Univerza v Ljubljani
Fakulteta za farmacijo

Na izsledkih temelječa medicina

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Univerza v Ljubljani- Fakulteta za farmacijo

Viri informacij

- biomedicinske revije
- pogovori s kolegi, ki imajo posebna znanja
- predavanja in seminarji
- informacije oz. “oglasi” v revijah
- pogovori s predstavniki farmacevtske industrije
- ipd.

Vrednotenje informacij

- Katere medicinske izsledke je smiselno in koristno vključiti v klinično prakso?

Kritična presoja (ang. Critical Appraisal)

- Canadian Medical Association Journal
  - serija člankov v 80. letih
  - Klinični epidemiologi s kanadske univerze McMaster
  - namen: zdravnikom svetovati kako naj berejo klinične revije

Vir: Anon. How to read clinical journals: I. Why to read them and how to start reading them critically. Can Med Assoc J 1981;124: 555–8.

Kritična presoja (ang. Critical Appraisal)

- Tradicionalni pristop zajema:
  - intuicijo
  - posameznikove klinične izkušnje
  - poznavanje načel patofiziologije

- Nov pristop "kritične presoje":
  - v klinično prakso vpeljati znanstvene izsledke iz medicinske literature ter le-te dejansko uporabljati pri kliničnem odločanju in delovanju.

Evidence- based medicine

- Termin EBM (Guyatt 1991)

- "Vestna, nedvoumna in razumna uporaba trenutno najboljših izsledkov v odločanju o medicinski oskrbi posameznega bolnika" (Sackett DL in sod. 1996)

Vir: Guyatt GH. Evidence-based medicine. ACP Journal Club 1991; 114: A–16.

Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. Brit Med J 1996; 312: 71–2.

Na izsledkih temelječa medicina

- Poredoš P, Šabovič M. Strokovne podlage za razvrščanje zdravil glede na učinkovitost. Zdrav Vestn 2000; 69: I–15–7.
- Komadina R, Rok-Simon M. Desetletje gibal 2000–2010 pod okriljem Svetovne zdravstvene organizacije. Zdrav Vestn 2001; 70: 493–5.
- Fuerst J. Odmev na članek »Zdravljenje rezistentnih depresij in primer uspešne uporabe donepezil HCl v njihovi obravnavi«. Zdrav Vestn 2002; 71: 115–5.

Znanstveno utemeljena medicina

- Švab I, Car J. Znanstveno utemeljena medicina v družinski oz. splošni medicini = Evidence based medicine in family medicine. Zdrav Varstvo 1999; 38: 295–7.
- Car J, Švab I, Rotar-Pavlič D. Znanstveno utemeljena družinska medicina. In: Kersnik J ed. Znanstveno utemeljena medicina (Zbirka PiP). Ljubljana: Združenje zdravnikov družinske medicine, Slovensko zdravniško društvo, 2000: 1–8.
- Švab I, Kersnik J. Kako ocenjujemo strokovno literaturo? In: Kersnik J ed. Znanstveno utemeljena medicina (Zbirka PiP). Ljubljana: Združenje zdravnikov družinske medicine, Slovensko zdravniško društvo, 2000: 33–46.
- Kersnik J, Švab I. Ocenjevanje in nadzor kakovosti s pomočjo dokazov. In: Kersnik J ed. Znanstveno utemeljena medicina (Zbirka PiP). Ljubljana: Združenje zdravnikov družinske medicine, Slovensko zdravniško društvo, 2000: 59–68.
- Petek D, Kopčavar-Guček N, Švab I. Znanstveno utemeljena družinska medicina. Zdrav Vestn 2001; 70: 235–7.

Z dokazi podprta medicina

- Grad A. Nekaj o »Evidence-based medicine«. Isis 1999; 8: 108–8.
- Vlaisavljević V, Gorišek B, Borko E. Centru za menopavzo na pot. Zdrav Vestn 2002; 71: Suppl I: I-1–39.
- Deffner H. Pomen in vloga inovacij v farmacevtskih raziskavah. Isis 2002; 11: 54–5.

Izsledki na drugih področjih

- Evidence- based practice
- Evidence- based pharmacy practice

The Cochrane Collaboration

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Cochrane in the News

Articles in Scientific American and Nursing Times discuss new evidence for the

Cochrane Collaboration

- Mednarodna, neodvisna, neprofitna organizacija
  - Ustanovljena l. 1993
  - 11.500 oseb, preko 90 držav
  - Ime po britanskem epidemiologu Archieju Cochraneu.
  - Splet: http://www.cochrane.org
- »Pripravlja, vzdržuje in pospešuje dostopnost sistematičnih pregledov o učinkih posegov v zdravstvu« v obliki Cochrane Library.
  - Pretežno sistematični pregledi kontroliranih kliničnih raziskav s področja zdravljenja.

Cochrane Collaboration

- 1016 sistematičnih pregledov, 50 skupin "Cochrane Collaboration Review Groups" v l. 2007:
- Izsledki glede intervencij:
  - 44% zelo verjetno, da koristi
    - "likely to be beneficial"
  - 7% zelo verjetno, da škoduje
    - "likely to be harmful"
  - 49% nezadostni izsledki glede koristi oz. škode
    - "did not support either benefit or harm"
  - 96% priporočilo za nadaljne raziskave

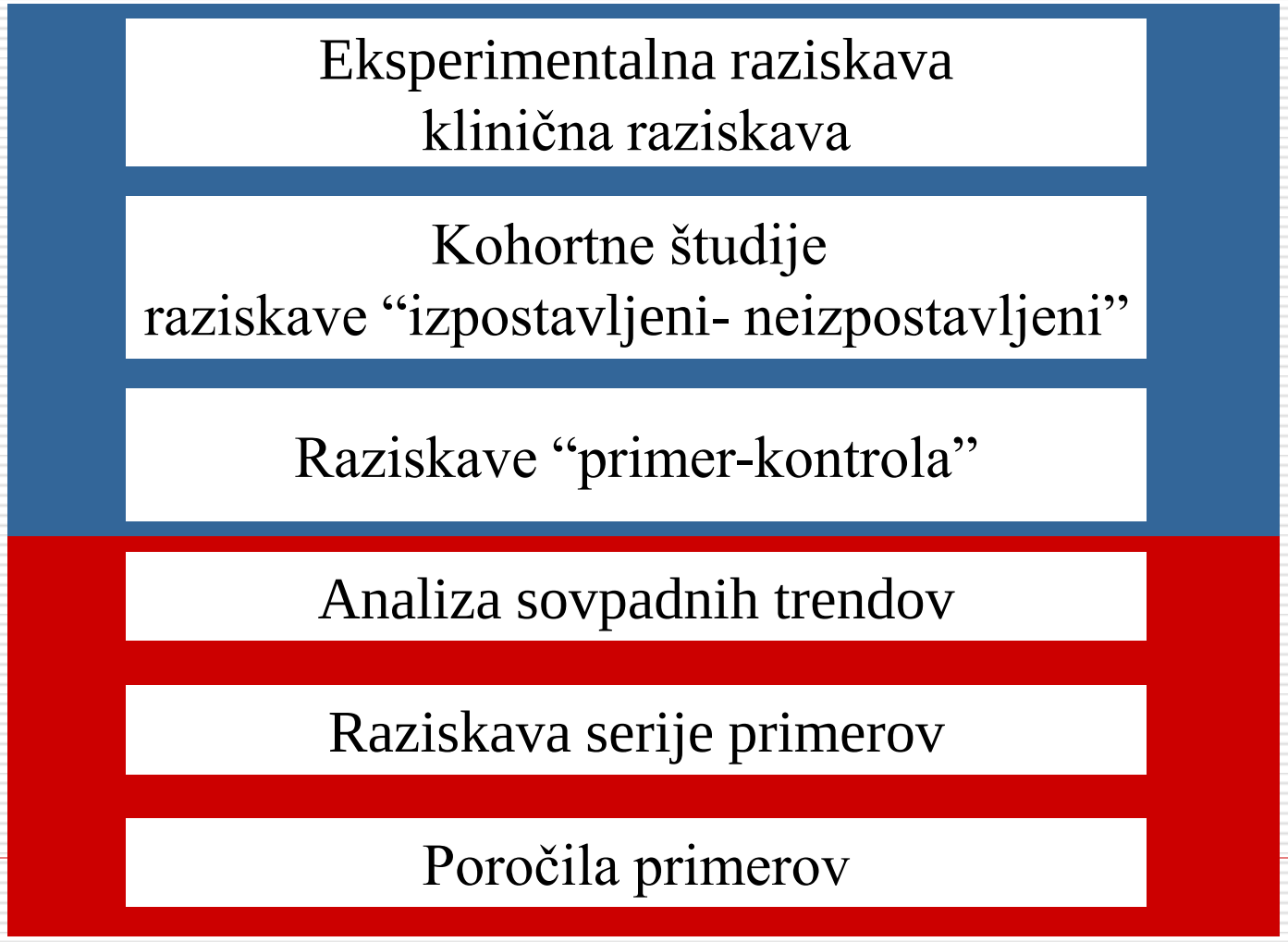
Vrste EBM

- "Evidence-based guidelines"
  - praksa EBM na ravni organizacij oz. institucije
  - priprava smernice, politik, zakonodaje
  - ime tudi "evidence based healthcare"
- "Evidence-based individual decision making"
  - EBM praksa posameznega zdravstvenega delavca

Kvaliteta izsledkov in hierarhičnost dokazov

Rangiranje izsledkov glede na kvaliteto in moč raziskave ter odsotnosti napak in pristranosti.

Vrste raziskav



U.S. Preventive Services Task Force

Rangiranje izsledkov o učinkovitosti zdravljenja in presejanja

- Stopnja I (angl. Level 1): Izsledki iz najmanj ene ustrezno izvedene randomizirane kontrolirane klinčne raziskave.
- Stopnja II:
  - Stopnja II-1: Izsledki iz ustrezno izvedenih kontroliranih kliničnih raziskav brez randomizacije.
  - Stopnja II-2: Izsledki iz ustrezno izvedenih kohortnih raziskav ter raziskav primer kontrola, po možnosti iz več centrov oz. raziskovalnih skupin.
  - Stopnja II-3: Izsledki iz več časovnih vrst z ali brez intervencije (sovpadni trendi). Dramatični rezultati iz nekontroliranih raziskav.
- Stopnja III: Mnenja uglednih strokovnjakov, ki so osnovana na kliničnih izkušnjah, opisnih raziskavah, poročilih ekspertnih odborov.

U.S. Preventive Services Task Force. http://www.ahrq.gov/

UK National Health Service

Podoben sistem, a različice v poimenovanju in načinu rangiranja

- Level A: Consistent Randomised Controlled Clinical Trial, cohort study, clinical decision rule validated in different populations.
- Level B: Consistent Retrospective Cohort, Exploratory Cohort, Ecological Study, Outcomes Research, case-control study; or extrapolations from level A studies.
- Level C: Case-series study or extrapolations from level B studies.
- Level D: Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.

UK NHS http://www.nhs.uk/

Drugi sistemi

- Poleg vrednotenja zdravljenja in intervencij še:
  - diagnostičnih postopkov
  - prognoz
  - ekonomskih analiz
  - itd.
- Zahteva drugačne raziskave, posledično tudi drugačna klasifikacija kvalitete raziskav

Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research

Oxford Centre for Evidence-based Medicine . http://www.cebm.net/index.aspx?o=1025

Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Oxford Centre for Evidence-based Medicine . http://www.cebm.net/index.aspx?o=1025

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
‡	See note above for advice on how to understand, rate and use trials or other studies with wide confidence
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 - 5 years chronic)

Oxford Centre for Evidence-based Medicine- Grades of Recommendation

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

Večina priporočil skušajo klasificirati ravnotežje med koristjo in škodo. Vrednotenje "Net Benefit"

Oxford Centre for Evidence-based Medicine . http://www.cebm.net/index.aspx?o=1025

Recommendation grades USPSTF

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small.	Offer or provide this service only if other considerations support the offering or providing the service in an individual patient.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

U.S. Preventive Services Task Force. http://www.ahrq.gov/clinic/uspstf/grades.htm

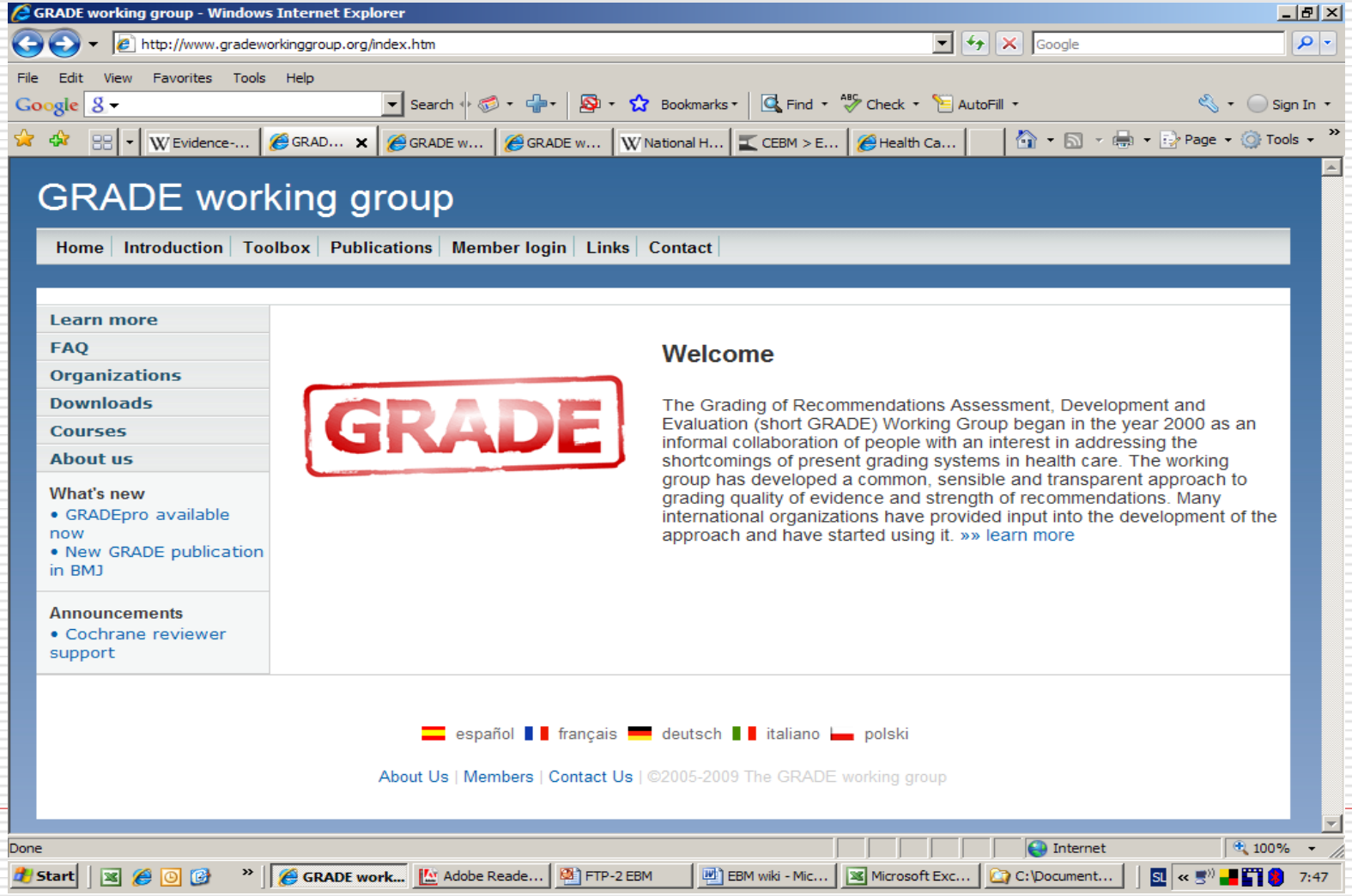
Levels of Certainty Regarding Net Benefit USPSTF

Level of Certainty*	**Description**
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies inconsistency of findings across individual studies limited generalizability of findings to routine primary care practice lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies important flaws in study design or methods inconsistency of findings across individual studies gaps in the chain of evidence findings that are not generalizable to routine primary care practice a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

*The U.S. Preventive Services Task Force (USPSTF) defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.

U.S. Preventive Services Task Force. http://www.ahrq.gov/clinic/uspstf07/methods/benefit.htm

GRADE working group



http://www.gradeworkinggroup.org/index.htm

GRADE working group

- GRADE: Grades of Recommendation, Assessment, Development and Evaluation
- Razvoj skupnega, transparentnega in občutljivega sistema za vrednotenje kvalitete izsledkov in stopenj priporočil
- Upošteva več dimenzij pri vrednotenju kot samo kvaliteto raziskav.
  - Problem ekstrapolacij iz raziskav
  - Kvaliteta izsledka za podporo odločitvi= kvaliteta raziskave + usmerjenost kliničnih podatkov ("clinical directness")

Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, for the GRADE Working Group. Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.
BMJ 2008;336:924-926

GRADE working group

- Poseben program: http://www.cc-ims.net/revman/gradepro/gradepro
- Extent of confidence in the estimate of effect:
  - high: considerable confidence in estimate of effect.
  - moderate: further research likely to have impact on confidence in estimate, may change estimate.
  - low: further research is very likely to impact on confidence, likely to change the estimate.
  - very low: any estimate of effect is very uncertain

Vrednotenje kvalitete publikacij

- Načrt raziskave.
  - natančno definirani vključitveni in izključitveni kriteriji, čim manj manjkajočih podatkov
- Prenosljivost:
  - lahko so veljavni samo za specifično populacijo pacientov in niso prenosljivi v klinično prakso
- Obdobje analize:
  - da lahko zaznamo izide
- Statistična moč raziskave:
  - Ali velikost vzorca zadostna, da sploh lahko odkrijemo razlike, ki jih iščemo.

Kritike EBM

- Učinkovitost EBM:
  - EBM na ravni organizacije lahko dokazuje
  - Težave pri EBM na ravni posameznega zdravstvenega delavca
- Kritiki: Manjkjoči podporni izsledki ni enako storitvi, ki ne prinaša koristi
- Več kot je agregiranja podatkov teže je primerjati dejanskega pacienta z agregirano populacijo iz študij. EBM deluje za populacijo in ne nujno za posameznega pacienta.
  - Tonelli: “the knowledge gained from clinical research does not directly answer the primary clinical question of what is best for the patient at hand”.

Problem ustreznih raziskav?

- V nekaterih primerih ni etično izvajati RCT (npr. kirurgija na odprtem srcu)
- Skupine, ki niso vključene v raziskave (npr. rasne manjšine, osebe z več sočasnih obolenj)
- Zlati standard raziskovanja (dvojno slepa RCT)- draga raziskava, vir financiranja ključnega pomena, industrija osredotoča samo na svoje izdelke
- Objavljene raziskave niso nujno reprezentativne glede na vse izvedene raziskave (publication bias)
- Problem pri generaliziranju rezultatov raziskav, ki variirajo v kvaliteti
- ...

Klinična pot

- Klinična pot je orodje, ki temelji na z dokazi podprti medicini, zdravstveni negi, itd. in krajevni organizaciji, s katerim je opredeljen standardni načrt večdisciplinarne zdravstvene oskrbe tipične vrste pacientov z določenim obolenjem ali načrtovanim posegom.
- Omogoča sledenje odklonom od standardnega postopka, ohranja utemeljeno samostojnost odločitve, poenoti klinično prakso, nenehno izboljšuje kakovost zdravstvene obravnave in spodbuja timsko delo.

Yazbeck in Robida. Metodološka priporočila za oblikovanje in uvajanje kliničnih poti. Ministrstvo za zdravje 2006.

Klinična smernica

- Klinična smernica je skupek sistematično oblikovanih stališč, ki zdravniku in drugemu zdravstvenemu osebju in pacientom pomaga pri odločanju za primerno zdravstveno oskrbo v posebnih kliničnih okoliščinah.