. Determining whether any clinically significant differences exist between the sample group and "typical" patients often requires expert opinion.

For example, it could make a difference if the study excluded elderly people, especially since most patients seen in general practice are elderly. In a review of 214 medical studies of heart attacks, the authors concluded that most of the studies had excluded those aged 75 or older – despite the fact that many heart attack patients belong to this age group.

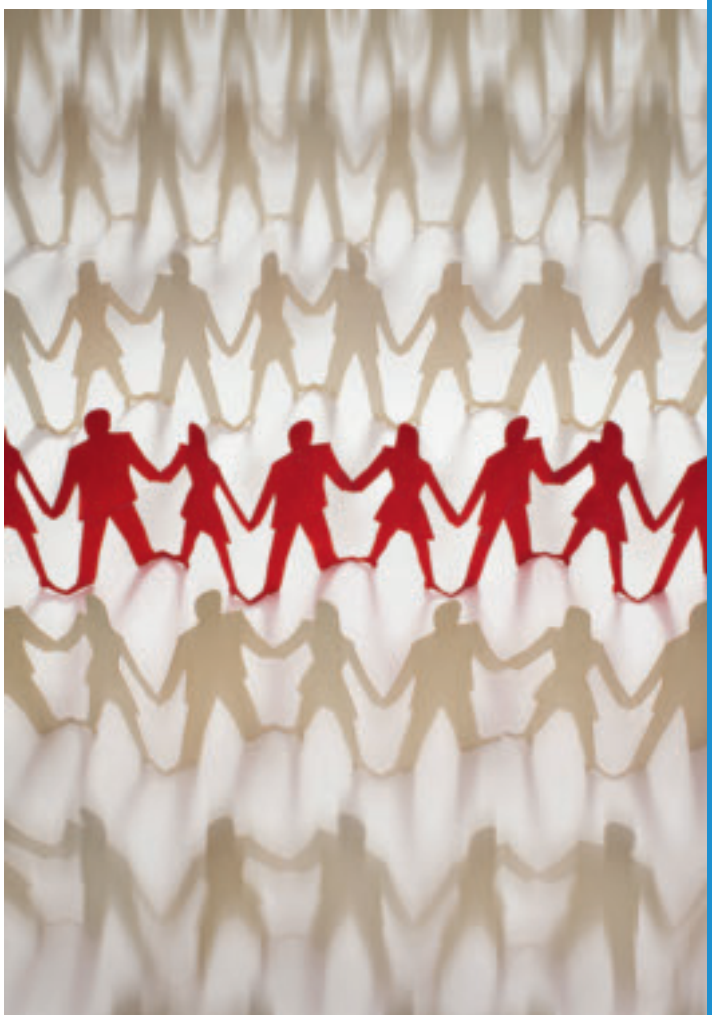
METHOD OF DIAGNOSIS

The methods used to diagnose a patient's condition can also skew the selection of participants in a study. SBU's review of osteoporosis, for example, shows that diagnosis by ultrasonography of the heel disclosed 2 to 3 times as many cases as diagnosis by dual energy x-ray absorption (DEXA) examination of the hip, or anteroposterior measurement of the lumbar spine.

In some studies it is the investigators, not the patients, who are specially selected. In a study of carotid artery surgery, researchers chose to include only surgeons with very good results. Eligibility was limited to the 60% of surgeons with the best outcomes. Later on in the study the researchers further excluded all surgeons whose patients had experienced any type of complication. The results of such a study would not be broadly applicable.

TREATMENT SETTING

Not only does the selection of participants and investigators need to be transferable. At



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times it is also important that the general care conditions in a study reflect the Swedish healthcare environment. For instance, significant factors might include the country in which the study was conducted, or whether the treatment was delivered in a hospital or a primary care setting. In an international study, researchers intended to investigate whether surgery to treat narrowing of the carotid artery is effective in minimising the risk of stroke. What the researchers had not allowed for was that the treatment waiting times varied significantly among the different countries. In Belgium and the Netherlands, patients had to wait 3 weeks from the onset of symptoms to participation in the study. In the UK the wait was 2 months – which reduced the effectiveness of the treatment.

Yet another factor that affects treatment outcome is how well the patient complies with instructions. Participants in research studies are often careful to follow any advice given. Also, they usually receive better aftercare and support than is normally provided. "Regular" patients, however, often fail to comply with instructions.

MOST IMPORTANT

Determining which factors are most important for transferability depends on the research field. The table below presents examples of factors that can influence transferability.

In SBU's evaluations, experts rate the strength of the total body of scientific evidence for each result as strong, moderately strong, limited, or insufficient. The judgment depends on, e.g. the quality and consistency of the studies, the size and range of the results, but also transferability. If this is lacking, SBU notes that the scientific support for the study is weaker.

Transferability must always be considered before research findings can be presented as guidelines or applied in routine clinical practice.

However, it is unreasonable to dismiss findings automatically just because the clinical setting is not quite the same as in the studies. Often it is better to ask why wouldn't the evidence be helpful here and now. [RL]

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REDUCING TRANSFERABILITY | EXAMPLES

Different treatment settings?

- Different country and healthcare system
- Primary care versus hospital care
- Special selection of participating centres/clinicians

Special selection method in the study?

- Unusual method of research or diagnosis
- Special criteria for including/excluding participants
- Treatment/placebo prior to the study, *run-in period*
- Reinforcement arrangements, *enrichment*
- Small number of participants selected from all eligible patients
- Many of those recruited declined to participate

Participants at baseline?

- Different state of health when study began
- Age, gender, ethnicity, socio-economic group
- Unusual illness phase/difficulty
- Comorbidity
- Risk of poor outcome in the control group

Typical treatment?

- Unusual features of treatment
- Therapy is started sooner/later than normal
- Irrelevant treatment in the control group
- Other measures taken alongside the method studied
- The method (for diagnosis/treatment) has advanced since the study was performed

Reasonable follow-up?

- No patient-centred outcomes measured, surrogate measures of low clinical relevance used instead
- Complicated scales for estimation: clinical relevance, reliability, and reproducibility
- Combination of several effects measured, obscuring less favourable effects on the most important aspects
- Short follow-up time, few measurements

Risk of side-effects and injuries?

- Incomplete and irrelevant reports of side-effects and complications
- A high proportion of discontinued treatments
- Highly experienced and skilled clinicians participating in the study
- High-risk patients and patients who develop problems are excluded early in the study
- Extra security measures in the study

Unequal Care of Prostate Problems

Clinicians often use drugs to treat moderate bother from benign prostatic hyperplasia. Since men who benefit from treatment cannot be identified in advance, health services must monitor outcomes. Surgery can be effective for those with severe problems, but quality of life declines in many who do not receive help.

Anna Molander

In many men, the prostate grows with age to the point it blocks urinary flow. They find it difficult to empty the urinary bladder, need to urinate more often and have an urgent need to use the toilet, and must get up several times at night. Untreated, this commonly disrupts sexual functions, e.g. erection and ejaculation. A new SBU report shows that prostate problems substantially lower the patient's quality of life and also affect his partner.

SBU's assessment shows that medication generally has a modest effect on moderate prostate bother, although some men might benefit. Nevertheless, according to the report, drugs are a cost-effective option in the initial treatment of moderate bother.

But to avoid unnecessarily prescribing drugs and delaying other treatment, it is important for health services to monitor outcomes in every patient receiving medication, asserts SBU.

Phytotherapeutic agents (herbal medicinal products) are used at times to treat symptoms of benign prostatic hyperplasia (BPH). Scientific studies provide some evidence that these agents can help, but the results are uncertain since studies are few and relatively small.

SEVERE PROBLEMS

Surgery is used primarily to treat more severe problems. The most common methods, TURP (transurethral resection of the prostate, where a thin electrical wire is used to remove tissue via the urethra) and TUMT (transurethral microwave thermotherapy) are effective and have limited adverse effects. TUMT is a milder procedure, but its effects on symptoms and urinary flow are not as good, and it needs to be repeated more frequently.

Alongside of these established methods, several

Brian Hagiwara/Getty

Spinal Fracture – Uncertain Benefits of Bone Cement

Whether or not bone cement is superior to placebo or standard treatment cannot be determined when it comes to patients with vertebral fractures from osteoporosis. Cement often leaks during treatment, but how this affects health is uncertain.

SBU recently reviewed treatment using bone cement in fractured and compressed vertebrae to increase stability and reduce pain. This method is called percutaneous vertebroplasty. SBU's review also includes a variant of the method, balloon kyphoplasty, which restores the height of the vertebra by using a small balloon prior to injecting the cement.

INSUFFICIENT EVIDENCE

The body of scientific evidence is insufficient to determine whether vertebroplasty or balloon kyphoplasty are better at reducing pain, improving function, and increasing quality of life than placebo (sham surgery) or standard treatment (pain relief, nursing, and gradual exercise, often assisted by a physiotherapist). Since little is known about the health effects, it is not possible to determine the cost effectiveness of these methods. Being able to determine the methods' benefits and risks requires systematic monitoring, e.g. a national quality register.

Several studies show that cement often leaks during vertebroplasty and balloon kyphoplasty, although the patient seldom notices this. The impact of leakage on health is uncertain. A cement fragment entering the bloodstream, causing a clot in the lung (pulmonary embolus), would create a dangerous situation. [JT]

BRITTLE SPINE

- Vertebral compression affects approximately 15 000 people every year and is often caused by osteoporosis. Vertebral compression occurs when vertebrae are compressed, fractured, and reduced in height.
- Patients can experience such intense pain that they become bed-ridden for a prolonged period. In turn, this creates a major risk for further osteoporotic fractures and other complications, e.g. pneumonia and blood clots.
- In placebo treatment, i.e. sham surgery, patients receive local anaesthetic for vertebral fractures, but no cement filling. Otherwise, the process is as similar as possible to active treatment.

This report updates an SBU report from 2007 (Percutaneous Vertebroplasty in Severe Back Pain Due to Compression). New research findings have emerged since the publication of the previous report.

new alternatives and refined versions of existing methods have been developed. These aim to achieve effects equalling those of TURP, but with lower risks for adverse effects. For instance, more intensive, localised heat directed at the prostate is being tested (vaporisation by electrical or laser energy). The SBU report asserts that such methods should be tested within the framework of scientific studies that can assess the effects.

UNEQUAL ROUTINES

Practice varies when it comes to treating BPH involving urinary outflow obstructions. Routines are unequal among Swedish county councils. In men above 50 years of age the number of daily doses varied between 18 (Blekinge) and 31 (Värmland). The national average was 25 daily doses per man.

Responsibilities between primary care and specialised urological services also differ depending on local resources and traditions.

One question concerns whether some county councils overprescribe medications for BPH symptoms, particularly in men above 80 years of age. Stockholm County Council reported the highest number of doses for this group (86 daily doses), while Blekinge reported the lowest number. The national average for the age group was 68 daily doses.

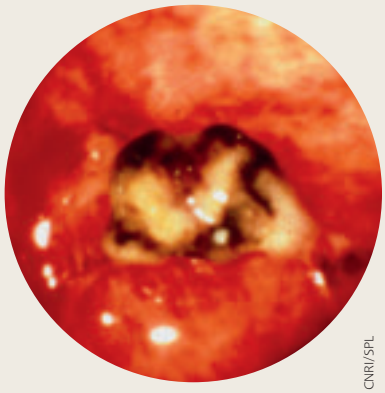
The risk of serious adverse effects from these drugs is relatively low, but it is important to avoid unnecessary reduction in blood pressure, which, for instance, could lead to falls among the oldest patients. Likewise, there could be reasons to avoid surgery in this age group.

CLEAR INFORMATION

Many men with prostate bother do not seek help. To enhance knowledge among those who want treatment and wish to participate in selecting a treatment method, health services should provide clear and factual information about the benefits and risks of different options. Informational material in different languages may be necessary.

The cost of treating prostate problems has been declining, which could be attributed to a more limited use of surgery, greater efficiency, or possibly deciding that other surgical interventions are more urgent. [RL]

Gastric Ulcers – Preventing Acute Bleeding Saves Lives



CNRI/SPL

Mortality is high in patients treated for gastric ulcer bleeding. SBU's new assessment shows that more would survive if given two antibiotics plus medication to reduce gastric acid, i.e. proton pump inhibitors.

Improving preventive interventions against gastric ulcer bleeding would probably save lives.

In patients who have experienced stomach bleeding, the risk of relapse decreases if they receive combination treatment for stomach ulcer bacteria (*H. pylori*) via two antibiotics plus proton pump inhibitors that reduce gastric acid. Registry data suggest that more patients should receive this treatment.

A group at higher risk of gastric ulcer bleeding are those treated with acetylsalicylic acid (ASA), a therapy that can help prevent blood clots that could lead to myocardial infarction or stroke.

People affected by stomach bleeding and who need to continue taking low-dose ASA to prevent blood clots could receive protection against new bleeding by taking antibiotics plus proton pump inhibitors.

PROTECTS PATIENTS

This treatment protects patients that have had gastric ulcer bleeding and, for a prolonged period, must take anti-pain and anti-inflammatory drugs in the NSAID category, e.g. diclofenac, ibuprofen, or COX-2 inhibitors. However, persons who have had gastric ulcer bleeding should avoid NSAIDs, if possible. Other interventions against pain and its causes could play a more important role instead.

Preventive treatment with proton pump inhibitors can protect against gastric ulcer bleeding even in individuals who have not had previous bleeding, but who take NSAIDs or ASA over a prolonged period. In particular, this group includes older persons, smokers, and heavy consumers of alcohol – and also presumably patients treated with cortisone agents or antidepressants (SSRI).

INCREASE MOVEMENT

SBU has also assessed therapy delivered via gastroscope (endoscopic) in conjunction with examining the stomach. A conclusion is that the stomach's surface can be better visualised if the patient receives a dose of erythromycin in advance to increase gastrointestinal movement.

Injecting the patient with adrenaline via a gastroscope in conjunction with mechanically or thermally closing the ulcer is shown to prevent new bleeding. This also results in fewer patients requiring surgery later. The risk of new bleeding also decreases if the patient takes proton pump inhibitors afterward.

POOR UNDERSTANDING

But the question is whether the bleeding risk is taken seriously enough. Currently, only 4 in 10 patients with gastric ulcer bleeding receive treatment against *H. pylori* within the first quarter after discharge. This finding appeared in a Swedish register study for 2006 and 2007 that SBU conducted within the scope of the project.

– We're afraid that this is due to a poor understanding amongst health services of how important it is to remove this bacteria following gastric ulcer bleeding, says surgeon and research fellow Christer Staël von Holstein, Chair of the SBU project group.

– However, we cannot rule out that the reason might be low prevalence of *H. pylori* in patients with stomach ulcers.

Every fifth patient affected by bleeding stomach ulcers had received, during the quarter prior to bleeding, on-going treatment to reduce gastric acid – usually proton pump inhibitors.

– Another sign that treatment for gastric acid is often inadequate is that so many people are still affected by bleeding ulcers, says Christer Staël von Holstein.

– Stomach ulcer bacteria must also be addressed. Mortality is substantially higher among those who have not been prescribed medication against these bacteria.

Bleeding stomach ulcers are common and acutely life-threatening, although the bleed itself is seldom the direct cause of death. Unstable blood circulation can damage the heart or other vital organ functions, and patients with bleeding stomach ulcers need to be quickly treated in hospital.

In Sweden, someone with this disorder dies every 2 or 3 days. The risk of bleeding is highest in the elderly. In the population as a whole, 38 people per 100 000 are affected, but the corresponding figure in those over 75 years of age is 170 per 100 000 population. [JT]

ACID PROMOTES BLEEDING

- Gastric fluid in the stomach and the duodenum is highly acidic, which inhibits the ability of blood to coagulate. Bleeds in the upper gastrointestinal tract are more serious than bleeds in the small or large intestine.
- Drugs that reduce the secretion of gastric acid – H2 blockers and proton pump inhibitors – raise the pH value in the stomach and improve the conditions that enable the blood to coagulate in case of a bleed.

Mother's Blood Tells Clinicians Foetal Sex and Blood Type

MedicalRF.com

Testing an expectant mother's blood shows, in 99% of cases, foetal sex and blood group. Analysing foetal DNA in this way can avoid using higher risk foetal diagnostics. The method can also be used in screening for foetal blood group.

Occasionally, for medical reasons, it can be important to identify foetal gender or blood group. A simple blood test from the expectant mother can provide this information. The method does not put the foetus at risk, in contrast to invasive methods where specimens are drawn from the placenta or amniotic fluid via a thin needle inserted through the abdominal wall and into the uterus.

Analysing foetal DNA ins a pregnant woman's blood is called non-invasive prenatal diagnosis (NIPD). The test can be performed as early as the seventh gestational week.

MEDICAL REASONS

SBU has reviewed the studies showing the accuracy of the method in determining foetal blood group and gender. The assessment addresses the medical reasons for prenatal diagnosis, e.g. women with a serious genetic disorder that can affect boys (X-chromosome-related diseases), or women with antibodies in blood that could destroy red blood cells in the foetus. Gender determination of the foetus without medical indications (e.g. family planning) was not assessed. Using NIPD in this way has been found unethical in other contexts.

There is some scientific evidence to show that NIPD accurately identifies foetal gender in 99% of cases. The method should help reduce the need for amniocentesis and testing of the placenta. At present, NIPD is not used in Sweden to identify foetal gender.

In Sweden, around 1000 pregnant women per year have antibodies against blood group antigens, including just over 150 with antibodies against RhD. Prenatal DNA testing is already being offered to these women. SBU's assessment shows that the method accurately identifies the RhD group of the foetus in 99% of cases.

SCREENING

Another use of the method involves screening – testing foetal blood group in all preg-

MORE ABOUT THE RH SYSTEM

- Rh are proteins in the cell membrane of red blood cells. Over 50 different Rh antigens exist, whereof RhD is the most important.
- Antibodies against RhD can be formed if a woman who lacks this antigen carries a foetus that inherited an RhD gene from the father. The blood cells of the foetus are then RhD positive. In conjunction with birth, there is a major risk that blood cells from the foetus enter the circulatory system of the mother, causing her to start producing antibodies. In her next pregnancy, these antibodies could harm an RhD-positive foetus.
- RhD prophylaxis can often prevent the formation of antibodies. Gamma globulin with concentrated RhD antibodies is given to the RhD-negative woman.
- Today, every pregnant woman is checked for blood group. RhD-negative women that give birth to an RhD-positive child then receive preventive treatment postpartum.

nant women in the RhD-negative blood group. In Sweden, this includes 16 500 pregnant women per year (15% of total). Six in 10 give birth to a child that is RhD positive and are at risk of forming antibodies. If the woman becomes pregnant again and the foetus is RhD positive, then these antibodies could lead to death in some cases.

AVOID ANTIBODIES

The aim of screening for foetal blood group in all RhD-negative women would be to initiate preventive treatment early in pregnancy to avoid formation of antibodies against RhD. Both the expectant mother and the foetus would benefit, according to SBU's review. Some EU Member States have recently introduced screening programmes. However, the consequences that screening might have regarding the organisation and economics of health services remains unclear. This is currently being investigated, e.g. by a study in Stockholm County Council.

Methods for examining genetic characteristics in the foetus raise difficult ethical questions for health services and society. In conjunction with SBU's assessment, the Swedish Medical Ethics Council (SMER) has presented a detailed analysis of these issues in a special report. [JT, RL]

Computer vs. Mammography Issue Still Pending

According to European recommendations, two specialists in breast radiology should read x-ray images from breast cancer screening. SBU's critical analysis shows that the evidence is insufficient to determine if a computer program can replace one of the physician's readings.

SBU has assessed a method called computer aided detection (CAD) where a breast radiologist reads mammography images with the help of a computer program. This was compared to current practice in Sweden – where two breast radiologists read the images independently.

SBU's assessment shows uncertainty concerning the benefits and risks of the CAD option. The body of scientific evidence is insufficient to determine whether the CAD-based diagnosis plus reading by a single breast radiologist is comparable to double reading.

RE-EXAMINATION

Furthermore, whether or not the method would result in calling back equally as many, or fewer, women for re-examination is uncertain. It is important not to call back too many since this could cause anxiety for the patient and delay the examination results.

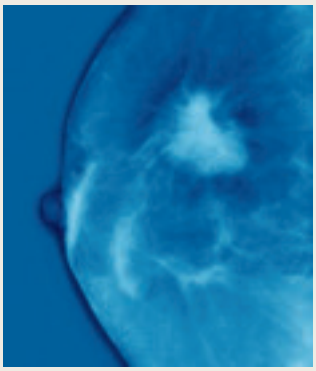
Since the medical benefits of this method are uncertain, its cost effectiveness cannot be determined. Nor is it possible to determine the socio-economic consequences of using CAD to replace one of the physician's readings of images from mammography screening.

Although the method has been used for more than a decade, the technology has advanced in recent years. Direct digital images have now replaced the scanned radiographs that were used in the studies. The computer programs have also advanced since the earlier studies were conducted.

NEW SPECIALISTS

To detect breast cancer, most county councils offer regular mammography examinations to women between 40 and 74 years of age.

According to Swedish and European guidelines, x-ray images should be reviewed by two specially trained radiologists, i.e. breast radiologists. One reason for the increased interest in computer aided detection in Sweden is the shortage of new specialists. At present, CAD is used only to a limited extent. [JT]



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SOME CURRENT SBU PROJECTS

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ACUTE CARE FOR THE ELDERLY
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