UNIVERSITÀ CATTOLICA del Sacro Cuore

Quali linee guida sono *evidence-based*?

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Agenda

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- The new USPSTF Guidelines (GLs)
- The Evidence base process
- The GRADE method
- The quality of genomics GLs

THE NEW USPSTF GL

Annals of Internal Medicine | CLINICAL GUIDELINE

Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2005 U.S. Preventive Services Task Force (USPSTF) recommendation on genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility.

Methods: The USPSTF reviewed the evidence on risk assessment, genetic counseling, and genetic testing for potentially harmful BRCA mutations in asymptomatic women with a family history of breast or ovarian cancer but no personal history of cancer or known potentially harmful BRCA mutations in their family. The USPSTF also reviewed interventions aimed at reducing the risk for BRCA-related cancer in women with potentially harmful BRCA mutations, including intensive cancer screening, medications, and risk-reducing surgery.

Population: This recommendation applies to asymptomatic women who have not been diagnosed with BRCA-related cancer.

Recommendation: The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. (B recommendation)

The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes. (D recommendation)

Ann Intern Med. www.annals.org

For author affiliation, see end of text.

* For a list of the members of the USPSTF, see the Appendix (available at www.annals.org).

This article was published online first at www.annals.org on 24 December 2013.

The U.S. Preventive Services Task Force (USPSTF)

- Makes recommendations based on rigorous review of existing peer-reviewed evidence
  - Does not conduct the research studies, but reviews & assesses the research
  - Evaluates benefits & harms of each service based on factors such as age & sex
- Is an independent panel of non-Federal experts in prevention & evidenced-based medicine

The U.S. Preventive Services Task Force (USPSTF)

- Makes recommendations on clinical preventive services to primary care clinicians
  - The USPSTF scope for clinical preventive services include:
    - screening tests
    - counseling
    - preventive medications
  - Services are offered in a primary care setting
  - Recommendations apply to adults & children with no signs or symptoms

Recommendation Grades

Letter grades are assigned to each recommendation statement. These grades are based on the strength of the evidence on the harms and benefits of a specific preventive service. http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm

Grade	Definition
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
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.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.
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.
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.

The aim of clinical guidelines

REPORT BRIEF MARCH 2011

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Clinical Practice Guidelines We Can Trust

Rather than dictating a one-size-fits-all approach to patient care, **clinical practice guidelines offer an evaluation of the quality of the relevant scientific literature and an assessment of the likely benefits and harms of a particular treatment**.

http://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx

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preferences, to inform their decisions. Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. Rather than dictating a one-size-fits-all approach to patient care, clinical practice guidelines offer an evaluation of the quality of the relevant scientific literature and an assessment of the likely benefits and harms of a particular treatment. This information enables healthcare providers to proceed accordingly, selecting the best care for a unique patient based on his or her preferences.

The U.S. Congress, through the *Medicare Improvements for Patients and Providers Act of 2008*, asked the Institute of Medicine (IOM) to undertake a study on the best methods used in developing clinical practice guidelines. To ensure that organizations developing such guidelines have information on approaches that are objective, scientifically valid, and consistent, the IOM formed an expert committee. The committee developed eight standards for developing rigorous, trustworthy clinical practice guidelines.

An Evidence Based GL should comply at least to the two principles above

The eight standards that all CGs should comply

Standards for Developing Trustworthy Clinical Practice Guidelines (CPGs)

STANDARD 1
Establishing transparency

1.1 The processes by which a CPG is developed and funded should be detailed explicity and publicly accessible.

STANDARD 2
Management of conflict of interest (COI)

2.1 Prior to selection of the Guideline Development Group (GDG), individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity, by written disclosure to those convening the GDG.

- Disclosure should reflect all current and planned commercial (including services from which a clinician derives a substantial proportion of income), non-commercial, intellectual, institutional, and patient/public activities pertinent to the potential scope of the CPG.

2.2 Disclosure of COIs within GDG

- All COI of each GDG member should be reported and discussed by the prospective development group prior to the onset of their work.
- Each panel member should explain how their COI could influence the CPG development process or specific recommendations.

2.3 Divestment

- Members of the GDG should divest themselves of financial investments they or their family members have in, and not participate in marketing activities or advisory boards of, entities whose interests could be affected by CPG recommendations.

2.4 Exclusions

- Whenever possible GDG members should not have COI.
- In some circumstances, a GDG may not be able to perform its work without members who have COIs, such as relevant clinical specialists who receive a substantial portion of their incomes from services pertinent to the CPG.
- Members with COIs should represent not more than a minority of the GDG.
- The chair or co-chairs should not be a person(s) with COI.
- Funders should have no role in CPG development.

STANDARD 3
Guideline development group composition

3.1 The GDG should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG.

3.2 Patient and public involvement should be facilitated by including (at least at the time of clinical question formulation and draft CPG review) a current or former patient and a patient advocate or patient/consumer organization representative in the GDG.

3.3 Strategies to increase effective participation of patient and consumer representatives, including training in appraisal of evidence, should be adopted by GDGs.

STANDARD 4
Clinical practice guideline–systematic review intersection

4.1 CPG developers should use systematic reviews that meet standards set by the Institute of Medicine's Committee on Standards for Systematic Reviews of Comparative Effectiveness Research.

4.2 When systematic reviews are conducted specifically to inform particular guidelines, the GDG and systematic review team should interact regarding the scope, approach, and output of both processes.

STANDARD 5
Establishing evidence foundations for and rating strength of recommendations

5.1 For each recommendation, the following should be provided:

- An explanation of the reasoning underlying the recommendation, including:
  - A clear description of potential benefits and harms.
  - A summary of relevant available evidence (and evidentiary gaps), description of the quality (including applicability), quantity (including completeness), and consistency of the aggregate available evidence.
  - An explanation of the part played by values, opinion, theory, and clinical experience in deriving the recommendation.
- A rating of the level of confidence in (certainty regarding) the evidence underpinning the recommendation.
- A rating of the strength of the recommendation in light of the preceding bullets.
- A description and explanation of any differences of opinion regarding the recommendation.

STANDARD 6
Articulation of recommendations

6.1 Recommendations should be articulated in a standardized form detailing precisely what the recommended action is and under what circumstances it should be performed.

6.2 Strong recommendations should be worded so that compliance with the recommendation(s) can be evaluated.

STANDARD 7
External review

7.1 External reviewers should comprise a full spectrum of relevant stakeholders, including scientific and clinical experts, organizations (e.g., health care, specialty societies), agencies (e.g., federal government), patients, and representatives of the public.

7.2 The authorship of external reviews submitted by individuals and/or organizations should be kept confidential unless that protection has been waived by the reviewer(s).

7.3 The GDG should consider all external reviewer comments and keep a written record of the rationale for modifying or not modifying a CPG in response to reviewers' comments.

7.4 A draft of the CPG at the external review stage or immediately following it (i.e., prior to the final draft) should be made available to the general public for comment. Reasonable notice of impending publication should be provided to interested public stakeholders.

STANDARD 8
Updating

8.1 The CPG publication date, date of pertinent systematic evidence review, and proposed date for future CPG review should be documented in the CPG.

8.2 Literature should be monitored regularly following CPG publication to identify the emergence of new, potentially relevant evidence and to evaluate the continued validity of the CPG.

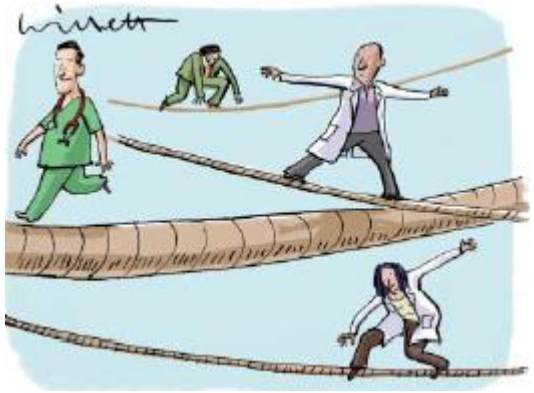
8.3 CPGs should be updated when new evidence suggests the need for modification of clinically important recommendations. For example, a CPG should be updated if new evidence shows that a recommended intervention causes previously unknown substantial harm, that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective, or that a recommendation can be applied to new populations.

The GRADE system

Grading quality of evidence and strength of recommendations

Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group

Clinical guidelines are only as good as the evidence and judgments they are based on. The GRADE approach aims to make it easier for users to assess the judgments behind recommendations



Quality of evidence= the extent to which one can be confident that a certain estimate of effect is correct.

Strenght of reccomandation= the extent to which one can be confident that adherence to raccomandation will do more benefit than harm.

BMJ VOLUME 328 19 JUNE 2004 bmj.com

The GRADE system

Box 1: Sequential process for developing guidelines

First steps
1. *Establishing the process*—For example, prioritising problems, selecting a panel, declaring conflicts of interest, and agreeing on group processes

Preparatory steps
2. *Systematic review*—The first step is to identify and critically appraise or prepare systematic reviews of the best available evidence for all important outcomes
3. *Prepare evidence profile for important outcomes*—Profiles are needed for each subpopulation or risk group, based on the results of systematic review, and should include a quality assessment and a summary of findings

Grading quality of evidence and strength of recommendations
4. *Quality of evidence for each outcome*—Judged on information summarised in the evidence profile and based on the criteria in table 2
5. *Relative importance of outcomes*—Only important outcomes should be included in evidence profiles. The included outcomes should be classified as critical or important (but not critical) to a decision
6. *Overall quality of evidence*—The overall quality of evidence should be judged across outcomes based on the lowest quality of evidence for any of the critical outcomes.
7. *Balance of benefits and harms*—The balance of benefits and harms should be classified as net benefits, trade-offs, uncertain trade-offs, or no net benefits based on the important health benefits and harms
8. *Balance of net benefits and costs*—Are incremental health benefits worth the costs? Because resources are always limited, it is important to consider costs (resource utilisation) when making a recommendation
9. *Strength of recommendation*—Recommendations should be formulated to reflect their strength—that is, the extent to which one can be confident that adherence will do more good than harm

Subsequent steps
10. *Implementation and evaluation*—For example, using effective implementation strategies that address barriers to change, evaluation of implementation, and keeping up to date

Box 2: Criteria for assigning grade of evidence

Type of evidence
Randomised trial – high
Observational study – low
Any other evidence – very low

Decrease grade if:
- Serious (–1) or very serious (–2) limitation to study quality
- Important inconsistency (–1)
- Some (–1) or major (–2) uncertainty about directness
- Imprecise or sparse data (–1)
- High probability of reporting bias (–1)

Increase grade if:
- Strong evidence of association—significant relative risk of >2 (<0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
- Very strong evidence of association—significant relative risk of >5 (<0.2) based on direct evidence with no major threats to validity (+2)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

Box 3: Definitions of grades of evidence

High—Further research is unlikely to change our confidence in the estimate of effect.
Moderate—Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low—Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low—Any estimate of effect is very uncertain.

Guidelines in Genomics

Many Groups have been involved in knowledge synthesis & guideline development in genomic medicine

- Government (FDA, NIH, CMS, etc)
- Private Payers (e.g. BCBSA)
- Professional Organizations (generic and by specialty, ACMG, AMP, AHA, NCCN)
- US and other countries (e.g. NICE)
- Advisory committees and task forces (SACHDNC, EGAPP, USPSTF)

M. Khoury, personal handouts

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group

Steven M. Teutsch, MD, MPH[1], Linda A. Bradley, PhD[2], Glenn E. Palomaki, BS[3], James E. Haddow, MD[3], Margaret Piper, PhD[4], Ned Calonge, MD, MPH[5], W. David Dotson, PhD[2,6], Michael P. Douglas, MS[2,6], and Alfred O. Berg, MD, MPH[7], Chair, on behalf of the EGAPP Working Group

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative, established by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention, supports the development and implementation of a rigorous, evidence-based process for evaluating genetic tests and other genomic applications for clinical and public health practice in the United States. An independent, non-federal EGAPP Working Group (EWG), a multidisciplinary expert panel selects topics, oversees the systematic review of evidence, and makes recommendations based on that evidence. This article describes the EGAPP processes and details the specific methods and approaches used by the EWG.
***Genet Med* 2009:11(1):3–14.**

Genetics inMedicine | SPECIAL ARTICLE

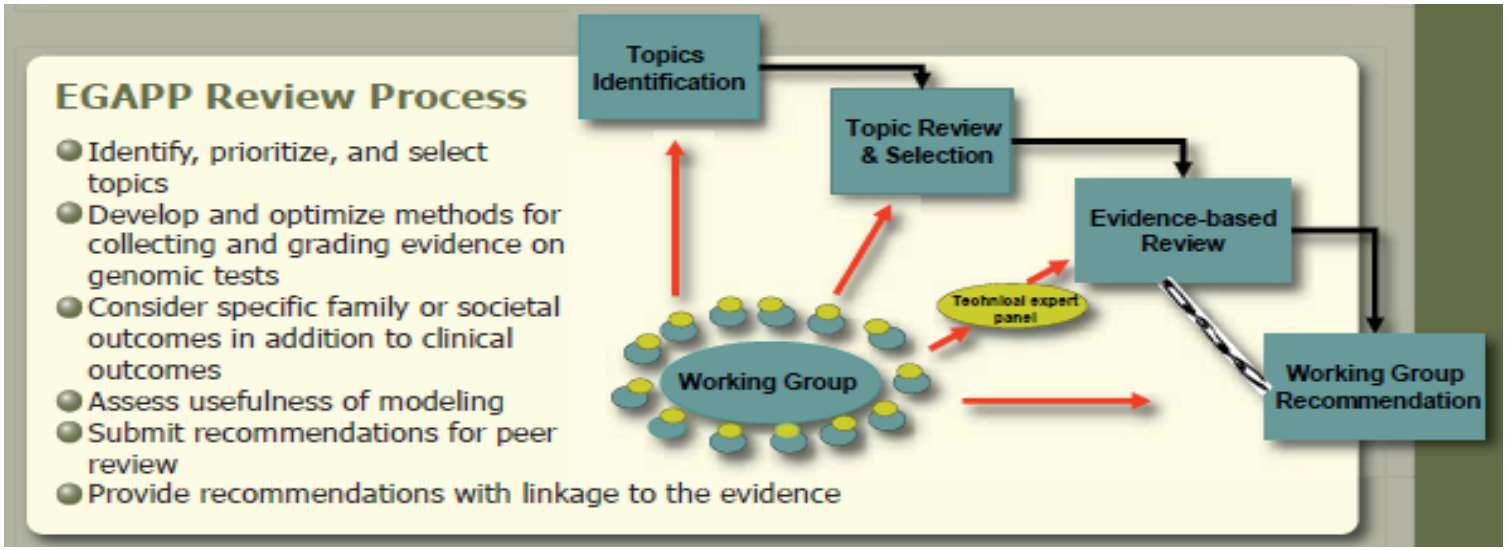
Improving the efficiency and relevance of evidence-based recommendations in the era of whole-genome sequencing: an EGAPP methods update

David L. Veenstra, PharmD, PhD[1], Margaret Piper, PhD, MPH[2], James E. Haddow, MD[3], Stephen G. Pauker, MD[4], Roger Klein, MD, JD[5], Carolyn Sue Richards, PhD[6], Sean R. Tunis, MD, MSc[7], Benjamin Djulbegovic, MD, PhD[8], Michael Marrone, MPH[9,10], Jennifer S. Lin, MD, MCR[11], Alfred O. Berg, MD, MPH[12] and Ned Calonge, MD, MPH[13]; on behalf of the EGAPP Working Group

Evidence to Practice

EGAPP

Evaluation of Genomic Applications in Practice and Prevention



www.egappreviews.com

CDC Evidence-based Classification of Genomic Tests and Family History to Inform Policy and Practice

Tier 1: Recommended for clinical use by evidence-based panels, based on systematic review of evidence of validity and utility (e.g., GL for hereditary BC)

Tier 2: May be useful for informed decision making, based on demonstrated validity, and promising utility.

Tier 3: Not ready for clinical use, due to validity or utility not demonstrated, or systematic assessment finding harms outweigh benefits.

M. Khoury, personal handouts

Comparing, Contrasting and Demystifying Methods for Knowledge Synthesis & Evidence-based Guideline Development in Genomic Medicine March 11, 2013 Bethesda, Maryland

- ISSUES
  - Admissibility of evidence and outcomes
  - Internal validity assessment criteria and hierarchies for rating
  - Factors affecting strength, grade or level of recommendations
- OUTCOMES
  - Comparative paper of methods and evidence thresholds used
  - Start of a dialogue to pursue broad-based consensus on elements & approaches needed to effect a smooth transition of genomic research into practice

M. Khoury, personal handouts

The Workshop Outcome_Survey on the quality of GLs in genomics

Organization	Target Audience	Have criteria for guideline/ recommendation	Have protocol to guide formation of the review panel	Have policy to manage conflict of interests	Have criteria for synthesizing the evidence	Use of systematic reviews [a]	Use of external review [b]
American College of Medical Genetics and Genomics (ACMG)	Practitioners, genetic laboratories and laboratorians	+	+	+	-	-	+
American Society of Clinical Oncology (ASCO)	Oncologists	+	+	+	+	++	++
Blue Cross Blue Shield Association (BCBS TEC)	Health plans and general public	+	+	+	+	++	++
Clinical Pharmacogenetics Implementation Consortium (CPIC)	Clinicians who use pharmacogenomic testing	+	+	+	+	++	+
Evaluation of Genomic Applications in Practice and Prevention (EGAPP)	Researchers and clinicians interested in genomic applications	+	+	+	+	++	++
Leiden University Medical Center / Dutch Pharmacogenetics Working Group (DPWG)	Clinicians and pharmacists	+	+	+	+	++	+
National Comprehensive Cancer Network (NCCN)	Oncologists and other clinicians	+	+	+	-	-	+
National Society of Genetic Counselors - Practice Guidelines Committee	Genetic counselors	+	+	+	+	+	+

Appraisal on the quality of GLs on the screening and management of hereditary breast cancer

Simone et al. BMC Medicine 2012, 10:143
http://www.biomedcentral.com/1741-7015/10/143

BMC Medicine

RESEARCH ARTICLE Open Access

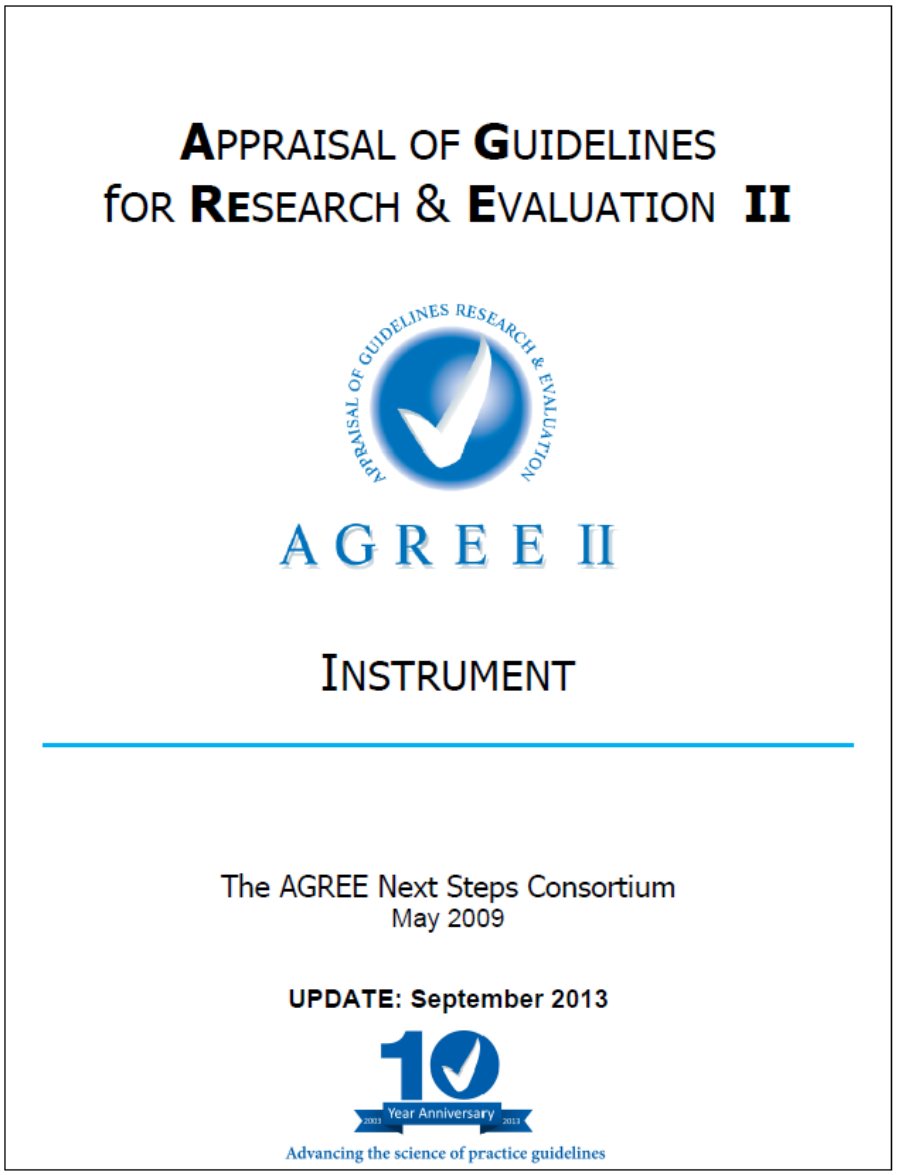
Methodological quality of English-language genetic guidelines on hereditary breast-cancer screening and management: an evaluation using the AGREE instrument

Benedetto Simone[1], Emma De Feo[1], Nicola Nicolotti[1], Walter Ricciardi[1] and Stefania Boccia[1,2*]

Acknowledgements
This work was supported by the Agenzia Sanitaria Regionale Abruzzo, Italy, 2009, within the project: 'I test di suscettibilità genetica al carcinoma mammario e colorettale: valutazione dell'appropriatezza dello screening in soggetti ad alto rischio in alcune regioni italiane' (Genetic susceptibility tests for colorectal and breast cancer: assessment of appropriateness of screening in high-risk individuals in four Italian regions).

ASR ABRUZZO
AGENZIA SANITARIA REGIONALE

AGREE



- AGREE è uno strumento validato a livello internazionale per la valutazione nel reporting delle linee guida
- Sei domini per un totale di 23 items
- Scala a 4 punti per la valutazione di ogni item
- E' uno strumento utile non solo ai fini di una valutazione retrospettiva di linee guida già pubblicate, ma anche come punto di riferimento nel corso della stesura delle linee guida stesse, al fine di migliorarne la qualità.

htpp.://www.agreetrust.org/resource-centre/agree-ii/

AGREE

Valutazione delle linee guida tramite **sei domini:**

1) Obiettivi e ambiti di applicazione

2) Coinvolgimento dei soggetti portatori di interesse

3) **Rigore nello sviluppo**

AGREE

4) Chiarezza espositiva

5) Applicabilità

6) Indipendenza editoriale

METODI

•Ricerca su Embase, Pubmed e Google (fino a maggio 2010) di linee guida aggiornate, in lingua inglese, con raccomandazioni originali sulle forme ereditarie di carcinoma della mammella

•Valutazione con strumento AGREE delle linee guida eleggibili, da parte di 3 valutatori indipendenti

•Score medi standardizzati in percentuale

•Confronto tra score assegnati a linee guida prodotte da società con endorsement nazionali\statali e linee guida di società indipendenti (test di Mann-Whitney)

RISULTATI_1

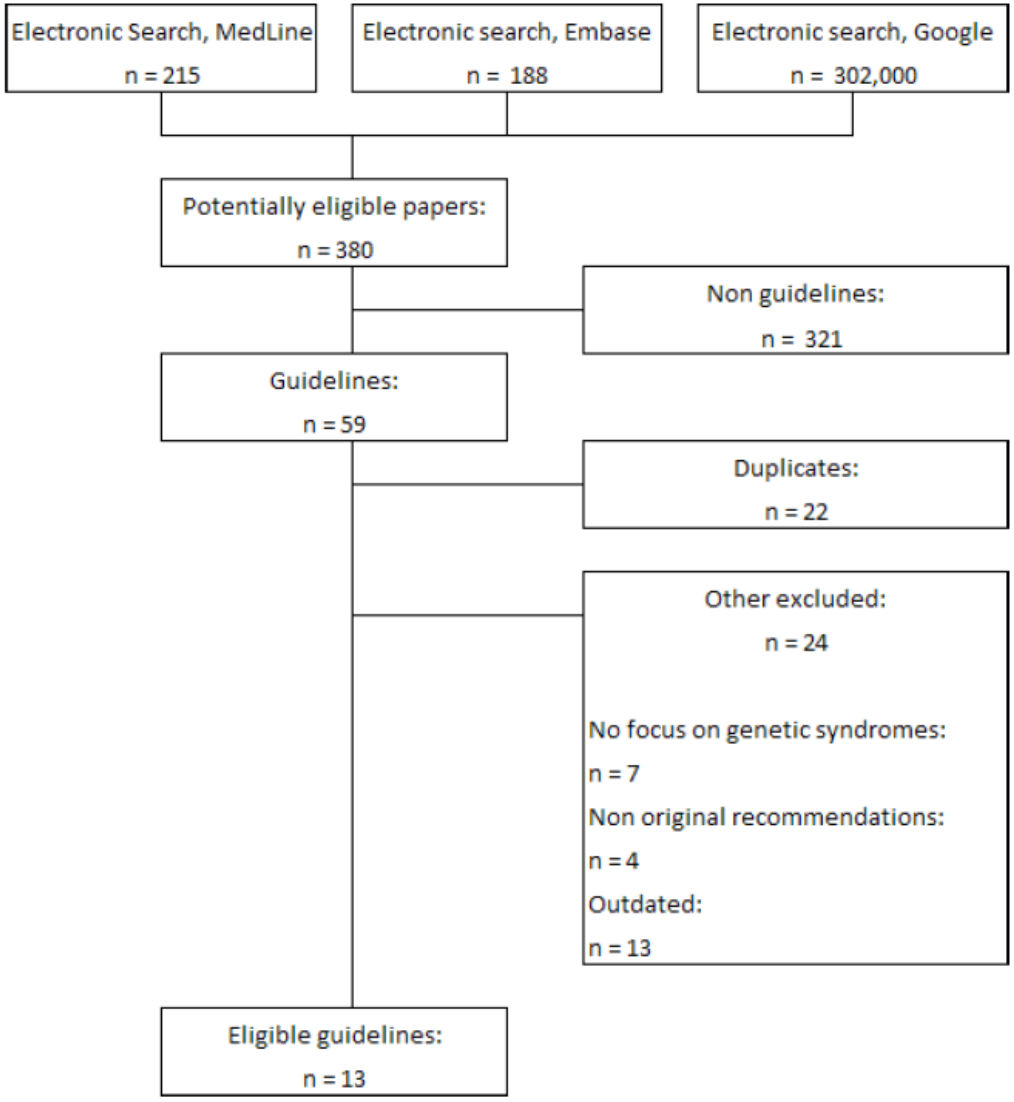


Figure 1 Flowchart of the guidelines selection process.

RISULTATI_2

Table 2 Standardized scores (%) on the Appraisal of Guidelines, Research and Evaluation (AGREE) instrument assigned to the 13 guidelines.

	Domain number (name)					
	1 (Scope and purpose)	2 (Stakeholder involvement)	3 (Rigour of development)	4 (Clarity and presentation)	5 (Applicability)	6 (Editorial independence)
National Cancer Comprehensive Network[1] [2]	92.6	63.9	50.8	83.3	7.4	100.0
Ministry of Health, Singapore[2] [15]	7.4	47.2	12.7	69.4	25.9	0.0
American College of Obstetricians and Gynecologists[1] [16]	100.0	44.4	33.3	77.8	18.5	0.0
Insitute for Clinical Systems Improvement[1] [17]	74.1	50.0	52.4	80.6	55.6	55.6
New Zealand Guidelines Group[2] [18]	81.5	75.0	81.0	100.0	85.2	100.0
American Cancer Society (MRI)[1] [19]	96.3	52.8	65.1	86.1	44.4	0.0
National Society of Genetic Counselors[1] [20]	100.0	41.7	69.8	72.2	44.4	50.0
University of Michigan[1] [21]	92.6	8.3	39.7	80.6	0.0	88.9
Towards Optimized Practice Alberta[2] [22]	74.1	33.3	7.9	69.4	18.5	0.0
National Health System[2] [23,24]	88.9	75.0	87.3	88.9	77.8	50.0
U.S. Preventive Services Task Force[2] [25]	96.3	72.2	69.8	86.1	3.7	50.0
Scottish Intercollegiate Guidelines Group[2] [26]	96.3	50.0	96.8	86.1	88.9	72.2
American Cancer Society[1] [27]	92.6	47.2	52.4	55.6	11.1	50.0

[1]Independent body/no endorsement,.

[2]National/state endorsement,

RISULTATI_3

Table 3 Mean scores for the 23 items and overall standardized scores for each domain from the 13 guidelines evaluated assessed with AGREE.

Domain	Item	Mean score (range)
1 (Scope and purpose)	• The overall objective(s) of the guideline is (are) specifically described	3.7 (2.3 to 4.0)
	• The clinical question(s) covered by the guideline is(are) specifically described	3.6 (2.7 to 4.0)
	• The patients to whom the guideline is meant to apply are specifically described	3.7 (3.3 to 4.0)
	Overall standardized score, %	89.5 (66.7 to 100.0)
2 (Stakeholder involvement)	• The guideline development group includes individuals from all the relevant professional groups	3.3 (1.3 to 4.0)
	• The patients' views and preferences have been sought	2.7 (1.3 to 4.0)
	• The target users of the guideline are clearly defined	3.0 (1.0 to 4.0)
	• The guideline has been piloted among end users	1.1 (1.0 to 1.7)
	Overall standardized score, %)	50.9 (8.3 to 75.0)
3 (Rigour of development)	• Systematic methods were used to search for evidence	2.6 (1.0 to 4.0)
	• The criteria for selecting the evidence are clearly described	2.8 (1.0 to 4.0)
	• The methods used for formulating the recommendations are clearly described	3.0 (1.0 to 4.0)
	• The health benefits, side effects, and risks have been considered in formulating the recommendations	3.1 (1.7 to 4.0)
	• There is an explicit link between the recommendations and the supporting evidence	3.1 (1.3 to 4.0)
	• The guideline has been externally reviewed by experts before its publication	2.3 (1.0 to 4.0)
	• A procedure for updating the guideline is provided	1.7 (1.0 to 4.0)
	Overall standardized score, %	55.5 (7.9 to 96.8)
4 (Clarity and presentation)	• The recommendations are specific and unambiguous	3.4 (2.3 to 4.0)
	• The different options for management of the condition are clearly presented	3.4 (2.3 to 4.0)
	• Key recommendations are easily identifiable	3.7 (2.7 to 4.0)
	• The guideline is supported with tools for application	3.0 (1.0 to 4.0)
	Overall standardized score, %	79.7 (55.6 to 100.0)
5 (Applicability)	• The potential organizational barriers in applying the recommendations have been discussed	2.2 (1.0 to 4.0)
	• The potential cost implications of applying the recommendations have been considered	2.4 (1.0 to 4.0)
	• The guideline presents key review criteria for monitoring and/or audit purposes	1.7 (1.0 to 3.7)
	• Overall standardized score, %	37.0 (0.0 to 88.9)
6 (Editorial independence)	• The guideline is editorially independent from the funding body	2.2 (1.0 to 4.0)
	• Conflicts of interest of guideline development members have been recorded	2.6 (1.0 to 4.0)
	Overall standardized score, %	47.4 (0.0 to 100.0)

RISULTATI 4

Table 1 Description of the thirteen breast cancer screening guidelines included in the study.

Guidelines (organization), year	Evidence base	Syndromes considered	Target population	Risk assessment	Criteria for genetic risk evaluation	Diagnosis and counselling	Treatment
Breast Cancer Screening and Diagnosis (National Cancer Comprehensive Network), 2010[1] [2]	Yes	*BRCA1/2*, CS, LFS	General population	Yes	Yes	Yes	Yes
Health Screening, MOH Clinical Practice Guidelines (Ministry of Health, Singapore), 2010[2] [15]	Yes	*BRCA1/2*	General population	No	No	No	Yes
Hereditary Breast and Ovarian Cancer Syndrome (American College of Obstetricians and Gynecologists), 2009[1] [16]	No	*BRCA1/2*	General population	Yes	Yes	Yes	Yes
Diagnosis of Breast Disease (Institute for Clinical Systems Improvement), 2008[1] [17]	Yes	*BRCA1/2*, CS, LFS, others[3]	General population	No	Yes	Yes	Yes
Management of Early Breast Cancer (New Zealand Guidelines Group), 2008[2] [18]	Yes	*BRCA1/2*, CS, LFS other [3]	General population	Yes	Yes	Yes	Yes
Guidelines for Breast Screening with MRI as an Adjunct to Mammography (American Cancer Society), 2007[1] [19]	Yes	*BRCA1/2*, CS, LFS	General population	Yes	Yes	No	Yes
Risk Assessment and Genetic Counseling for Hereditary Breast and Ovarian Cancer: Recommendations (National Society of Genetic Counselors), 2007[1] [20]	No	*BRCA1/2*, CS, LFS, other[3]	General Population	Yes	Yes	Yes	Yes
Adult Preventive Health Care: Cancer Screening (University of Michigan), 2007[1] [21]	No	*BRCA1/2*	General population	No	No	No	Yes
The Early Detection of Breast Cancer (Towards Optimized Practice Alberta), 2007[2] [22]	Yes	*BRCA1/2*	General population	Yes	Yes	Yes	Yes
Familial breast cancer + Update (NHS), 2006[2] [23,24]	Yes	*BRCA1/2*, LFS	General population	Yes	Yes	Yes	Yes
Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility: Recommendation Statement (U.S. Preventive Services Task Force), 2004[2] [25]	Yes	*BRCA1/2*	General population	Yes	Yes	Yes	No
Management of Breast Cancer in Women (Scottish Intercollegiate Guidelines Group), 2004[2] [26]	Yes	*BRCA1/2*	General population	Yes	Yes	Yes	Yes
Guidelines for Breast Cancer Screening (American Cancer Society), 2003[1] [27]	Yes	*BRCA1/2*, CS, LFS	General population	Yes	Yes	Yes	Yes

Abbreviations: CS, Cowden syndrome; LFS, Li-Fraumeni syndrome
[1]Independent body/no endorsement

Evidence-based:

- ~~the search strategy has been~~ explicitated;
- the quality of evidence classified
- the strength of recommendations reported.

CONCLUSIONI del Lavoro

•Le linee guida con endorsement nazionale sono mediamente migliori in tutti e 6 i domini AGREE, ma non sono state rilevate differenze statisticamente significative.

•Le linee guida disponibili in letteratura trascurano elementi importanti come il coinvolgimento di tutte le figure professionali rilevanti e dei rappresentanti dei pazienti, le politiche per l'applicazione delle raccomandazioni, e le dichiarazioni di indipendenza editoriale.

•Le migliori linee guida analizzate sono quelle prodotte dallo Scottish Intercollegiate Guidelines Network, dal New Zealand Guidelines Group, dal National Health care system e dall' Institute for Clinical System improvement.

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CONCLUSIONI del lavoro

Le linee guida analizzate convergono relativamente alle raccomandazioni da adottare:

1) Sottoporre al test individui ad alto rischio sulla base della storia familiare, clinica, o di un alto punteggio ottenuto con BOADICEA o BRCAPRO.
2) E' auspicabile l'effettuazione di una consulenza genetica pre e post test.
3) Un test predittivo andrebbe offerto ai familiari di un soggetto portatore di mutazione.
4) Agli individui portatori di mutazione andrebbero consigliati interventi di prevenzione secondaria.

Grazie dell’attenzione