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Diagnostic agreement of digital whole slide imaging and routine light microscopy

Lindsköld L, Samuelsson B, Carlberg I, Kjellström C, Wikberg Adania U, Wolving M, Sjögren P, Svanberg T, Samuelsson O.

Diagnostic agreement of digital whole slide imaging and routine light microscopy
[Diagnostisk överensstämmelse mellan inscannade digitala histopatologiska preparat och konventionell ljusmikroskopisk histopatologi]

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Summary of the Health Technology Assessment

Method and patient group

The use of histopathology to decide a pathological anatomical diagnosis (PAD) is the most important diagnostic method for many diseases. For malignant diseases it is of paramount importance for diagnosis, determination of the stage of the disease, and follow-up of the effects of treatment.

Presently, the diagnostic analyses are made with the use of conventional light microscopy. During the last decade the technical development has created methods to digitise the glass slides. Lately, scanners that automatically scan the glass slides and create digital image files have been produced. These whole slide images (WSI or virtual slides) can be distributed to, and viewed at a modern workstation, and the large volumes of data can be stored and handled digitally.

Questions at issue

Do scanned digital images have sufficiently high quality for diagnostic purposes, and does this type of digital pathology also offer further advantages, or have some important disadvantages?

Results and conclusions

The systematic literature search identified twenty studies that compared diagnostic agreement, or concordance, of virtual slide imaging (whole slide imaging = WSI) with light microscopy (LM). Ten of these studies reported ***intraobserver*** comparisons. Eighteen studies reported ***interobserver*** comparisons.

The diagnostic agreement was good for both intraobserver and interobserver comparisons when the two methods were compared. The diagnostic intraobserver agreement, across the studied organ systems, ranged from 61-100 % agreement and the Cohen's kappa coefficient between 0.55 to 0.81 (i.e. moderate to almost perfect agreement). For interobserver comparisons the percentage agreement ranged from 70-100% and the Cohen's kappa coefficients were in the range 0.36 – 0.84. For acute rejection of kindney transplants both LM and WSI had 35 % diagnostic interobserver agreements with Cohen's kappa coefficients of 0.28 – 0.42 (i.e. fair agreement). The quality of evidence is low (GRADE ⊕⊕OO).

All the studies that report disagreements in individual cases also state that the respective discrepancies were not due to a difference in diagnosis that would be associated with clinical and prognostic important implications, but rather with differences of minor clinical importance.

It is important to point out that the two diagnostic methods, LM or WSI, have not been studied and compared in terms of important clinical patient outcomes such as disease progression, morbidity and mortality. Thus, presently it is not known whether one of these two methods has a better prognostic impact or diagnostic precision than the other.

It is also important to realize that further validation of the diagnostic accuracy of WSI is necessary for each specific organ system as well as for specific types of diagnosis. In this HTA the diagnostic agreement of LM and WSI has only been assessed overall by putting various types of organ systems and diseases together.

Ethically, there are no major reasons to object to an introduction of digital pathology provided that the personal integrity of the digitised data are secured.

Which health technology or method will be assessed?

1a **Who will lead the project?**

Lars Lindsköld, PhD. Project leader, Department of Healt Care Regional Secretariat, Region Västra Götaland, Sweden.

1b **Who posed the question?**

Jan Eriksson, Chief Executive Officer, Sahlgrenska University Hospital, Göteborg, Sweden, at the time the question was posed.
Ingela Tuvegran, Chair IT council, Region Västra Götaland, Sweden.

1c **Co-workers:**

Christer Kjellström, Head of Pathology, UNILABS Ltd., Göteborg, Sweden.
Bo Samuelsson, Professor emeritus, Sahlgrenska Academy, University of Göteborg, Göteborg, Sweden, and Department of Health Care Regional Secretariat , Region Västra Götaland, Sweden.
Mats Wolving, Head of the Department of Pathology and Cytology, Sahlgrenska University Hospital, Göteborg, Sweden.
Ingvar Karlberg, Professor, Nordic School of Public Health, Göteborg, Sweden.

1d **Other participants, from the HTA centrum and external reviewers**

Ola Samuelsson, Associate professor, MD, Sahlgrenska University Hospital, Göteborg, Sweden.
Petteri Sjögren DDS, PhD, HTA centrum, Region Västra Götaland, Göteborg, Sweden.
Therese Svanberg, HTA-librarian, Sahlgrenska University Hospital, Göteborg, Sweden.
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Sweden.

External reviewers
Michael Breimer, Professor, MD, Department of Surgery, Sahlgrenska University Hospital, Göteborg, Sweden.
Krister Järbrink, PhD, Health and Medical Care, Region Västra Götaland, Sweden.

1e **Are there any conflicts of interest for the proposer or any of the participants in the work group?**

Christer Kjellström, employed by UNILABS Ltd, was during a limited period of time involved in a tender procedure involving pathology services for Sahlgrenska University Hospital. During this period he, and Mats Wolving, Head of the Department of Pathology and Cytology, did not participate in the health technology assessment.

Disease/disorder of Interest and Present Treatment

2a Disease/disorder of interest and its degree of severity

√ Risk of premature death
√ Risk of permanent illness or damage, or reduced quality of life
√ Risk of disability and health-related quality of life

2b Prevalence and incidence of the disease/disorder

Not applicable

2c Present treatment of the disease/disorder in the outpatient setting/ in-patient setting.

Currently only conventional light microscopy of glass slides is used.

2d Number of samples per year which undergo current diagnostic examinations?

Approximately 115,000 histopathology samples (biopsies or organ samples) are examined histopathologically each year in Region Västra Götaland.

2e The normal pathway through the health care system

The use of histopathology to decide a pathological anatomical diagnosis (PAD) is the most important diagnostic method for many diseases. For malignant diseases it is of paramount importance to get a diagnosis, to determine the stage of the disease, and for the follow-up of the effects of treatment.

The tissue/organ sample from a patient could be collected in the outpatient setting as well as during hospitalisation. The sample is immediately transported to a laboratory of pathology department together with a referral document. At the laboratory a pathologist or a technician will handle the sample, and put relevant parts into liquid paraffin. After cooling it results in a solid block, from which ultrathin slices are cut. These slices are then placed on glass slides. They can be coloured with different dyes, or targeted with different specific antibodies. At the end of the preparation the slides are covered with a thin glass slide or plastic film.

The prepared microscopic slides are finally analysed by a pathologist using conventional light microscopy. The diagnosis is documented on the referral document that is returned to the referring doctor.

2f Actual wait time in days for medical assessment /treatment

The time delay between the sampling of the tissue specimens and the final PAD is of great importance since the decision on treatment and its initiation is directely related to the PAD. At present the average response time varies between the different departments of pathology.

Hospital	Time to PAD (working days)
Sahlgrenska University Hospital	16
Södra Älvsborg Hospital	9
Unilabs	9
NU hospital group	7

Present Health Technology

3a Name/description of the health technology at issue

As stated above light microscopic analysis of ultra-thin sections of organ tissue in glass slides is used to decide a PAD.

Presently, the diagnostic analyses are made with the use of conventional modern light microscopes, and the results of the diagnostic examinations are finally described in text. The glass slides and the paraffin embedded blocks (see 2e) are then stored for future use. There is an interobserver variability when the same glass slides are observed by two or more pathologists. As can be seen below (Appendix 1-2, 5a) the interobserver diagnostic agreement for glass slides never reaches 100 %.

During the last decade the technical development has created methods to digitise the glass slides. This new concept is called *digital pathology*. Initially digital cameras were used. However, the problem with the cameras has been the limitation to handle large volumes of digitised data. Lately, scanners have been developed that automatically scan the glass slides and produce digital image files. These whole slide images (WSI or virtual slides) can be distributed to, and viewed at modern workstations. Furthermore, large volumes of data can be stored digitally and handled this way.

Although the presently available technique of digital pathology has a high image resolution when glass slides are scanned and distributed, the analogous image seen in the microscope theoretically has a higher resolution. The questions are whether the scanned digital images have sufficiently high quality for diagnostic purposes, and whether this type of digital pathology also offers further advantages, and whether it may have some important disadvantages.

3b The work group's understanding of the potential value of the health technology

Digital pathology allows a new way to manage data and images generated in the pathology department. It offers three advantages:

I. *Instant access.*
The digitally stored data can easily be used as reference files, and can be accessed instantly. This new technology will enable new workflow strategies with efficient team work. By sharing the information instantly, and "on-line", more complex teamwork, and more dispersed tasks can be handled than one single person can deal with on his/her own. Large digitally stored databases will most probably also be of great future importance for research and development.

II. *Real-time conferences and discussions*.
The digitally collected information can quickly, and efficiently, be transferred and managed throughout, and beyond, the pathology department, both within as well as outside the hospital. This enables a new way to collaborate with other pathologists, and thereby generates added value services for both patients and professionals with immediate second opinions, and clinical conferences. It also allows for shared education both locally and at a distance.

III. *Improved ergonomy.*
The virtual slides can be handled on high-resolution screens rather than in the light microscope. This can improve the ergonomic conditions for the pathologists. Also, the need to manually get old slides from a glass archive and transport them to the microscope will no longer be necessary.

Early published retrospective studies also indicate that digital pathology has the potential to improve the prognostic accuracy in comparison to manually judged glass slides in the case of malignant diseases (Beck *et al*., 2011).

Finally, it is believed that digital pathology also has a potential to be of economical benefit for the healthcare system.

3c **The central question for the current HTA project in one sentence**

Do scanned digital images have sufficiently high quality for diagnostic purposes, and does this type of digital pathology also offer further advantages, or have some important disadvantages?

3d **PICO**

P= Patients, I= Intervention, C= Comparison, O=Outcome

P= Organ or tissue samples for histopathology examination

I= Diagnostic work-up of digitised glass slides (scanned to whole slide images, WSI)

C= Diagnostic work-up of glass slides with light microscopy

O= Diagnostic agreement
Quantification of pathological findings
Mortality
Progression of disease/disorder
Complications and risks

3e **Key words**

Image processing, histopathology, whole slide imaging, digital microscopy

Review of the Quality of Evidence

4 Search strategy, study selection and references – Appendix 3

During March, 2012, two librarians performed searches in PubMed, EMBASE, the Cochrane Library, and in a number of HTA-databases. Reference lists of relevant articles were also searched for additional references. A total of 522 articles were identified after removal of duplicates, of which 467 abstracts were excluded by the librarians. Another 18 articles were excluded by the librarians after having been read in full text. 37 articles were sent to the work group for assessment. 20 of these articles are included in the report, all have been critically appraised using the Swedish version of the QUADAS 1 checklist.

Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in Appendix 3. The literature search and exclusion of abstracts were done by two librarians (TS, UWA) in consultation with the HTA-centrum and the work group.

5a Describe briefly the present knowledge of the health technology

The literature search did not find any study that compared the effect of virtual slide imaging and light microscopy as diagnostic tools on the prognosis, i.e. mortality, morbidity and progression of disease in patients. Neither was any study found of possible risks for the patients by the use of either of the diagnostic tools.

The systematic literature search identified 20 studies that have compared diagnostic agreement of virtual slide imaging (whole slide imaging = WSI) with light microscopy (LM).
Ten of these studies reported ***intraobserver*** comparisons, and 18 studies reported ***interobserver*** comparisons.

Intraobserver agreement is the amount of agreement one observer experiences when observing the same material more than once, i.e. in these particular comparisons when the same histopathology sample is evaluated by one pathologist using the glass slide and then the virtual slide (or vice versa). ***Interobserver agreement*** is the amount of agreement obtained by two or more observers examining the same material, i.e. in these particular comparisons the agreement between different pathologists of the same glass slides, or of the same virtual slides, respectively.

The organ, or organ system, of interest differed in the studies, see table below.

Organ/organ system	Number of studies
Dermis	4
Prostate gland	3
Mammary gland	4
Gastrointestinal system	1
Colon and rectum	1
Liver	1
Central nervous system	1
Genitourinary system	1
Renal transplant	1
Case-mix	3

Diagnostic agreement was defined and calculated in two ways:

1. *Percentage agreement*, i.e. the number of cases that got the same diagnosis after examination of the glass slides in a light microscope (LM) and examination of the scanned virtual slide (WSI), respectively, divided by all the examined cases. This means, that if only half of the cases receive the same diagnosis after each of the separate examinations (LM and WSI) the diagnostic agreement will be 50 %, whereas it will be 100 % agreement if all the cases received the same diagnosis with both diagnostic methods.

2. C*oncordance* measured by the Cohen's kappa coefficient (K) (Carletta J, 1996). Cohen's kappa measures the agreement between two raters/observers who each classify *N* items into *C* mutually exclusive categories. The equation for K is:

$$K = [Pr(a) - Pr(e)] / [1-Pr(e)]$$

Pr(*a*) is the relative observed agreement among raters.
Pr(*e*) is the hypothetical probability of chance agreement, using the observed data to calculate the probabilities of each observer randomly saying each category.

If the raters are in complete agreement then K = 1. A value of the K-coefficient below zero means that there is poor agreement between two observations/examinations. Positive values between 0 – 1 are interpreted as follows; 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61 – 0.80 substanstial agreement, > 0.80 almost perfect agreement.

Intraobserver comparison (Appendix 1-1 and appendix 4)
Five of the studies that reported diagnostic agreement had no major limitations with regard to directness, study design and precision.

The studies reported a percentage agreement that varied from 61 % to 100 %. The agreement was good for dermatopathology (94 %), gastrointestinal tract pathology (95 %) and breast cancer pathology (61 % - 100 %), but lower for diagnosing acute rejection of renal transplants (63 % - 73 %).

Three of the studies that reported concordance by the kappa coefficient (K) had no major limitations with regard to directness, study limitations and precision. In two of these studies (colon and prostate pathology) a substantial to almost perfect intraobserver agreement was observed with a K-coefficient above 0.60, or above 0.80. In the third study (of breast cancer pathology) the agreement was moderate to substantial.

All the studies report disagreements in individual cases also state these were not due to differences in diagnoses that would be associated with clinical and prognostic important implications, such as for example a diagnosis of a malignant tumour. The types of disagreements were minor, which would not have any significant clinical implication, such as for instance the specification of an acute colitis.

Conclusion: The diagnostic agreement between WSI and LM is good in intraobserver comparisons. Low quality of evidence (GRADE ⊕⊕OO).

Interobserver comparison (Appendix 1-2 and appendix 4)
Five of the studies that reported percentage agreement had no major limitations with regard to directness, study design and precision. The agreement was good in all three studies of breast cancer, ranging from 70 % - 100 % in the different comparisons. Also in the study of genitourinary pathology the interobserver agreement was good for both LM and WSI when they were compared to a "reference standard" (92 % and 88 %, respectively). However, the percentage agreement was only 35 % for either diagnostic tools in the diagnosis of acute rejection of renal transplants.
The agreement was of the same magnitude in three studies that had some limitations with regard to any of directness, study design or precision (two dermatopathology studies and one prostate pathology study).

Three of the studies that reported concordance by the kappa coefficient (K) had no major limitations with regard to directness, study limitations and precision, and two studies had some limitations in any of them Four of them reported moderate to substantial agreement with a K-coefficient 0.41-0.60, or 0.61-0.80 (one colorectal pathology study, two prostate pathology studies and one breast cancer study). The diagnostic agreement measured by the K-coefficient was only fair (0.21-0.40) for both diagnostic tools in the diagnosis of acute rejection of renal transplants.

Similar to intraobserver disagreements (see above) the studies report that neither the interobserver disagreements were due to differences in the decisions of clinical important diagnoses, such as for example malignant tumours, but rather to differences of minor clinical importance.

Conclusion: The diagnostic agreement between WSI and LM is good in interobserver comparisons. Low quality of evidence (GRADE ⊕⊕OO).

5b Outcome tables – appendix 1

5c Excluded articles – appendix 2

5d Ongoing research?
A search in clinicaltrials.gov (2012-06-12) using the keywords *virtual slides OR virtual slide OR digital slides OR digital slide OR whole slide image OR whole slide images OR digital pathology OR virtual microscopy OR "virtual pathology" OR "digital microscopy" OR telepathology* resulted in 55 studies. None of them were of relevance for the question at issue of this HTA-report.

6 Which medical societies or health authorities recommend the new health technology?

☐ The National Board of Health and Welfare
☐ Medical societies
☑ Other health authority

Which medical society or health authority?

a. Digital Pathology Association, Indianapolis, Indiana, USA
b. VINNOVA (Sweden's Innovation Agency) has funded a project at the University of Linköping, Sweden, with 9.2 million SEK to design and implement a system of digital pathology.

Ethical aspects - dessa skall besvaras efter litteratursökning/läsning

7 Ethical consequences

It is important that only medical personnel directly involved in the diagnostic work-up and treatment of the patient will have access to the digitised data. The implementation of digital pathology therefore requires special precautions with regard to the IT systems in order to protect the personal integrity.
The ethical analysis is presented in Appendix 5.

Organisation

8a When can this new health technology be put into practice?

At each laboratory of pathology in Region Västra Götaland digital pathology can be introduced within one year. Within two years a functional collaboration between the four laboratories in the region can be in full operation.

8b Is this technology used in other hospitals in Region Västra Götaland or in Sweden?

At the Department of Pathology, Kalmar hospital, digital pathology using scanners has been in use since 2009.
During 2012 region Skåne is implementing digital pathology in their pathology laboratories.
Other regions are doing field testings of the technology.
At the University of Linköping a system of digital pathology is currently under development (see 6)

During 2010 all the four hospital pathology laboratories in Region Västra Götaland were testing scanners in a one-year pilot project. It showed that an introduction of digital pathology is feasible, and the overall experience was very positive.

8c According to the work group, will there be any consequences of the new health technology for personnel?

Each laboratory will need to make adjustment in their local workflow in order to maximize the benefits of the new technology used for collaboration between the laboratories.This will lead to changes of some responsibilities for different categories of the staff, as well as education and training. All this will take time.

To work at workstations and high-resoultion screens, rather than at a light microscope, will change the ergonomic conditions for the pathologist. Also, the alleviation of manually transporting glass slides from an archive and to the microscope will change the ergonomic conditions for other personnel in the laboratory.

8d Will there be any consequences for other departments or supporting functions at the hospital or in the whole Western Region of Sweden?

The IT organization must participate in the planning and introduction of the new technology. Extra resources will be necessary to prepare the infrastructure (network) for the demands of the digital pathology solution. A service agreement of a helpdesk for the medical staff utilizing the new digital pathology service must be created.

Economy

9a **Present costs of currently used technologies**

Annual cost for pathology staff in VGR: 133 million SEK (Unilabs is not included)
Annual operating budget for pathology departments/ laboratories in VGR: 88 million SEK (Unilabs included)
Annual total cost: 221 million SEK

9b **Expected costs of the new health technology?**

For digital pathology to be in full operation throughout Region Västra Götaland 20 - 30 scanners will be needed. The cost per scanner is about 1.2 million SEK.
Thus, the total investment cost will be about 24-36 million SEK.

Additional cost for distribution and storage, network improvement and integration with national / regional applications will occur but are hard to define.

9c **Total change of cost**

In the range of 30 – 40 million SEK.

9d **Can the new technology be adopted and used within the present budget (clinic budget/hospital budget)?**

No

9e **Are there any available analyses of health economy? Cost advantages or disadvantages?**

Gothia Forum is performing a model for an economic evaluation, exemplified by a single diagnosis. The model will be presented during last quarter 2012.

No health economic analysis of digital pathology has been identified in the literature search.

Unanswered Questions

10a **Important gaps in scientific knowledge?**

The diagnostic methods, conventional light microscopy or whole slide imaging, have not been thoroughly studied in terms of important clinical patient outcomes such as disease progression, morbidity and mortality.

Thus, presently it is not known whether one of these two methods has a better prognostic impact or diagnostic precision than the other.

10b **Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?**

No.

Statement from HTA-centrum of Region Västra Götaland, Sweden

Diagnostic agreement of digital whole slide imaging and routine light microscopy

Question at issue: Do scanned digital images have sufficiently high quality for diagnostic purposes, and does this type of digital pathology also offer further advantages, or have some important disadvantages?

PICO (Patient, Intervention, Comparison, Outcome)

P = Organ or tissue samples for histopathology examination
I = Diagnostic work-up of digitised glass slides (scanned to whole slide images, WSI
C = Diagnostic work-up of glass slides with light microscopy
O = Diagnostic agreement
Quantification of pathological findings
Mortality
Progression of disease/disorder
Complications and risks

Summary of the health technology assessment:

Method and patient category:
The use of histopathology to decide a pathological anatomical diagnosis (PAD) is the most important diagnostic method for many diseases. For malignant diseases it is of paramount importance for diagnosis, determination of the stage of the disease, and follow-up of the effects of treatment.

Presently, the diagnostic analyses are made with the use of conventional light microscopy. During the last decade the technical development has created methods to digitise the glass slides. Lately, scanners that automatically scan the glass slides and create digital image files have been produced. These whole slide images (WSI or virtual slides) can be distributed to, and viewed at a modern workstation, and the large volumes of data can be stored and handled digitally.

Documentation:
The systematic literature search identified twenty studies that compared diagnostic agreement, or concordance, of virtual slide imaging (whole slide imaging = WSI) with light microscopy (LM). Ten of these studies reported *intraobserver* comparisons. Eighteen studies reported *interobserver* comparisons.

The diagnostic *intraobserver* agreement, across the studied organ systems, ranged from 61-100 % agreement and the Cohen's kappa coefficients between 0.55 to 0.81 (i.e. moderate to almost perfect agreement). For *interobserver* comparisons the percentage agreement ranged from 70-100% and the Cohen's kappa coefficients were in the range 0.36 – 0.84. For acute rejection of kindney transplants both LM and WSI had 35 % diagnostic interobserver agreements with Cohen's kappa coefficients of 0.28 – 0.42 (i.e. fair agreement).
The quality of evidence is low (GRADE ⊕⊕OO).

All the studies that report disagreements in individual cases also state that the discrepancies were not due to differences in a diagnosis that would be associated with clinical and prognostic important implications, but rather with differences of minor clinical importance.

Ethical aspects:
There are no major reasons to object to an introduction of digital pathology provided that the personal integrity of the digitised data are secured.

Economical aspects
20 -30 scanners will be needed for digital pathology to be in full operation throughout Region Västra Götaland. The cost per scanner is about 1.2 million SEK. Thus, the total investment cost will be about 24-36 million SEK. Additional cost for distribution and storage, network improvement and integration with national / regional applications will occur but are hard to define.

Concluding remarks
The diagnostic agreement was good for both intraobserver and interobserver comparisons when the two methods were compared. However, it is important to point out that the two diagnostic methods, LM or WSI, have not been studied and compared in terms of important clinical patient outcomes such as disease progression, morbidity and mortality. Thus, presently it is not known whether one of these two methods has a better prognostic impact or diagnostic precision than the other.
It is also important to realize that further validation of the diagnostic accuracy of WSI is necessary for each specific organ system as well as for specific types of diagnosis. In this HTA the diagnostic agreement of LM and WSI has only been assessed overall by putting various types of organ systems and diseases together.

The Regional Health Technology Assessment Centre (HTA-centrum) of Region Västra Götaland, Sweden (VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.
HTA was accomplished during the period of
2012-03-20 – 2012-11-28. Last search updated in Mars 2012

On behalf of the HTA quality assurance group, in Region Västra Götaland, Sweden
Göteborg, Sweden, 2012-11-28

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden

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Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

Diagnostisk överensstämmelse mellan digital bildhantering och konventionell ljusmikroskopi

Frågeställning: Har inscannade digitala bilder tillräckligt hög kvalitet för mikroskopisk diagnostik, och kan denna nya teknik med digital bildhantering erbjuda ytterligare fördelar, eller är den förenad med viktiga nackdelar?

PICO: (Patient, Intervention, Comparison, Outcome)

P = Organ eller vävnadsprover för histopatologisk undersökning
I = Diagnostisk bedömning av inscannade digitala bilder av prover på objektsglas (WSI)
C = Diagnostisk bedömning av prover på objektsglas med konventionell ljusmikroskopisk teknik
O = Diagnostisk överensstämmelse
Kvantifiering av patologiska fynd
Dödlighet
Progress av sjukdom
Komplikationer och risker

Resultatet av HTA-processen:

Metod och målgrupp:
Mikroskopisk undersökning av organ och vävnader är den viktigaste undersökningen för många sjukdomar när det gäller att fastställa en patologisk anatomisk diagnos (PAD). För maligna sjukdomar är PAD av avgörande betydelse för såväl diagnos som bedömning av svårighetsgrad av sjukdomen, och för att följa effekter av behandling.

För närvarande används konventionell ljusmikroskopisk teknik för histopatologisk diagnostik. Under det senaste årtiondet har den tekniska utvecklingen lett till möjligheter att digitalisera vävnadsprover från sedvanliga objektsglas. Det finns idag scanners som automatiskt kan scanna objektsglas och skapa en digital bild. Dessa inscannade bilder (whole slide images = WSI) kan skickas till, och lagras på, moderna digitala arbetsstationer. Stora datavolymer kan på detta sätt lagras och hanteras digitalt.

Dokumentation:
Den systematiska litteratursökningen fann tjugo studier som jämfört den diagnostiska överensstämmelsen mellan digitaliserade bilder (WSI) och prover bedömda med konventionell ljusmikroskopi (LM). Tio av dessa studier har rapporterat överensstämmelsen då en och samma observatör bedömer samma prov med de båda teknikerna (WSI vs LM), s.k ”intraobserver agreement”. Arton studier har rapporterat överensstämmelse då olika observatörer bedömer samma prov med respektive teknik (WSI vs WSI eller LM vs LM), s.k ”interobserver agreement”

”Intraobserver” överenstämmelse
Överenstämmelsen för olika diagnoser i flera olika organssystem varierade mellan 61 – 100 % avseende överenstämmelse i procentuella termer, eller uttryckt med Cohens kappa koefficient mellan 0,55 till 0,81 (= måttlig till nästan perfekt överensstämmelse), när olika observatörer granskade samma vävnadsprov som WSI eller som LM.
Låg evidenskvalitet (GRADE ⊕⊕OO)

”Interobserver” överenstämmelse
Överenstämmelsen för olika diagnoser i flera olika organssystem varierade mellan 70 – 100 % avseende överenstämmelse i procentuella termer, eller uttryckt med Cohens kappa koefficient mellan 0,36 till 0,84, när samma observatör granskade samma vävnadsprov som WSI och som LM.

För diagnostik av rejektion av njurtransplantat var resultatet sämre, 35 % respektive 0,28 – 0,42. Låg evidenskvalitet (GRADE ⊕⊕OO)

Samtliga studier har rapporterat att de skillnader i individuella patientfall som förekom i den diagnostiska bedömningen inte var av någon avgörande klinisk betydelse för patientens prognos och behandling, utan i alla fall hade dessa avvikelser mycket ringa klinisk betydelse.

Etiska aspekter:
Under förutsättning att den individuella integriteten kan skyddas och bevaras föreligger inga avgörande etiska problem att införa digital bildhantering inom hälso- och sjukvården.

Ekonomiska aspekter
För att införa digital bildhantering i hela Västragötalandsregionen behövs 20 - 30 scanners. En scanner kostar 1.2 miljoner kronor. Detta innebär en total investeringskostnad på 24 – 36 miljoner kronor. Storleken på kostnaderna för distribution och lagring av bilder, underhållet av nätverksfunktioner, och den integrering med regionala och nationella tillämpningar som tillkommer är i dagsläget svåra att uppskatta.

Sammanfattning och slutsats
Den diagnostiska överenstämmelsen mellan inscannade digitaliserade bilder och konventionell ljusmikroskopi är god både när det gäller jämförelser mellan samma observatör som mellan olika obeservatörer.
Det är viktigt att poängtera att ingen av de två diagnostiska teknikerna (WSI eller LM) har studerats var för sig eller jämförts med varandra när det gäller prediktion av framtida sjuklighet och dödlighet. Detta innebär att vi i dag inte vet om WSI eller LM är bättre än den andra ur prognostisk aspekt.
Det är även viktigt att konstatera att ytterligare utvärdering av de två diagnostiska teknikerna behövs för specifika organsystem och särskilda diagnoser. I denna HTA har den diagnostiska överensstämmelsen mellan de två teknikerna endast jämförts generellt genom att göra en sammanvägd bedömning av deras resultat för flera olika organsystem och diagnoser.

HTA-kvalitetssäkringsgruppen har ett uppdrag att yttra sig över genomförda HTA i Västra Götalandsregionen. Yttrandet skall innefatta sammanfattning av frågeställning, samlat evidensläge, patientnytta, risker samt ekonomiska och etiska aspekter för den studerande teknologin.

Projektet har pågått under perioden 2012-03-20 –2012-11-28.
Sista uppdatering av artikelsökning mars 2012

För HTA-kvalitetssäkringsgruppen 2012-11-28

Christina Bergh
Ordförande

HTA-kvalitetssäkringsgruppen:

Christina Bergh	Anders Larsson	Maria Skogby
Professor, överläkare	Med dr, överläkare	Med dr, vårdenhetschef
Thomas Franzén	Christian Rylander	Annika Strandell
Bibliotekschef	Med dr, överläkare	Docent, överläkare
Magnus Hakeberg	Ola Samuelson	Therese Svanberg
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Lennart Jivegård	Petteri Sjögren	Kjell-Arne Ung
Universitetslektor, överläkare	Med dr, tandläkare	Docent, överläkare
Peter Johansson	Henrik Sjövall	Margareta Warrén Stomberg
Med dr, överläkare	Professor, överläkare	Universitetslektor

Appendix 1-1: Intraobserver diagnostic agreement .
Percentage agreement; defined as number of cases with the same diagnosis divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Intraobserver		Comments	
					Percentage agreement	K coefficient		
Al-Janabi, 2012	Nether-lands	100 patient cases - selected cases of "good quality" 6 pathologists	Dermis	100	<u>Glass vs WSI:</u> 94 % (0.87 -0.97)		Each pathologist reviewed his/her own cases. Concordant = complete agreement of clinically significant diagnosis	Moderately large study
Al-Janabi, 2011	Nether-lands	100 patient cases - selected cases of "good quality" 5 pathologists	Gastro-intestinal	100	<u>Glass vs WSI:</u> 95 % (0.89 -0.98)		Each pathologist reviewed his/her own cases. Concordant = complete agreement of clinically significant diagnosis.	Moderately large study
Fine, 2008	USA	30 patient cases - selected cases with typical 5 pathologists	Prostate	30		<u>Glass vs WSI:</u> Dr 1: 0.59 Dr 2: 0.81 Dr 3: 0.62 Dr 4: 0.73 Dr 5: 0.80		Small study

Footnote: WSI = whole slide image = virtual slide, i.e. a digital slide produced by scanning a glass microscopic slide

Appendix 1-1: Intraobserver diagnostic agreement .
Percentage agreement; defined as number of cases with the same diagnosis divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Intraobserver		Comments	
					Percentage agreement	K coefficient		
Nassar, 2011 Am J Clin Pathol	USA	Selected cases with typical findings 3 clinical sites 3 pathologists at each site	Breast cancer	Clinical site 1: 80 Clinical site 2: 100 Clinical site 3: 80	<u>Glass vs WSI-ER:</u> 88 – 99 % <u>Glass vs WSI-PR:</u> 79 – 100 %		Comparison pair-wise of 3 pathologists at each of 3 clinical sites, i.e. 9 comparisons ER = estrogen receptor PR = progesterone receptor Both ER and PR are evaluated as percentage of positive nuclei and average "intensity score".	Moderately large study
Nassar, 2011 Appl Immun Mol	USA	Selected cases with typical findings 2 clinical sites 3 pathologists at each site	Breast cancer	Clinical site 1: 80 Clinical site 2: 100	<u>Glass vs WSI-HER2:</u> 61 – 93 %		Comparison pair-wise of 3 pathologists at each of 2 clinical sites, i.e. 6 comparisons HER2 = human epidermal growth factor receptor HER 2 is evaluated as a "HER2 score".	Moderately large study
Ozluk, 2011	Turkey & Canada	38 patient cases -randomly selected cases 1+3 pathologists	Kidney transplants	120	<u>Glass vs WSI-Acute rejection :</u> 63 – 73 %		1 pathologist was the reference, i.e. decided the "gold standard". Organ rejection is yes/no	Small study

Footnote: WSI = whole slide image = virtual slide, i.e. a digital slide produced by scanning a glass microscopic slide

Appendix 1-1: Intraobserver diagnostic agreement .
Percentage agreement; defined as number of cases with the same diagnosis divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Intraobserver		Comments	
					Percentage agreement	K coefficient		
Risio, 2012	Italy	457 patient cases - consecutive cases 2 pathology units	Colon	457		<u>Glass vs virtual slides:</u> <u>Unit 1:</u> 0.76 (95 % CI: 0.69 – 0.83) <u>Glass vs virtual slides:</u> <u>Unit 2:</u> 0.81 (95 % CI: 0.75 – 0-87)	The number of pathologists at each unit was not reported Concordant = complete agreement of diagnosis	Large study
Rodriguez-Urrego, 2011	USA	50 patient cases - selected as "challenging" or "unusual" cases 4 pathologists	Prostate	50		<u>Glass vs virtual slides:</u> Dr 1: 0.75 Dr 2: 0.96 Dr 3: 0.65 Dr 4: 0.83	Evaluation of primary Gleason grade	Small study

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Appendix 1-1: Intraobserver diagnostic agreement .
Percentage agreement; defined as number of cases with the same diagnosis divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Intraobserver		Comments	
					Percentage agreement	K coefficient		
Shaw, 2012	UK	222 patient cases - randomly selected cases	Breast cancer	69		Glass vs WSI-Vascular invasion: 0.66 Virtual vs WSI-Vascular invasion: 0.58 Glass vs WSI-Vascular invasion: 0.55	Each case reviewed by 2 pathologists, i.e. pair-wise comparisons. The total number of pathologists in the study was not reported. 12 different histopathological findings per slide. Only vascular invasion included in the table.	Moderately large study
Wendum, 2009	France	54 patient cases - unclear how cases were selected 1 pathologist	Liver	54		Glass vs WSI-Fibrosis : 0.80 Glass vs WSI-Activity: 0.68	Fibrosis and activity of HIV-Hepatitis B coinfection evaluated by METAVIR score and Landis and Koch scale	Small study

Footnote: WSI = whole slide image = virtual slide, i.e. a digital slide produced by scanning a glass microscopic slide

Appendix 1-2: Interobserver diagnostic agreement

Percentage agreement; defined as number of cases with the same diagnose divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Interobserver		Comments	
					Percentage agreement	K coefficient		
Al Habeeb, 2012	Canada	Three slide sets - consecutive cases 2 pathologists	Dermis	Set 1: 79 Set 2: 12 Set 3: 12	Glass vs WSI: Set 1: 96 % Set 2: 92 % Set 3: 100 %		Pathologist no.1: Glass slides Pathologist no 2: WSI slides Concordant = complete agreement of clinically significant diagnosis	Moderately large study
Fine, 2008	USA	30 patient cases -selected cases with typical findings 5 pathologists	Prostate	30		Glass vs glass slides: 0.50 – 0.68 WSI vs WSI: 0.36 – 0.68	The method-section of the paper does not clearly state how the final "consensus diagnosis" was derived to which the initial diagnosis of each pathologist was compared.	Small study
Graham, 2009	USA	329 patient cases - consecutive cases 1 pathologist vs 1 consensus group	Case-mix	329	Glass vs WSI: 92 %		In 60 % of all cases the comparison was made between 2 pathologists, and in the remaining cases the glass slide was diagnosed by 1 and the WSI slide by 2 or more pathologists together. Concordant = complete agreement of diagnosis The comparison was made with a consensus group and not between separate observers.	Large study

Footnote: WSI = whole slide image = virtual slide, i.e. a digital slide produced by scanning a glass microscopic slide

Appendix 1-2: Interobserver diagnostic agreement

Percentage agreement; defined as number of cases with the same diagnose divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Interobserver		Comments	
					Percentage agreement	K coefficient		
Harnden, 2011	UK	20 patient cases - selected cases with typical findings 5 expert pathologists	Prostate	20	WSI vs WSI-Diagn category: 86%	Glass vs glass slides-Diagn. category: 0.71 WSI vs WSI-Diagn. category: 0.68 Glass vs glass slides-Gleason score: 0.57 WSI vs WSI-Gleason score: 0.56	Diagnostic category and Gleason sum score	Small study
Ho, 2006	USA	24 patient cases - randomly selected cases 3 pathologists – cases randomly assigned	Uro-genital	391	Glass slide vs "gold standard": 92 % WSI vs "gold standard": 88 %		"Gold standard" determined by a reference panel of experts. Concordant = complete agreement of clinically significant diagnosis	Small study

Footnote: WSI = whole slide image = virtual slide, i.e. a digital slide produced by scanning a glass microscopic slide

Appendix 1-2: Interobserver diagnostic agreement

Percentage agreement; defined as number of cases with the same diagnose divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Interobserver		Comments	
					Percentage agreement	K coefficient		
Lloyd, 2010	USA	33 patient cases - randomly selected cases	Breast cancer	10 ER 23 PR	<u>Glass slide vs WSI – ER:</u> 100 % <u>Glass slide vs WSI-HER2::</u> 100%		Semi-quantitative manual scoring (0 to +3) of biomarkers in glass slides vs automated scoring in WSI slides ER = estrogen receptor HER2 = human epidermal growth factor receptor	Small study
Mooney, 2011	Denmark	20 patient cases-selected cases with typical findings 10 pathologists	Dermis	20	<u>Glass vs glass slides:</u> 85 % <u>WSI vs WSI:</u> 81 %		Every pathologist reviewed all the 20 cases as a glass as well as a WSI. Areement of clinically significant diagnosis	Small study

Footnote: WSI = whole slide image = virtual slide, i.e. a digital slide produced by scanning a glass microscopic slide

Appendix 1-2: Interobserver diagnostic agreement

Percentage agreement; defined as number of cases with the same diagnose divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Interobserver		Comments	
					Percentage agreement	K coefficient		
Nassar, 2011 Am J Clin Pathol	USA	Selected cases with typical findings 3 clinical sites 3 pathologists at each site	Breast cancer	Clinical site 1: 80 Clinical site 2: 100 Clinical site 3: 80	<u>Glass vs glass slides- ER:</u> 91 - 99 % <u>WSI vs WSI – ER:</u> 91 - 100% <u>Glass vs glass slides- PR:</u> 84 - 99 % <u>WSI vs WSI – PR:</u> 78 - 100%		Comparison pair-wise of 3 pathologists at each of 3 clinical sites, i.e. 9 comparisons. Agreement of four categories of percentage "positive nuclei". ER = estrogen receptor PR = progesterone receptor Both ER and PR are evaluated as percentage of positive nuclei and average "intensity score".	Moderately large study
Nassar, 2011 Appl Immun Mol	USA	Selected cases with typical findings 2 clinical sites 3 pathologists at each site	Breast cancer	Clinical site 1: 80 Clinical site 2: 100	<u>Glass vs glass slides- HER2:</u> 76 - 91 % <u>WSI vs WSI- HER 2:</u> 70 - 86%		Comparison pair-wise of 3 pathologists at each of 2 clinical sites, i.e. 6 comparisons. Agreement of four categories of percentage "positive nuclei". HER2 = human epidermal growth factor receptor HER 2 is evaluated as a "HER2 score".	Moderately large study

Footnote: WSI = whole slide image = virtual slide, i.e. a digital slide produced by scanning a glass microscopic slide

Appendix 1-2: Interobserver diagnostic agreement

Percentage agreement; defined as number of cases with the same diagnose divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Interobserver		Comments	
					Percentage agreement	K coefficient		
Ozluk, 2011	Turkey & Canada	38 patient cases - randomly selected cases 1+3 pathologists	Kidney transplants	120	<u>Glass vs glass slides-Acute rejection:</u> 35 % <u>WSI vs WSI slides-Acute rejection:</u> 35 %	<u>Glass vs glass slides-Banff-score:</u> 0.28 <u>WSI vs WSI – Banff-score:</u> 0.42 <u>Glass vs glass slides-Acute rejection:</u> 0.31 <u>WSI vs WSI -Acute rejection:</u> 0.33	1 pathologist was the reference, i.e. decided the "gold standard" and compared with 3 other pathologists. Banff lesion score is a score (0 - +3) of 11 lesions.(The tabulated result is the overall K coefficient of 11 lesions) Organ rejection is Yes/No	Small study
Pagni, 2011	Italy	261 patient cases - selected cases with undecided diagnosis 2 pathologists	Case mix	261	<u>Glass vs WSI:</u> 88 %		Comparison of "final diagnoses"	Moderately large study

Footnote: WSI = whole slide image = virtual slide, i.e. a digital slide produced by scanning a glass microscopic slide

Appendix 1-2: Interobserver diagnostic agreement

Percentage agreement; defined as number of cases with the same diagnose divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Interobserver		Comments	
					Percentage agreement	K coefficient		
Risio, 2010	Italy	457 patients - consecutive cases 2 pathology units	Colon	457		<u>Glass vs glass slides:</u> 0.63 (95 % CI: 0.55 – 0.70) <u>WSI vs WSI :</u> 0.65 (95 % CI: 0.57 – 0.73)	The number of pathologists at each unit was not reported Concordant = complete agreement of diagnosis of advanced adenoma	Large study
Rodriguez-Urrego, 2011	USA	50 patient cases -selected as "challenging" or "unusual" cases 4 pathologists	Prostate	50		<u>Glass vs glass slides:</u> 0.72 <u>WSI vs WSI:</u> 0.64	Evaluation of primary Gleason grade. Agreement of same Gleason grade.	Small study

Footnote: WSI = whole slide image = virtual slide, i.e. a digital slide produced by scanning a glass microscopic slide

Appendix 1-2: Interobserver diagnostic agreement

Percentage agreement; defined as number of cases with the same diagnose divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Interobserver		Comments	
					Percentage agreement	K coefficient		
Shaw, 2011	UK	222 patient cases - randomly selected cases	Breast cancer	86 20 222		<u>Glass vs glass slides- Vascular invasion:</u> 0.78 <u>WSI vs WSI - Vascular invasion:</u> 0.58 <u>Glass vs WSI - Vascular invasion:</u> 0.55	Each case reviewed by 2 pathologists, i.e. pair-wise comparisons. The total number of pathologists in the study was not reported. 12 different histopathological findings per slide. Only vascular invasion included in the table.	Moderately large study
Slodkowska, 2011	Poland	20 patient cases - selected cases with typical findings	Central nervous system	20	No descriptive statistics. "..average weight values of Ki-67 obtained by the whole slide imaging method are higher than parallel values of the light microscopy		Semi-quantitative manual scoring of glass slides vs automated scoring of biomarkers (Ki-67) in WSI slides Percentage of positive tumour cells calculated as Ki-67 labelling index.	Small study
Velez, 2008	USA	45 patient cases - selected typical cases 3 pathologists	Dermis	45	<u>Glass vs glass slides:</u> 98% <u>WSI vs WSI:</u> 89 %		Comparison of "final diagnosis". The description of the study procedure is lacking in many details.	Small study

Footnote: WSI = whole slide image = virtual slide, i.e. a digital slide produced by scanning a glass microscopic slide

Appendix 1-2: Interobserver diagnostic agreement

Percentage agreement; defined as number of cases with the same diagnose divided by total number of cases (%); or Cohen's kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

Author, year	Country	Study design	Organ system	Number of slides n=	Interobserver		Comments	
					Percentage agreement	K coefficient		
Wendum, 2009	France	54 patient cases - unclear how cases were selected 3 pathologists	Liver	54		WSI vs WSI: 0.52 – 0.84	3 pair-wise comparisons. Cirrhosis of HIV-Hepatitis B coinfection evaluated by Landis and Koch scale.	Small study
Wilbur, 2009	USA	53 patient cases - selected "challenging" cases	Case mix	53	Glass vs WSI: 91 %		Comparison of "final diagnosis". The number of pathologists was not reported	Small study

Footnote: WSI = whole slide image = virtual slide, i.e. a digital slide produced by scanning a glass microscopic slide

Virtual slides in digitalized pathology
Appendix 2 – excluded articles

Study (author, publication year)	Reason for exclusion
Boon *et al*., 2006	Wrong technology of digitalisation
Butrheim 2005	Wrong technology of digitalisation
Chargari *et al*., 2011	Wrong technology of digitalisation
Evans *et al*.,2009	Wrong comparison
Furness, 2007	Wrong technology of digitalisation
Gimbel *et al*., 2012	Wrong technology of digitalisation
Glotsos *et al*., 2009	Wrong technology of digitalisation
Helin *et al*., 2005	Wrong technology of digitalisation
Jukic *et al*.,2011	Wrong technology of digitalisation
Koch *et al*.,2009	Wrong technology of digitalisation and wrong comparison
Leinweber *et al*., 2006	Wrong technology of digitalisation
Li *et al*., 2007	Wrong technology of digitalisation
Massone *et al*., 2007	Wrong technology of digitalisation
Nassar *et al.* 2011 Appl Immuno Mol Morphol	Substudy of Nassar *et al* . 2011 Am J Clin Pathol
Nielsen *et al*., 2010	Wrong technology of digitalisation

Virtual slides in digitalized pathology
Appendix 2 – excluded articles

Study (author, publication year)	Reason for exclusion
Slodkowska *et al*., 2008	Wrong technology of digitalisation
Tsiambas *et al*., 2006	Wrong technology of digitalisation

Appendix 3, Search strategy, study selection and references

Question(s) at issue:
Do scanned digital images have sufficiently high quality for diagnostic purposes, and does this type of digital pathology also offer further advantages, or have some important disadvantages?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)
P= Organ or tissue samples for histopathology examination

I= Diagnostic work-up of digitised glass slides (scanned to whole slide images, WSI)

C= Diagnostic work-up of glass slides with light microscopy

O= Diagnostic agreement
Quantification of pathological findings
Mortality
Progression of disease/disorder
Complications and risks

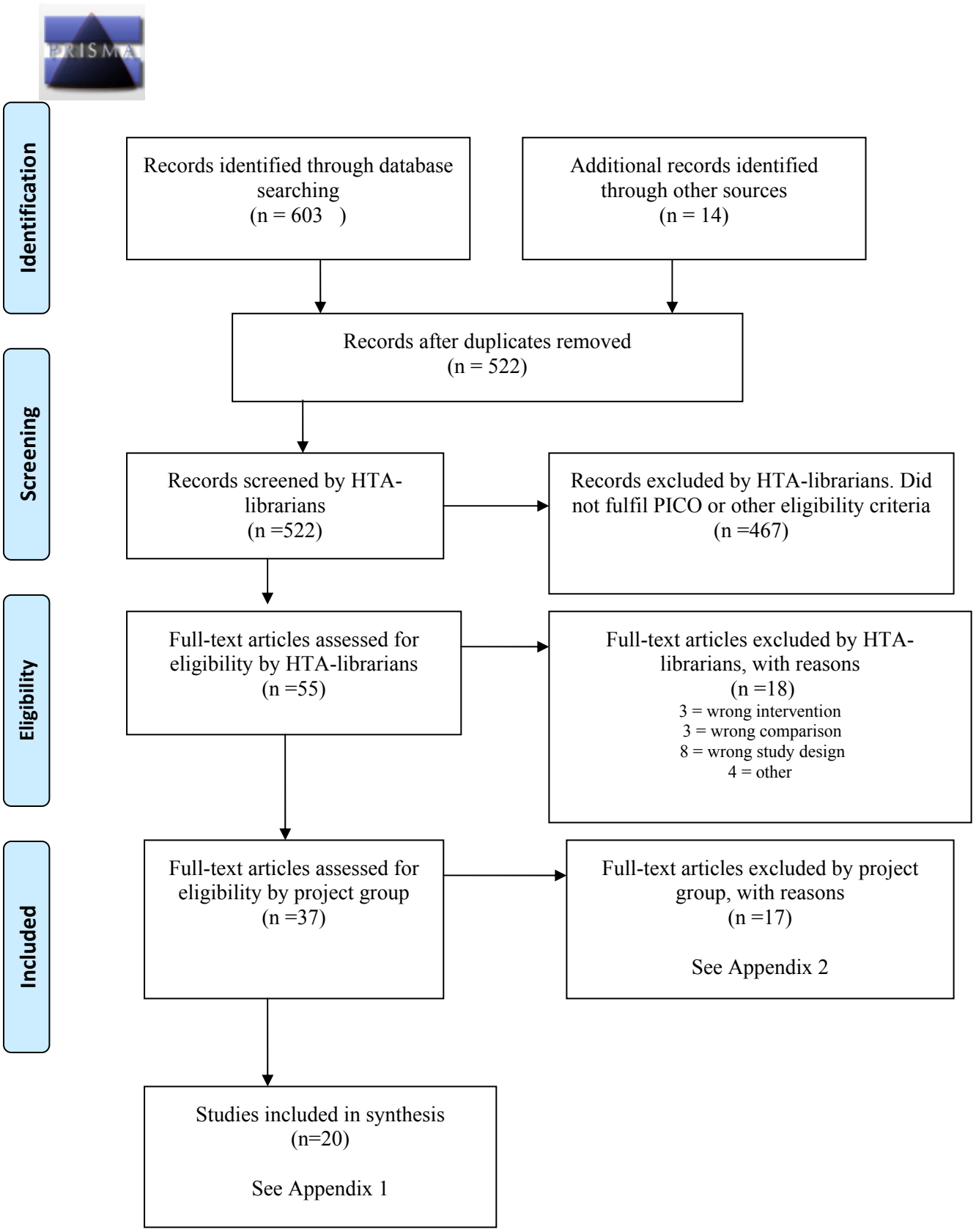
<u>Eligibility criteria</u>

Study design:
Studies with some kind of control group
Systematic reviews & meta-analyses

Language:
English, Swedish, Norwegian, Danish

Publication date: 2005-

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 2012-03-27
No of results: 426 results

Search	Query	Items found
#45	**Search #43 NOT #32 Limits: English, Danish, Norwegian, Swedish, Publication Date from 2005/01/01**	**426**
#44	Search #43 NOT #32	758
#43	Search #28 AND #42	913
#42	Search "diagnosis"[Subheading] OR "diagnosis"[tiab] OR "diagnosis"[MeSH Terms] OR diagnoses[tiab] OR diagnostic[tiab] OR diagnostics[tiab] OR diagnosing[tiab] OR "sensitivity and specificity"[MeSH Terms] OR "specificity"[tiab] OR sensitivity[tiab] OR observer agreement[tiab]	8154010
#32	Search (#30) OR #31	6149162
#31	Search Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp] OR case reports[ptyp]	2561069
#30	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	3655502
#28	Search (#20) AND #26	1125
#26	Search microscopy[tiab] OR microscope[tiab] OR glass[tiab]	374334
#20	Search (#18) OR #19	3079
#19	Search (#13) OR #12	2526
#18	Search (#17) OR #16	755
#17	Search telepathology[Title/Abstract]	492
#16	Search telepathology[MeSH Terms]	597
#13	Search (digital[tiab] AND pathology[tiab]) OR (virtual[tiab] AND microscopy[tiab]) OR "virtual pathology" OR "digital microscopy"	1773
#12	Search virtual slides OR virtual slide OR digital slides OR digital slide OR whole slide image OR whole slide images	1049

Database: EMBASE (OVID SP)
Date: 2012-03-27
No of results: 125 results

#	Searches	Results
1	exp telepathology/	459
2	(virtual slides or virtual slide or digital slides or digital slide or whole slide image or whole slide images).ti,ab.	404
3	(digital pathology or virtual microscopy or "virtual pathology" or "digital microscopy" or telepathology).ti,ab.	1058
4	(microscopy or microscope or glass).ti,ab.	385504
5	exp diagnosis/	3893449
6	exp "sensitivity and specificity"/	163960
7	(diagnosis or diagnoses or diagnostic or diagnostics or diagnosing or specificity or sensitivity or observer agreement).ti,ab.	2108896
8	1 or 2 or 3	1435

9	5 or 6 or 7	5033423
10	4 and 8 and 9	473
11	limit 10 to (embase and (danish or english or norwegian or swedish) and yr="2005 -Current")	257
12	**limit 11 to human**	**125**

Database: The Cochrane Library
Date: 2012-03-27
No of results: 50 results
Cochrane reviews 0
Other reviews 0
Clinical trials 47
Technology assessments 2
Economic evaluations 1

ID	Search	Hits
#1	(virtual slides OR virtual slide OR digital slides OR digital slide OR whole slide image OR whole slide images):ti,ab,kw OR (digital pathology OR virtual microscopy OR "virtual pathology" OR "digital microscopy" OR telepathology):ti,ab,kw, from 2005 to 2012	**50**

Database: CRD
Date: 2012-03-27
No of results: 2

ID	Search	Hits
#1	virtual slides OR virtual slide OR digital slides OR digital slide OR whole slide image OR whole slide images OR digital pathology OR virtual microscopy OR "virtual pathology" OR "digital microscopy" OR telepathology	**2**

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited 2012-03-27
Nothing relevant to the question at issue was found

Reference lists
14 results

Reference lists

Included studies:

Al Habeeb A, Evans A, Ghazarian D. Virtual microscopy using whole-slide imaging as an enabler for teledermatopathology: A paired consultant validation study. J Pathol Inform. 2012;3:2. Epub 2012/03/23.

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Graham AR, Bhattacharyya AK, Scott KM, Lian F, Grasso LL, Richter LC, et al. Virtual slide telepathology for an academic teaching hospital surgical pathology quality assurance program. Hum Pathol. 2009;40(8):1129-36.

Harnden P, Coleman D, Moss S, Kodikara S, Griffin NR, Melia J. Evaluation of the use of digital images for a national prostate core external quality assurance scheme. Histopathology. 2011;59(4):703-9.

Ho J, Parwani AV, Jukic DM, Yagi Y, Anthony L, Gilbertson JR. Use of whole slide imaging in surgical pathology quality assurance: design and pilot validation studies. Hum Pathol. 2006;37(3):322-31.

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Appendix 4. Summary of Findings.
Diagnostic agreement of digital whole slide imaging and routine light microscopy.

Outcome variable Number of studies	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Absolute effect	Quality of evidence GRADE
Interobserver agreement 18	7 studies with randomly or consecutively selected cases 10 studies with selected cases 1 study in which selection of cases was unclear	Some limitations[1,2]	No important inconsistency	Serious indirectness[3]	Uncertain precision [4]	Unlikely	Not relevant	Percentage agreement [5] Range: 75 % - 100 % in 11 studies (one exception; 35 %) K-coefficient [5] Range: 0.52 – 0.84 in 5 studies (2 studies;0.28 -0.68)	⊕⊕◯◯ Low
Intraobserver agreement 10	3 studies with randomly or consecutively selected cases 6 studies with selected cases 1 study in which selection of cases was unclear	Serious limitations[6,7]	No important inconsistency	Serious indirectness[8]	Uncertain precision [9]	Unlikely	Not relevant	Percentage agreement [5] Range: 61 % - 100 % in 5 studies K-coefficient [5] Range: 0.55 – 0.96 in 5 studies (2 studies;0.28 -0.68)	⊕⊕◯◯ Low

Footnotes

[1] 7 of 18 studies had a random selection of cases or included consecutive patients, whereas 10 studies selected either “typical” or ”challenging” cases and 1 study did not present how the selection of patients had been done.

[2] 5 of 18 studies presented the cases to the observers in the same systematic order (first glass slides and then WSI).
Another 4 studies did not describe how cases were presented to the observers.

[3] The studies are heterogenous with regard to organ systems, and to the type of diagnosis within the respective organ systems.

[4] Only 1 study reported confidence intervals of the K-coefficient. 11 studies were rather small and included less than 100 cases.

[5] Percentage agreement; defined as number of cases with the same diagnose divided by total number of cases (%); or Cohen’s kappa coefficient (K; ≤ 0 poor agreement, 0.01 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61. – 0.80 substantial agreement, > 0.80 almost perfect agreement)

[6] 3 of 10 studies had a random selection of cases or included consecutive patients, whereas 6 studies selected either “typical” or ”challenging” cases and 1 study did not present how the selection of patients had been done.

[7] 6 of 10 studies presented the cases to the observers in the same systematic order (first glass slides and then WSI).
Another 2 studies did not describe how cases were presented to the observers.

[8] The studies are heterogenous with regard to organ systems, and to the type of diagnosis within the respective organ systems.

[9] Only 1 study reported confidence intervals of the K-coefficient. 7 studies were rather small and included less than or equal to 100 cases.

Appendix 5.

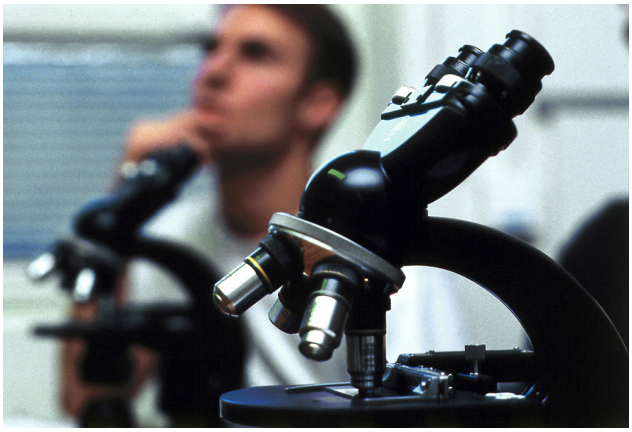
ETHICAL ANALYSIS OF WHOLE SLIDE IMAGING (WSI)

Question	Answer/ comment
1. From the patient's perspective, how does digital pathology affect the patient's quality of life and life expectancy?	A shorter handling time between tissue sampling and histopathologic diagnosis has the potential to increase life expectancy and a better quality of life for the patients. If the diagnostic accuracy is improved this will add further beneficial effects. Presently, there are no indications that WSI has a lower diagnostic accuracy than conventional light microscopy.
2. How severe is the patient's need that the digital pathology must meet?	The present shortage of pathologists and long handling times can cause delay of the diagnosis for the patient. Long handling times may delay proper treatment and add psychological stress to the patient.
3. Does digital pathology have any influence on how others view the patient (concerning humanity and human dignity), or on how the patient views himself or herself (concerning humanity and human dignity)?	No.
4. Can digital pathology affect the patient's ability and possibility to be independent?	No.
5. If implemented, does digital pathology require any special steps to not compromise the patient's autonomy?	It is important that only medical personnel directly involved in the diagnostic work-up and treatment of the patient will have access to the digitised data. The implementation of digital pathology therefore requires special precautions with regard to the IT systems in order to protect the personal integrity.
6. How does digital pathology affect the patient's physical, moral and personal integrity?	See above 1,2 and 5.
7. Is digital pathology cost-effective?	Probably.
8. How will digital pathology affect resources?	At present, this is difficult to estimate since we lack large-scale studies.Presumably it will be cost neutral at best for the health care system but cost-effective for society.
9. Is digital pathology in conflict with professional values?	No.
10. Does digital pathology change the role of the professional in relation to the patient?	No.
11. Does digital pathology affect, or does it put any new demands on, a third party?	Yes. Since digital slides require much more storage room than for example X-ray images in a server the IT organisations in the health care system must take part in the implementation.
12. Is there any legislation of relevance with	Not in Sweden

regard to digital pathology?	
13. Is there any risk of conflict between the procedure of digital pathology and values of the society, or values of different groups?	Probably not.
14. Is there a risk that an introduction of digital pathology will cause a conflict with particular interests?	Professionals of an older generation may prefer light microscopy due to mere conservatism, and less interest to change their working routine.
15. Can an introduction digital pathology influence the trust of the health care system?	Probably not.
CONCLUSIONS	There are no major ethical reasons to object to an introduction of digital pathology.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

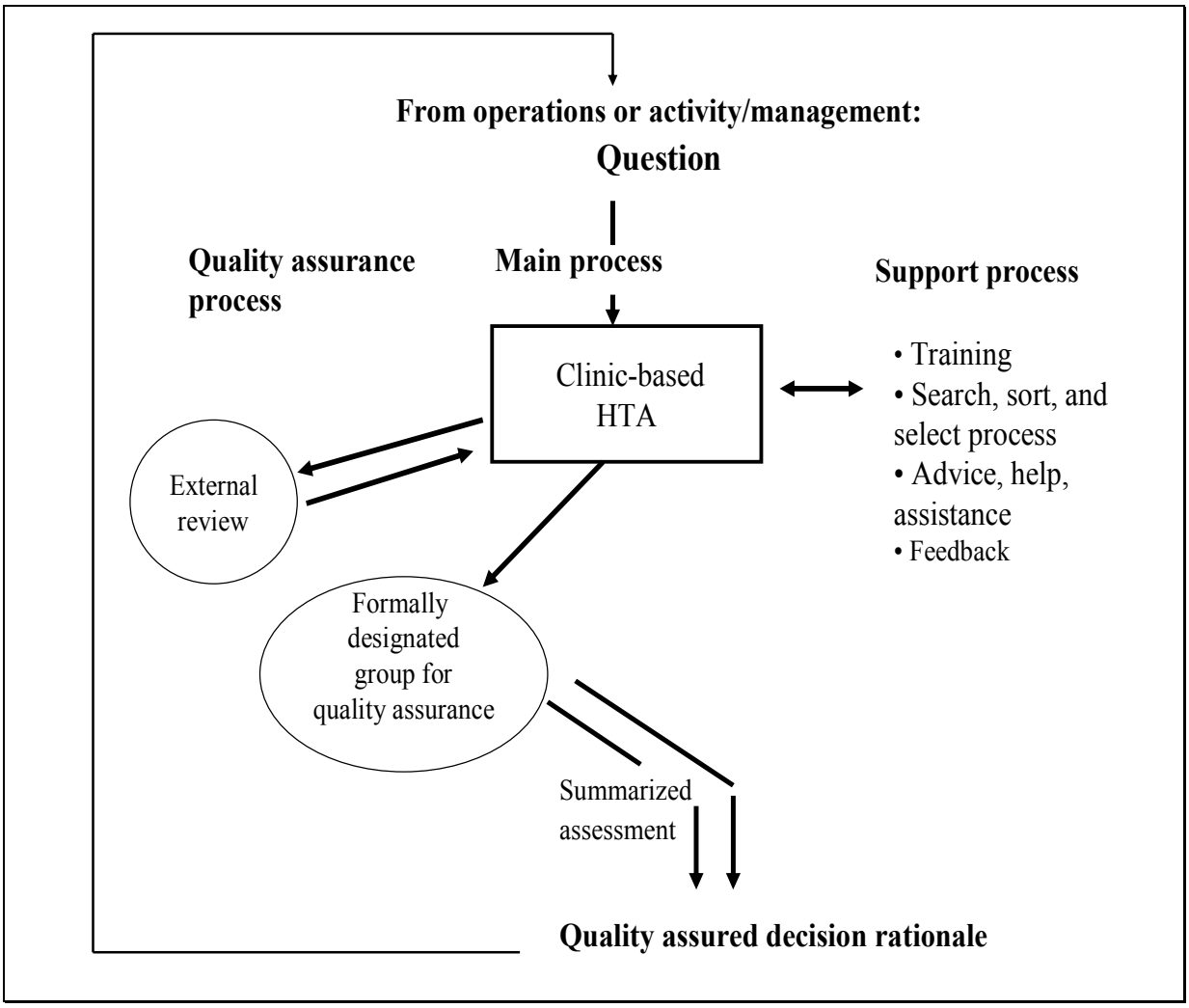
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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