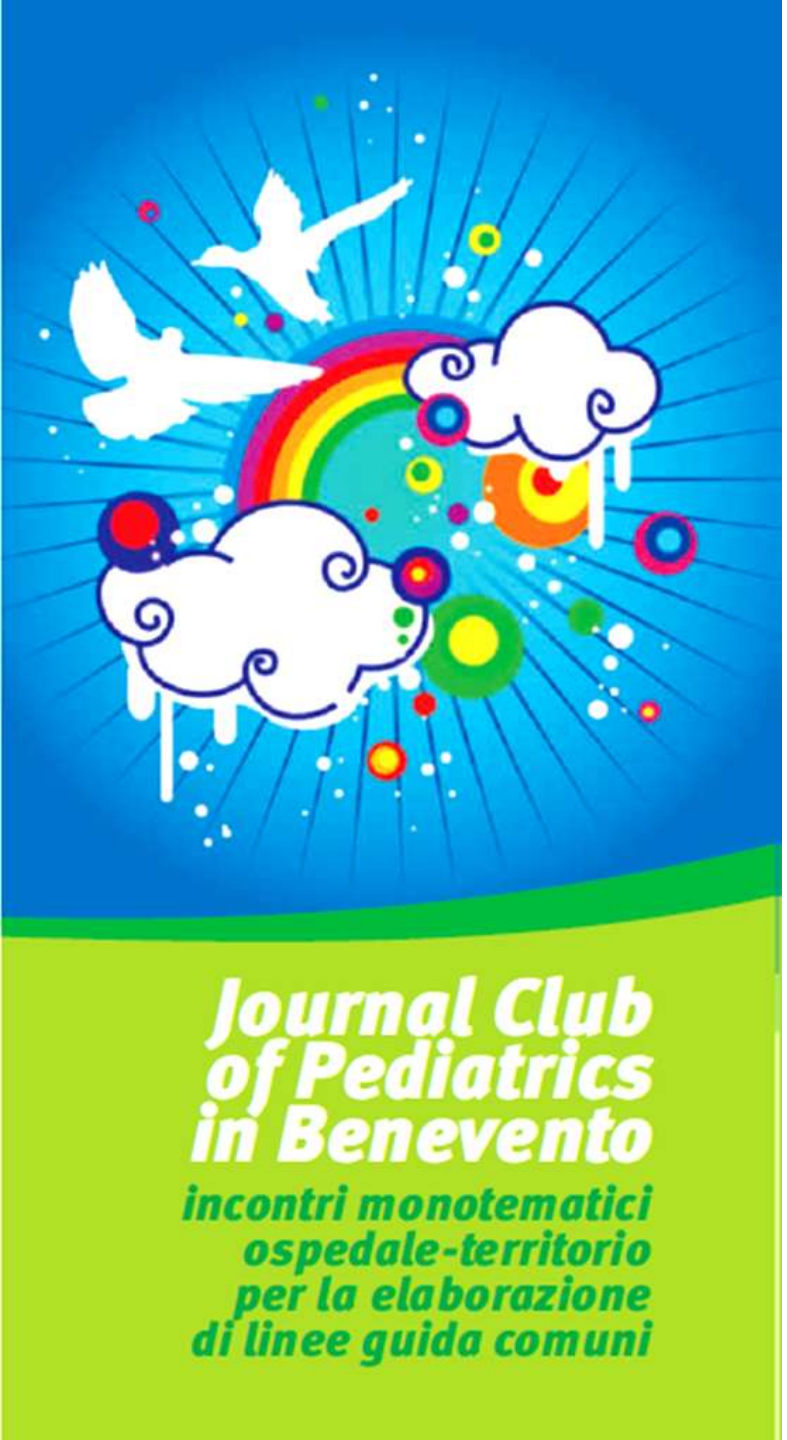


Allergologia

Pillola di EBM

Diagnosi di Allergia all'uovo

E' possibile evitare il Test di Provocazione Orale?

Maria Carmen Verga

24 maggio 2014

Scenario clinico

Andrea è un lattantino di 9 mesi.

LM dalla nascita. **Al 6° mese** di vita **aggiunta, in due occasioni, di ½ tuorlo d'uovo cotto nella pappa senza alcun problema**.

A 9 mesi, **dopo assunzione di uovo sodo intero**, dopo circa **mezz'ora manifesta orticaria generalizzata ed edema dei padiglioni auricolari**.

Da allora il pediatra ha **consigliato di eliminare l'uovo dalla dieta del bambino + latte materno con dieta libera della nutrice**.

Consulenza e test allergologici

Istamina	4 mm
Estratto di albume SPT	6 mm
Albume fresco PbP	15 mm
Uovo crudo IgEs	5 KU/l
Altri test	negativi

E' necessario confermare la diagnosi di allergia all'albume con il Test di Provocazione Orale (TPO)?

Modificato da Anna Maria Bianchi

Quesito clinico strutturato

Popolazione, paziente, problema: *In un lattante con storia suggestiva di reazione allergica (reazione IgE-mediata dopo circa 30 minuti dall'ingestione dell'alimento)*

Eventi/Test: *gli SPT e le IgEs positivi*

Confronto: *rispetto al Test di Provocazione Orale*

Outcome, esito: *consentono di confermare la diagnosi di allergia alimentare?*

Cercare la risposta

1. Definire il tipo di quesito

4 fondamentali, relativi a:

Terapia: determinare l'effetto di differenti trattamenti nel migliorare le condizioni del paziente o evitare eventi avversi

Fattori di rischio: Valutare l'effetto dell'esposizione ad un fattore di rischio sulle condizioni del paziente, sulla morbidità e sulla mortalità

Diagnosi: Determinare la capacità di un test diagnostico nel discriminare i soggetti che hanno o non hanno la patologia o la condizione *target*

Prognosi: Valutare la capacità di un determinato fattore di modificare la prognosi di un esito target. L'esposizione è il tempo.

Ricercare le evidenze scientifiche
Due principi

1. La gerarchia delle evidenze
2. La saturazione teoretica

1. La gerarchia delle evidenze



2. La saturazione teoretica o teorica



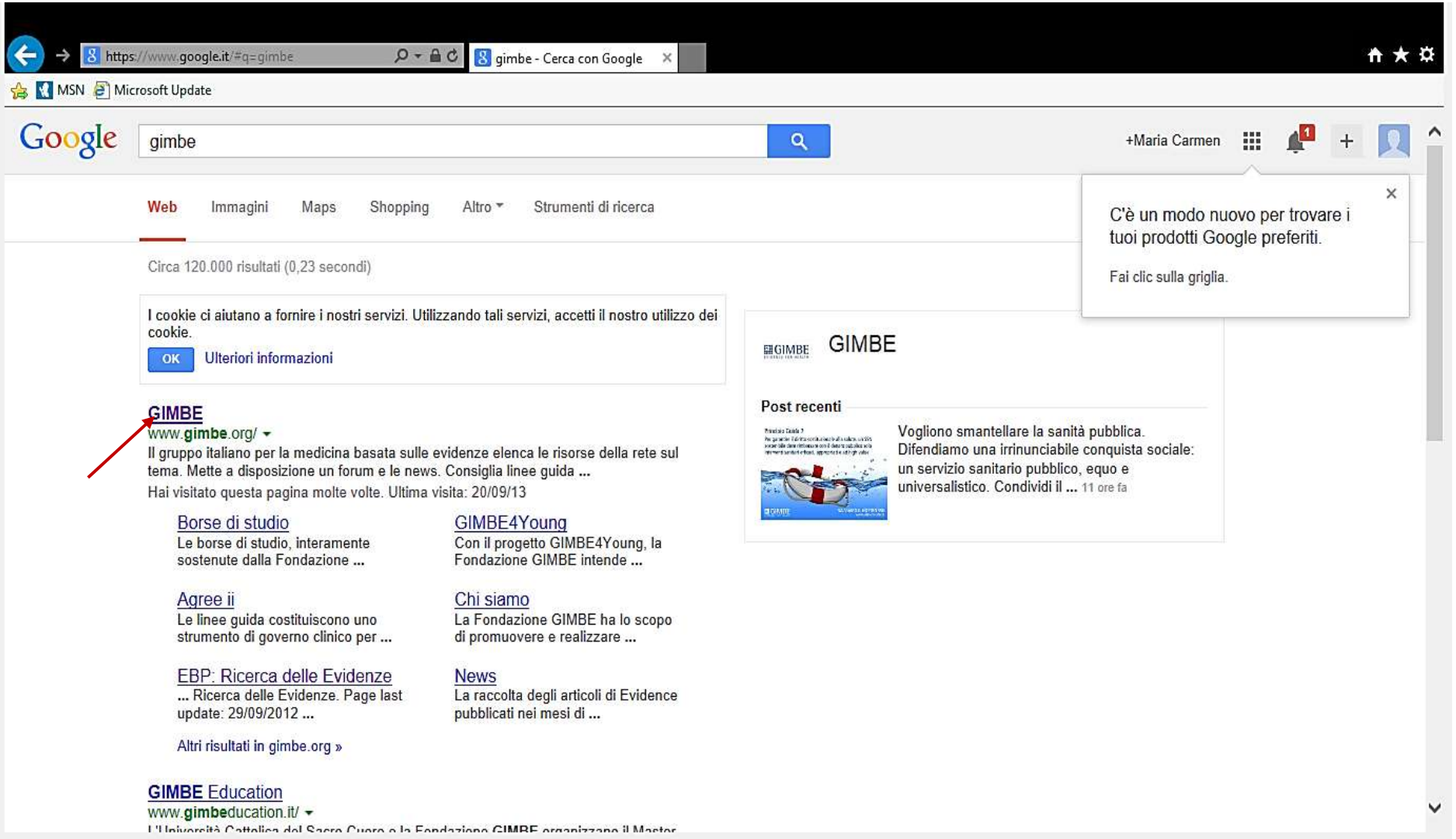
Il principio che guida questa procedura è quello della saturazione teorica per il quale si decide di sospendere il processo di incremento della base empirica quando il contributo che potrebbe essere ottenuto dall'aggiunta di un altro caso potrebbe essere nullo.

Nella ricerca delle evidenze scientifiche comporta **l'interruzione di ulteriori ricerche su evidenze meno valide** (es. case report, studi osservazionali o non randomizzati) **se già si sono trovate evidenze più rilevanti ed esaustive** (es. RCT ben disegnati e ben condotti)

***1. GIMBE** (Gruppo Italiano di Medicina Basata sulle Evidenze); Getting evidence;*
***BD Linee Guida**: NICE, SIGN, National Guideline Clearinghouse, CMA Infobase, NZ Guideline Group, Prodigy, PNLG*

***2. PubMed** http://www.ncbi.nlm.nih.gov/pubmed*
Clinical Queries
Stringa di ricerca: "(food hypersensitivity children OR egg allergy) AND diagnosis AND guidelines"
Filters activated: Practice Guideline, Guideline, published in the last 5 years.

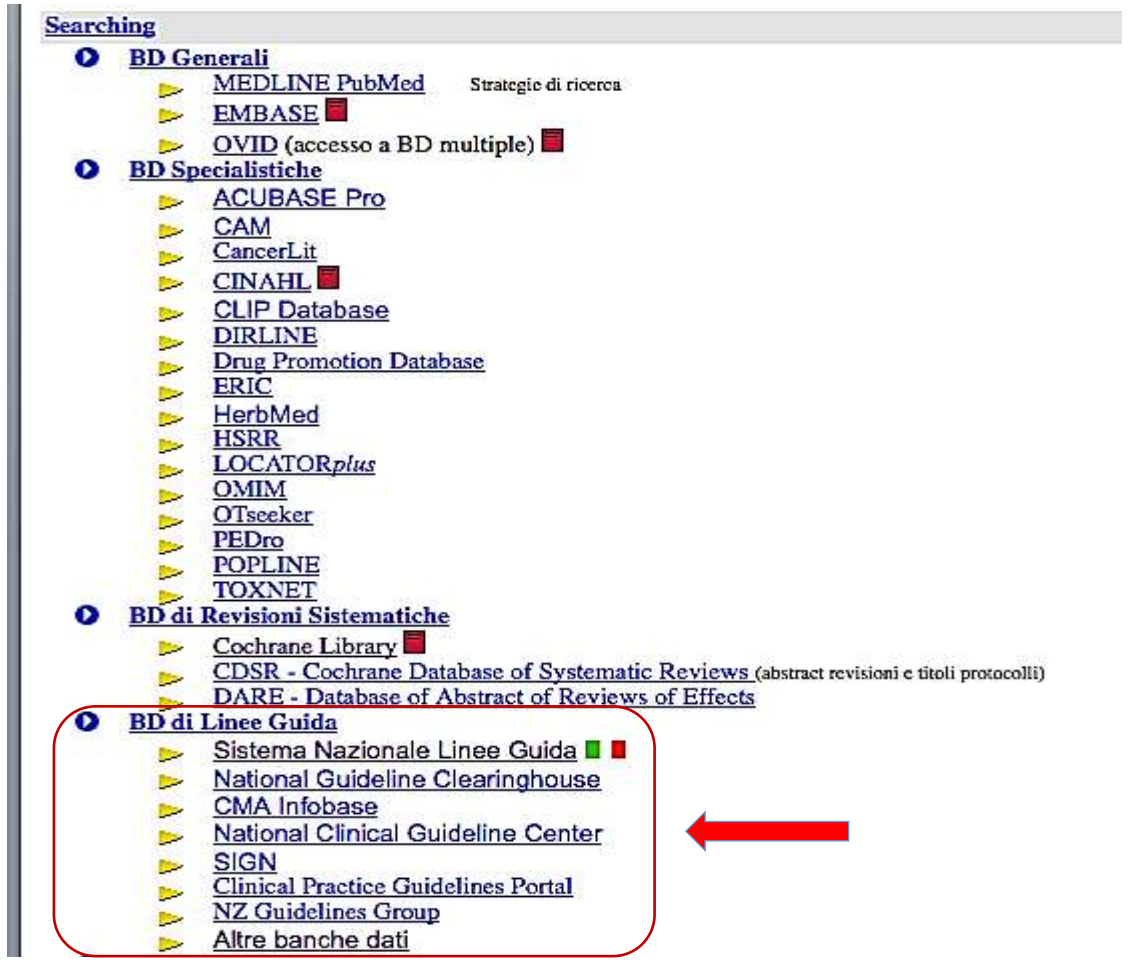
3. Società scientifiche
SIAIP http://www.siaip.it/show/Linee%20guida/8
EAACI http://www.eaaci.org/resources/food-allergy-and-anapyhlaxis-guidelines.html
AAP http://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Pages/Committee-On-Nutrition.aspx


https://www.google.it/#q=gimbe
gimbe - Cerca con Google
MSN
Microsoft Update
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gimbe
+Maria Carmen
C'è un modo nuovo per trovare i tuoi prodotti Google preferiti.
Fai clic sulla griglia.
Web
Immagini
Maps
Shopping
Altro
Strumenti di ricerca
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Il gruppo italiano per la medicina basata sulle evidenze elenca le risorse della rete sul tema. Mette a disposizione un forum e le news. Consiglia linee guida ...
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Gli interventi del Presidente sul Sole 24 Ore Sanità
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Portale destinato all'aggiornamento continuo di tutti i professionisti sanitari che fornisce:
Banca dati in lingua italiana delle migliori evidenze scientifiche selezionate dalla letteratura internazionale secondo criteri espliciti; per ciascun articolo viene fornito un abstract strutturato integrato da un commento metodologico.
Accesso a riviste e banche dati biomediche
(già Getting Evidence)
evidence
Diagnosi e terapia della malattia tromboembolica
La malattia tromboembolica (MTE) spazia da forme asintomatiche di trombosi venosa profonda (TVP) a casi fatali di embolia polmonare (EP). Anche le forme non fatali di MTE possono determinare gravi conseguenze a lungo termine,
GIMBE Solutions presto online
Soluzioni personalizzate a criticità, sfide e nuove esigenze di organizzazioni sanitarie pubbliche e private per favorire l'integrazione delle migliori evidenze scientifiche nelle decisioni manageriali e di politica sanitaria e garantire la qualità dell'assistenza sanitaria, rispettando il vincolo delle risorse

GIMBE
EVIDENCE FOR HEALTH

Banche Dati di Linee Guida

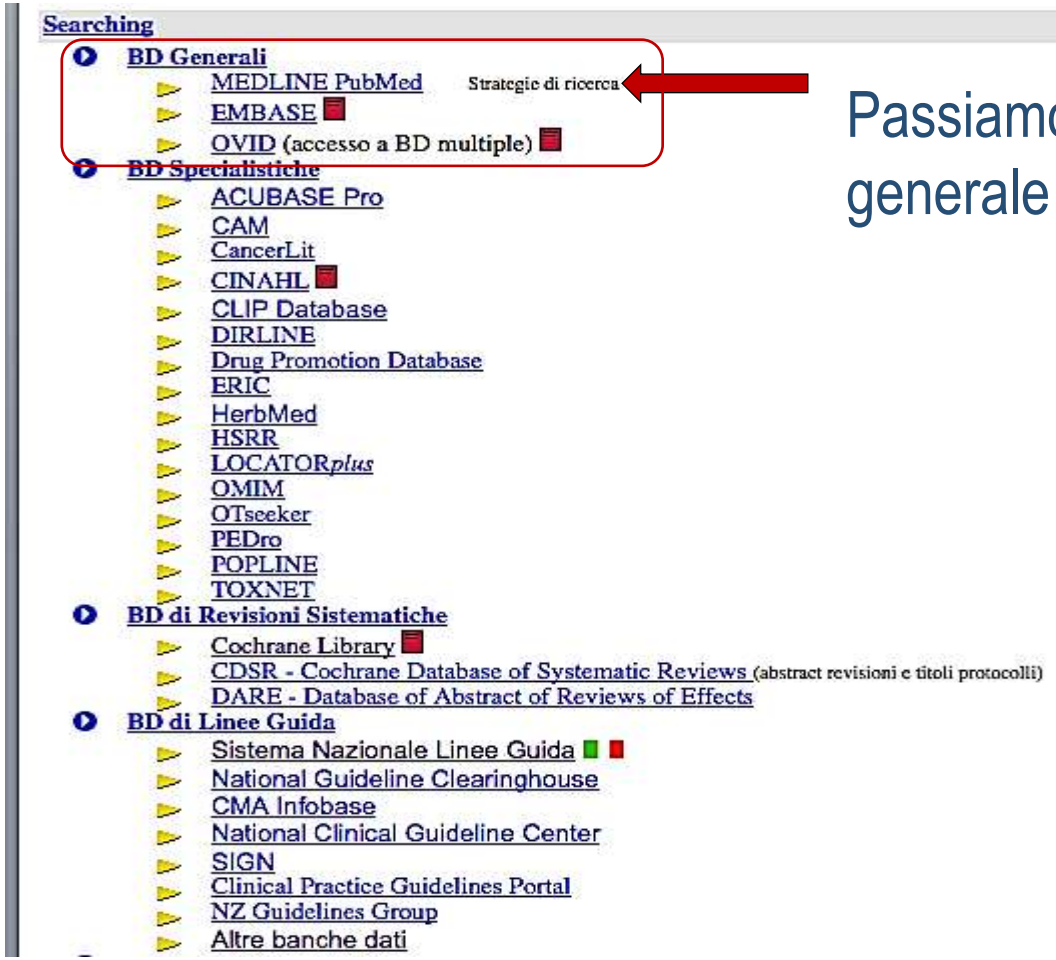


1. Food allergy in children and young people. Diagnosis and assessment of food allergy in children and young people in primary care and community settings
National Institute for Health and Clinical Excellence
NICE clinical guideline 116. 2011

2. Linee guida diagnostiche e terapeutiche per reazioni avverse ad alimenti
SNLG-Regioni – regione Toscana - Linee guida per la diagnosi e la cura delle allergopatie 2011

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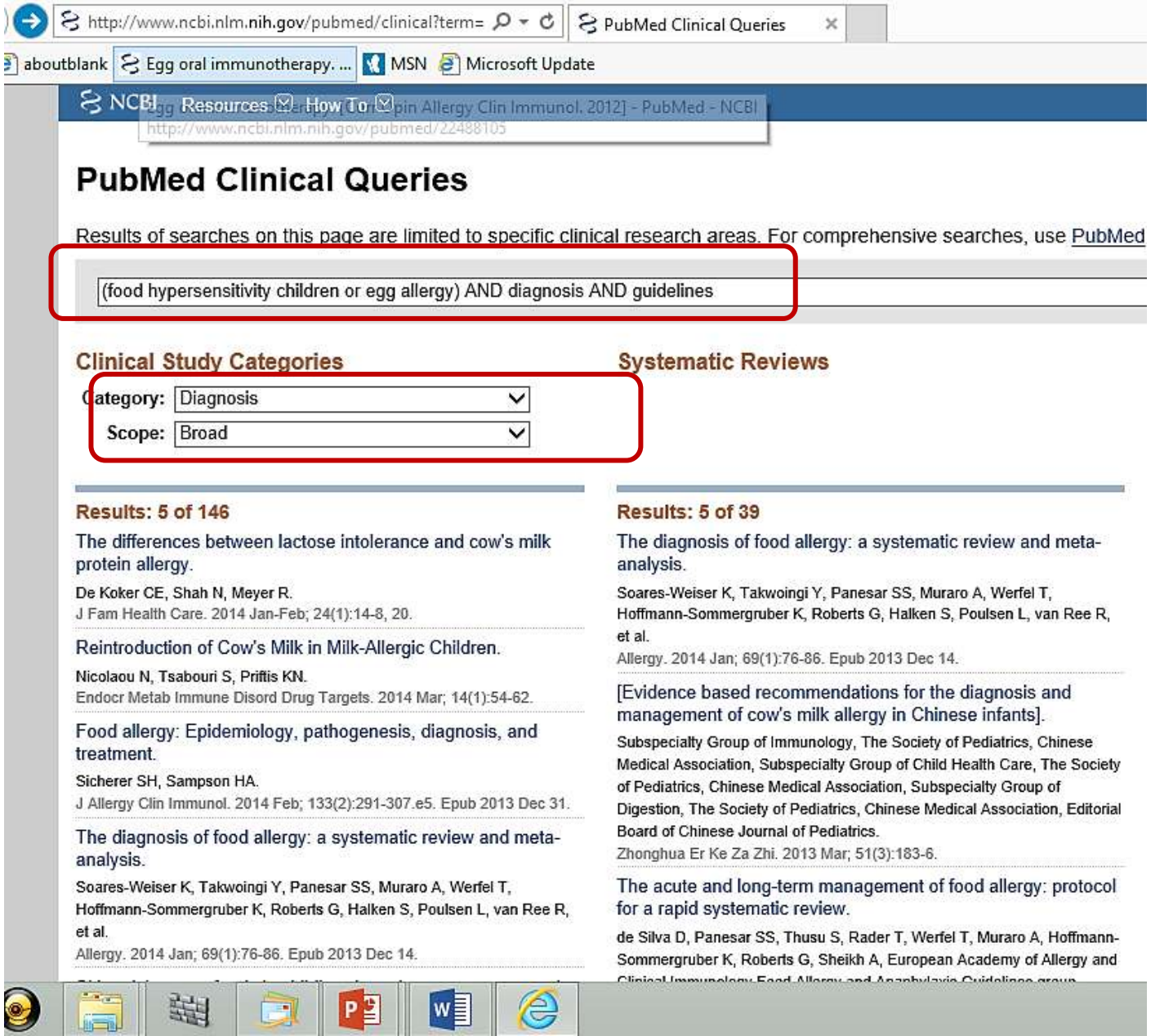
Gruppo Italiano Medicina Basata sull'Evidenza

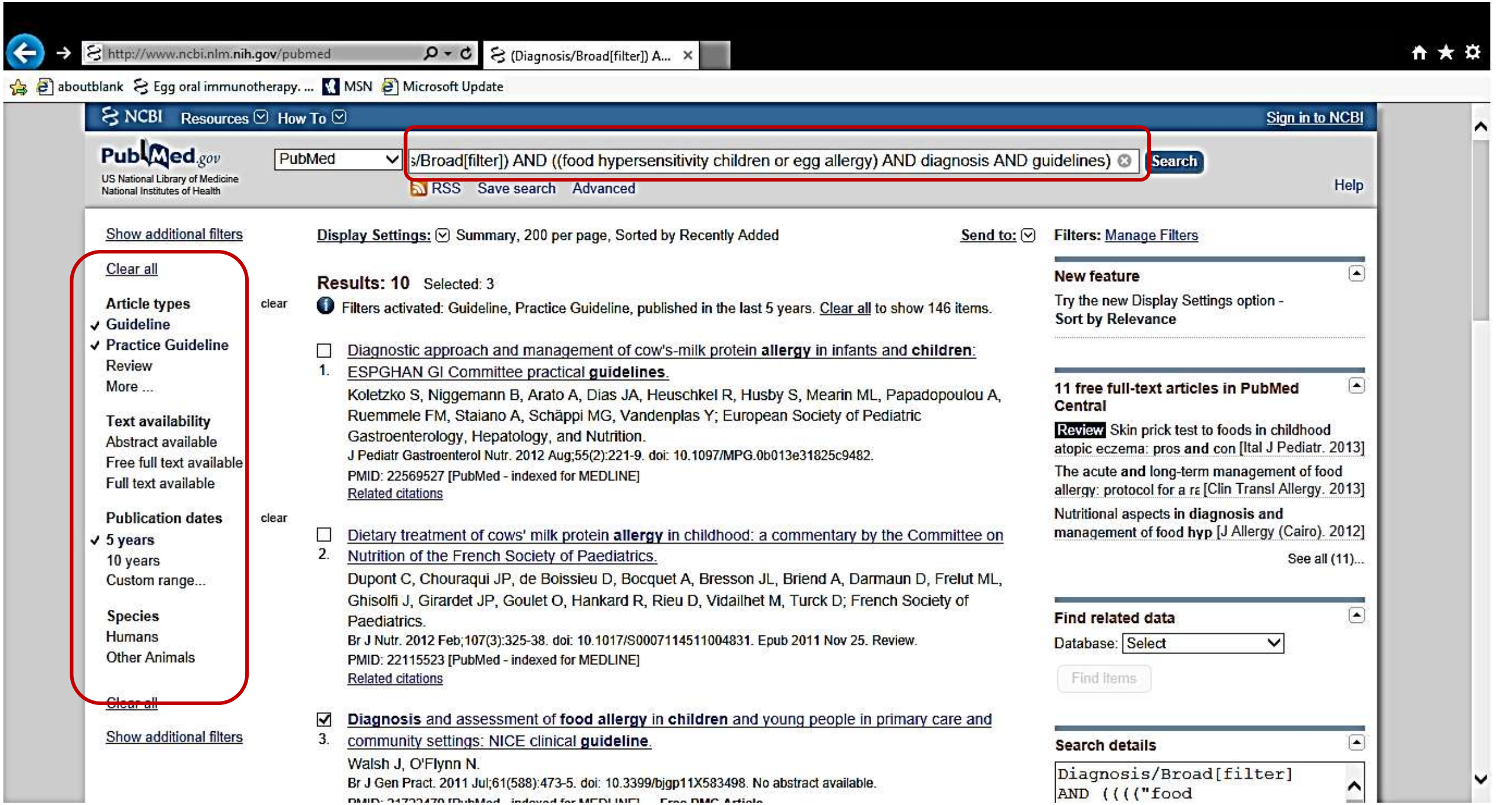


Passiamo alla Banca Dati generale di MedLine, **PubMed**

PubMed - Clinical Queries

Stringa di ricerca (food hypersensitivity children or egg allergy) AND diagnosis AND guidelines




http://www.ncbi.nlm.nih.gov/pubmed
(Diagnosis/Broad[filter]) A...
aboutblank
Egg oral immunotherapy. ...
MSN
Microsoft Update
NCBI Resources How To
Sign in to NCBI
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National Institutes of Health
PubMed
s/Broad[filter]) AND ((food hypersensitivity children or egg allergy) AND diagnosis AND guidelines)
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Show additional filters
Clear all
Article types
clear
Guideline
Practice Guideline
Review
More ...
Text availability
Abstract available
Free full text available
Full text available
Publication dates
clear
5 years
10 years
Custom range...
Species
Humans
Other Animals
Clear all
Show additional filters
Display Settings: Summary, 200 per page, Sorted by Recently Added
Send to:
Results: 10 Selected: 3
Filters activated: Guideline, Practice Guideline, published in the last 5 years. Clear all to show 146 items.
1. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines.
Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, Mearin ML, Papadopoulou A, Ruemmele FM, Staiano A, Schäppi MG, Vandenplas Y; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition.
J Pediatr Gastroenterol Nutr. 2012 Aug;55(2):221-9. doi: 10.1097/MPG.0b013e31825c9482.
PMID: 22569527 [PubMed - indexed for MEDLINE]
Related citations
2. Dietary treatment of cows' milk protein allergy in childhood: a commentary by the Committee on Nutrition of the French Society of Paediatrics.
Dupont C, Chouraqui JP, de Boissieu D, Bocquet A, Bresson JL, Briend A, Darmaun D, Frelut ML, Ghisolfi J, Girardet JP, Goulet O, Hankard R, Rieu D, Vidailhet M, Turck D; French Society of Paediatrics.
Br J Nutr. 2012 Feb;107(3):325-38. doi: 10.1017/S0007114511004831. Epub 2011 Nov 25. Review.
PMID: 22115523 [PubMed - indexed for MEDLINE]
Related citations
3. Diagnosis and assessment of food allergy in children and young people in primary care and community settings: NICE clinical guideline.
Walsh J, O'Flynn N.
Br J Gen Pract. 2011 Jul;61(588):473-5. doi: 10.3399/bjgp11X583498. No abstract available.
Filters: Manage Filters
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11 free full-text articles in PubMed Central
Review Skin prick test to foods in childhood atopic eczema: pros and con [Ital J Pediatr. 2013]
The acute and long-term management of food allergy: protocol for a ra [Clin Transl Allergy. 2013]
Nutritional aspects in diagnosis and management of food hyp [J Allergy (Cairo). 2012]
See all (11)...
Find related data
Database: Select
Find items
Search details
Diagnosis/Broad[filter]
AND ((((("food

1. **Diagnosis** and assessment of **food allergy** in **children** and young people in primary care and community settings: NICE clinical **guideline**

Walsh J, O'Flynn N.

Br J Gen Pract. 2011 Jul;61(588):473-5

2. **Guidelines** for the **diagnosis** and management of **food allergy** in the United States: report of the NIAID-sponsored expert panel.

NIAID-Sponsored Expert Panel, Boyce JA,.

J **Allergy** Clin Immunol. 2010 Dec;126(6 Suppl):S1-58

3. British Society for **Allergy** and Clinical Immunology **guidelines** for the management of **egg allergy**.

Clark AT; British society for **Allergy** and Clinical Immunology.

Clin Exp **Allergy**. 2010 Aug;40(8):1116-29

Società scientifiche
SIAIP, EAACI, AAP

EAACI Food Allergy and Anaphylaxis Guidelines
Primary prevention of food allergy 30.3.2013
http://www.eaaci.org/resources/food-allergy-and-anapyhlaxis-guidelines.html

Facciamo ora l'analisi qualitativa delle 5 LG selezionate, basandoci essenzialmente sui

3 criteri fondamentali

1. Multidisciplinarietà del Panel degli estensori
2. Ricerca sistematica delle Evidenze
3. Grading delle raccomandazioni

LG escluse

Non rispondono ai criteri minimi di validità

BSACI 2010	No multidisciplinarietà Ricerca delle evidenze non esplicitata No GRADING
LG Toscana 2011	NO multidisciplinarietà Ricerca non esplicitata e non esaustiva

Le raccomandazioni delle LG incluse

Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel

2010

Notably, the new US Guidelines are specifically aimed at all health care professionals who care for adult and pediatric patients with FA and related comorbidities. Thus, it is hoped that these Guidelines will have broad impact and benefit for all health care professionals.

TABLE I. Prevalence of allergy to peanut, milk, egg, fish, and crustacean shellfish[30]

Diagnostic criteria	Overall prevalence	Peanut	Milk	Egg	Fish	Crustacean shellfish
Self-reported symptoms: Children	12%					
Self-reported symptoms: Adults	13%					
Self-reported symptoms: All ages		0.6%	3%*	1%	0.6%	1.2%
Symptoms plus SPT or serum IgE: All ages	3%	0.75%	0.6%	0.9%	0.2%	0.6%
Food challenge: All ages	3%	NE	0.9%	0.3%	0.3%	NE

NE, Not estimated; *SPT*, skin prick test.

4.2.2.1. Skin prick test.

Guideline 4: The EP recommends performing an SPT (also known as a skin puncture test) to assist in the identification of foods that may be provoking IgE-mediated food-induced allergic reactions, but the SPT alone cannot be considered diagnostic of FA.

Rationale: SPTs are safe and useful for identifying foods potentially provoking IgE-mediated food-induced allergic reactions, but they have a low positive predictive value for the clinical diagnosis of FA.

…uno SPT aiuta ad identificare gli alimenti probabilmente responsabili
…, ma da solo non può essere considerato diagnostico di AA.
…hanno un basso VPP per la diagnosi clinica di AA.

4.2.2.4. *Allergen-specific serum IgE.*

Guideline 7: The EP recommends sIgE tests for identifying foods that potentially provoke IgE-mediated food-induced allergic reactions, but alone these tests are *not* diagnostic of FA.

Rationale: sIgE tests are useful for identifying foods potentially provoking IgE-mediated food-induced allergic reactions, and specified "cutoff" levels, defined as 95% predictive values, may be more predictive than SPTs of clinical reactivity in certain populations, but when used alone they are not diagnostic of FA.

Balance of benefits and harms: sIgE tests are very useful for

…raccomanda la ricerca delle IgEs per identificare gli alimenti probabilmente responsabili

…, ma da solo non può essere considerato diagnostico di AA.

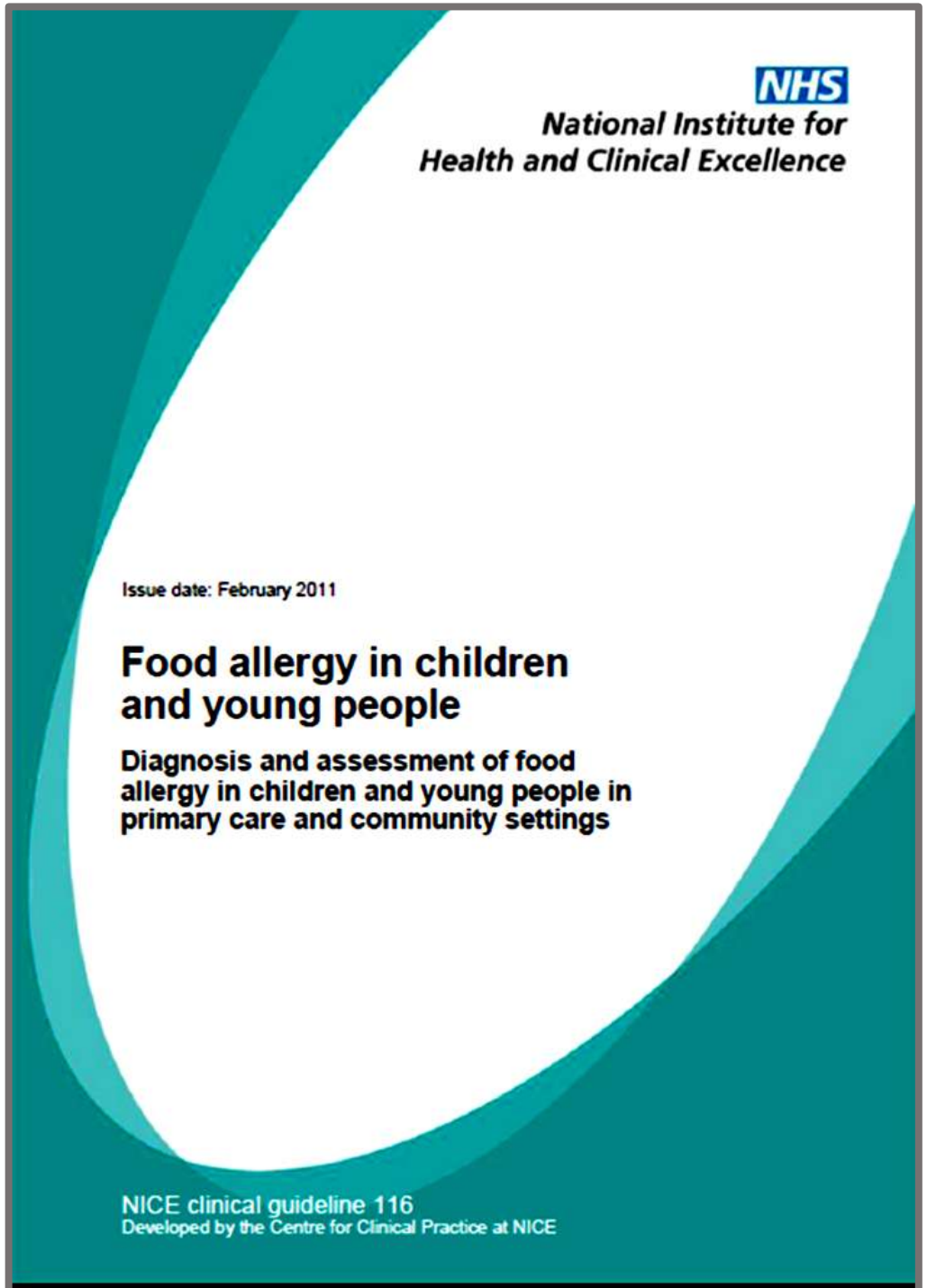
…specifici valori di cut-off, definiti come VPP al 95%, possono essere più predittivi degli SPT in alcune popolazioni, ma, quando usati da soli, non sono diagnostici di AA.

4.2.2.8. *Oral food challenges.*

Guideline 11: The EP recommends using oral food challenges for diagnosing FA. The DBPCFC is the gold standard. However, a single-blind or an open-food challenge may be considered diagnostic under certain circumstances: if either of these challenges elicits no symptoms (ie, the challenge is negative), then FA can be ruled out; but when either challenge elicits objective symptoms (ie, the challenge is positive) *and* those objective symptoms correlate with medical history *and* are supported by laboratory tests, then a diagnosis of FA is supported.

…raccomanda il TPO per diagnosticare l'AA.

Il DBPCFC è il gold standard



NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appendix 1.0

SCOPE

1 Guideline title

Diagnosis and assessment of food allergy in children and young people in primary care and community settings

IgE-mediated food allergy

1.1.5 Based on the results of the allergy-focused clinical history, if IgE-mediated allergy is suspected, offer the child or young person a skin prick test and/or blood tests for specific IgE antibodies to the suspected foods and likely co-allergens

Se si sospetta un'allergia IgE-mediata praticare SPT e/o IgEs

1.1.10 Do not use atopy patch testing or oral food challenges to diagnose IgE-mediated food allergy in primary care or community settings.

Non praticare APT o TPO in setting ambulatoriali di 1° livello

- diagnostic process, which may include:
  - an elimination diet followed by a possible planned rechallenge or initial food reintroduction procedure
  - skin prick tests and specific IgE antibody testing, including the safety and limitations of these tests
  - referral to secondary or specialist care.

L'iter diagnostico deve includere:
- Dieta di eliminazione seguita da un possibile programma di riesposizione o di reintroduzione dell'alimento
- SPT e IgEs
- Invio ad un centro specialistico di 2° livello

GRADE profile 1 The diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated allergy to hens' eggs

Studies	Outcome: diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated allergy to hens' eggs Evaluation of 18 individual studies for allergy to hens' eggs	Diagnostic test	Limitations*	Inconsistency*	Indirectness	Imprecision*	Other considerations*	Quality
Sixteen studies (Vierrucci et al. 1989, Niggemann et al. 2002, Dieguez et al. 2008, Hill et al. 2004, Sampson et al. 1998, Eigenmann & Sampson 1998, Roehr et al. 2001, Dieguez et al. 2009, Verstege et al. 2005, Mehl et al. 2006, Caffarelli et al. 1995, Hansen et al. 2004, Knight 2006, Canani et al. 2007, Osterballe et al.2004, Monti et al. 2002)	Sensitivities ranged from 57.8% to 100% Specificities ranged from 20% to 99% Positive predictive values ranged from 40% to 93%. Negative predictive values ranged from 50% to 100%	Skin prick test	Y	Y	N	Y	Y	Very Low
Eleven studies (Vierrucci et al. 1989, Sampson et al. 1998, Roehr et al. 2001, Celik-Bilgili et al. 2005, Dieguez et al.2009, Mehl et al. 2006, Ando et al. 2008, Caffarelli et al. 1995, Knight et al. 2006, Canani et al. 2007, Osterballe et al. 2004)	Sensitivities ranged from 31.5% to 100% Specificities ranged from 20% to 69% Positive predictive values ranged from 40% to 84%. Negative predictive values ranged from 50% to 100%	IgE	Y	Y	N	Y	Y	Very low

Setting di Centri di ricerca e specialistici di 3° livello!

Riduzione della prevalenza ad ¼ >>>> riduzione del VPP a ~ ½.

1.1.14 If a food elimination diet is advised as part of the diagnostic process (see recommendation 1.1.11), offer the child or young person and their parent or carer, taking into account socioeconomic status and cultural and religious issues, information on:

- when, where and how an oral food challenge or food reintroduction procedure may be undertaken
- the safety and limitations of the oral food challenge or food reintroduction procedure.

3.4 *Values of skin prick testing and specific IgE antibody testing and their predictive value*

and would reduce patient risk. There are published data available from the US, Australia and Europe, but allergists argue that these cut-off points are population-specific and should not be used in the UK.

Tuttavia…

tra i criteri di accesso al 2° livello ***manca l'indicazione al TPO***

2.6.4 Recommendations

Recommendation 1.1.17

Based on the allergy-focused clinical history, consider referral to secondary or specialist care in any of the following circumstances.

- The child or young person has:
  - faltering growth in combination with one or more of the gastrointestinal symptoms described in recommendation 1.1.1
  - not responded to a single-allergen elimination diet
  - had one or more acute systemic reactions
  - had one or more severe delayed reactions
  - confirmed IgE-mediated food allergy and concurrent asthma
  - significant atopic eczema where multiple or cross-reactive food allergies are suspected by the parent or carer.
- There is:
  - persisting parental suspicion of food allergy (especially in children or young people with difficult or perplexing symptoms) despite a lack of supporting history
  - strong clinical suspicion of IgE-mediated food allergy but allergy test results are negative
  - clinical suspicion of multiple food allergies.



These guidelines aim to provide evidence-based recommendations from around 100 authors and ***expert panel members*** *representing* ***a range*** *of* ***European countries****, and* ***disciplinary*** *and* ***clinical backgrounds*** *(including medical and nursing, hospital and primary care), and patient groups.*

…

Therefore, the 51 target audience is ***health care professionals*** *(e.g. medical doctors, nurses, 52 pharmacists and paramedics) who are involved in the diagnosis and management of 53 food allergy, taking care of these patients in* ***emergency departments, hospital and 54 primary care***

Table 2: Food-induced allergic disorders (classified based on the underlying immunopathology)

Immunopathology	Disorder	Clinical features	Typical age group	Prognosis
IgE mediated	Urticaria/ angioedema	Triggered by ingestion or direct contact	Children > adults	Depends on food

Diagnostic tests for food allergy

The tests should be undertaken after a careful history/clinical assessment. Determination of in vivo SPT and sIgE for food allergens are the first line tests to assess IgE sensitization. However, it is well known that neither the patient history nor the measurement of sensitization by itself can accurately diagnose food allergy. Elimination diet for diagnostic purposes (D) and oral food challenges are still required both for IgE and non-IgE mediated food allergy in order to define the clinical relevance of the initial investigations. For some clinical manifestations such as food-

In our systematic review we found reasonable sensitivity (70-100%), (although less for most plant food allergies) but moderate specificity (40-70%) both for sIgE and SPT using the DBPCFC as a reference test (9). Sensitivity and specificity of serum

clinical relevant allergy and tolerance. Raising the cut-off levels improves specificity for some foods but that cannot replace oral challenges for the diagnosis of food allergy. The estimation of likelihood ratios of history, sensitization and clinical

- SPT e IgEs sono i tests di prima linea
- Né la storia clinica, né la sensibilizzazione possono consentire di diagnosticare un'AA.
- Sono tuttora richiesti dieta di eliminazione per fini diagnostici e TPO

- Negli studi di confronto con il GS (DBPCFC):

sensibilità = 70-100%
specificità = 40-70%

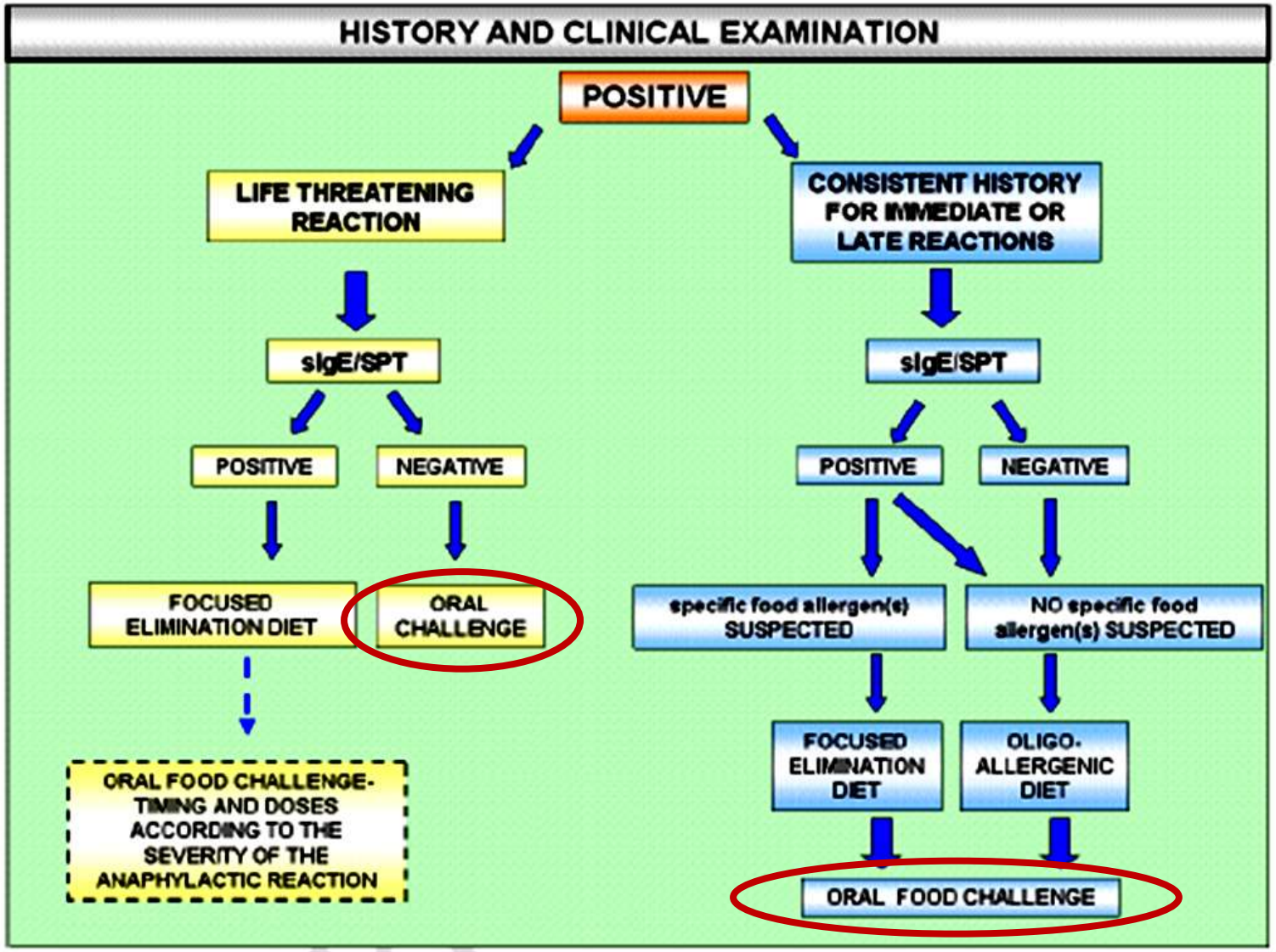
9. Soares-Weiser K, et al. Diagnosis of Food Allergy: a systematic review. In; 785 2013.

- Aumentando il livello di cut-off migliora la specificità per qualche alimento, ma **ciò non consente di sostituire il TPO**

Raccomandazioni

IgE sensitization to common food and appropriate aeroallergens is determined by SPT and serum IgE tests are used as a support to the diagnosis of food allergy by clinical history and/or food challenge.	I-III*	A-C	Soares-Weiser Systematic Review 2013(9)
If clinical history combined with SPT and/or sIgE results are not *highly predictive* (see figure 1), an OFC is required.	IV	D	Expert Opinion
Where the elimination diet leads to a significant relief of symptoms, it should be continued until the provocation test is performed.	V	D	Expert Opinion
D- Oral food challenge (OFC)			
The OFC (particularly the double-blind placebo-controlled food challenge) is the gold standard investigation for the objective diagnosis of IgE-and non-IgE mediated food allergy.	IV	D	Expert Opinion
OFC's should be used to demonstrate allergy or tolerance and in so doing facilitate safe dietary expansion or appropriate allergen avoidance.	IV	D	Expert Opinion

Figure 1 Algorithm on the diagnosis of food allergy



Tuttavia…

In appendice…

		Likelihood of clinical allergy from specific IgE (KU/L) or SPT (mm) results		
		Low (<0.35 or <3)	**Intermediate** (0.35 to <15 or 3 to <8)	**High** (≥15 or ≥8)
Likelihood of clinical allergy from history	**High** eg urticaria and wheeze on 2 exposures	Possible allergy	Probable allergy	Allergy
	Intermediate eg urticaria on a single exposure	Possible allergy	Possible allergy	Probable allergy
	Low eg non-IgE symptoms	No allergy	Possible allergy	Possible allergy

Children and adolescents in the possible allergy box require an OFC for a definitive diagnosis. Specific IgE and SPT values are specific for peanuts. Values associated with a high likelihood of clinical allergy are lower for egg, milk and fish Modified from Stiefel G, Roberts G. How to use serum specific IgE measurements in diagnosing and monitoring food allergy. Arch Dis Child Educ Pract Ed 2012; 97: 29–36.

Table 3: Indications of oral challenge tests

Indication	Rationale
Demonstrate Allergy	Equivocal diagnostic outcome despite use of detailed clinical history and allergy testing.
	Suspected food allergic reaction for which the cause is uncertain despite allergy testing (e.g. composite meal eaten).
	Determine threshold dose of causative allergen source.

La valutazione di un test diagnostico



I criteri di validità di un test diagnostico

Sensibilità

Proporzione di persone con la malattia che risultano positive a test

es. sensibilità= 97% >>> Su 100 malati, 97 risultano positivi al test e 3 non vengono diagnosticati (falsi negativi)

Minore sensibilità >>> ↑ falsi negativi

Specificità

Proporzione di persone senza la malattia che risultano negative al test

es. specificità = 97% >>> Su 100 persone sane, 97 risultano negative al test e 3 risultano positivi (falsi positivi)

Minore specificità >>> ↑ falsi positivi

Può bastare? Sempre? In tutti i pazienti?

Caso n° 5

Mese di febbraio.

Bambino di 5 anni, moderatamente febbrile (t = 38°C), tonsille iperemiche aumentate di volume ma senza essudato, assenza di linfoadenopatia satellite, assenza di tosse.

E' in corso una piccola epidemia di infezioni streptococciche. Il bambino frequenta l'asilo, alcuni suoi compagni sono assenti da qualche giorno perché affetti da tonsillite streptococcica o scarlattina

Punteggio proposto da McIsaac = **3**

Segno/sintomo e età	**Punteggio**
Temperatura > 38° C	1
Assenza di tosse	1
Linfoadenopatia satellite	1
Essudato o aumento di volume tonsillare	1
Età 3-14 anni	1
Età 15 – 44 anni	0
Età > 44 anni	-1

Score di McIsaac e rischio di infezione streptococcica

Numero di segni e sintomi	Rischio di infezione streptococcica (%)
≥ 4	51-53
3	28-35
2	11-17
1	5-10
≤ 0	1-2.5

MA…

lo *score* non deve essere utilizzato in situazione di epidemia . In questo caso il rischio, potremmo anche dire la **Probabilità pre-test,** è senz'altro alto, superiore al 35% (70%? 80%?)

Test Rapido: Negativo

MA…

Se la probabilità pre-test è così alta, non sarà un falso negativo?

Dovrei confermare la negatività con l'esame colturale.

Quindi…

Quando c'è un basso rischio di infezione streptococcica, cioè la probabilità pre-test è bassa, attribuisco al test una validità abbastanza alta da non richiedere la conferma con l'esame colturale.

Quando c'è un alto rischio di infezione streptococcica, cioè la probabilità pre-test è alta, attribuisco al test una validità inferiore, tale da richiedere, in caso di test negativo, la conferma con l'esame colturale.

La validità di un test non è quindi un parametro fisso, ma varia in funzione del rischio di contrarre la malattia, cioè varia in funzione della probabilità pre-test

Ancora un po’ di terminologia

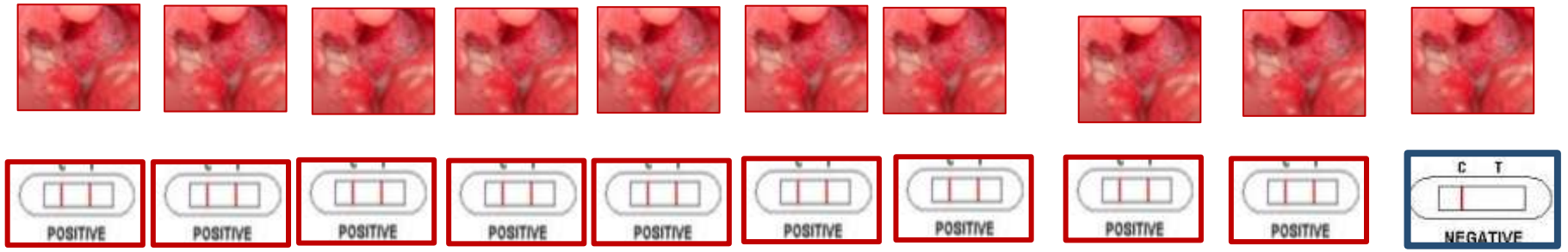
Valore Predittivo Positivo (VPP)

% di soggetti ammalati tra quelli che presentano un test positivo

Valore Predittivo Negativo (VPN)

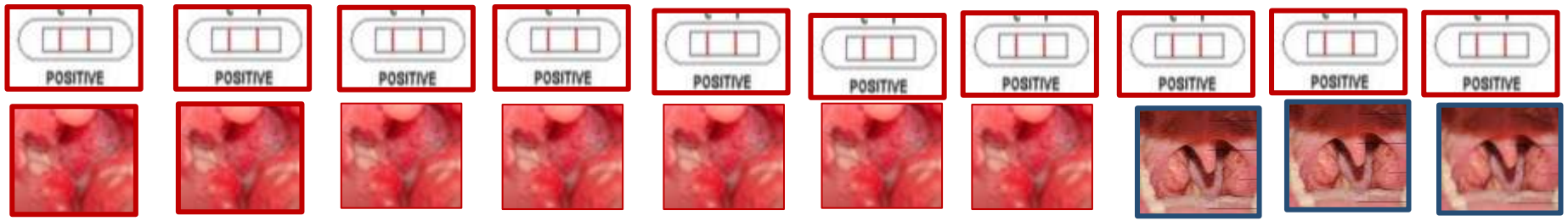
% di soggetti sani tra quelli che presentano un test negativo

La **sensibilità** parte dalla osservazione (dal n°) di tutti coloro che sono malati e su questi verifica quanti test risultano positivi ed in che percentuale. **Valuta la performance del test su pazienti che noi già sappiamo essere malati**



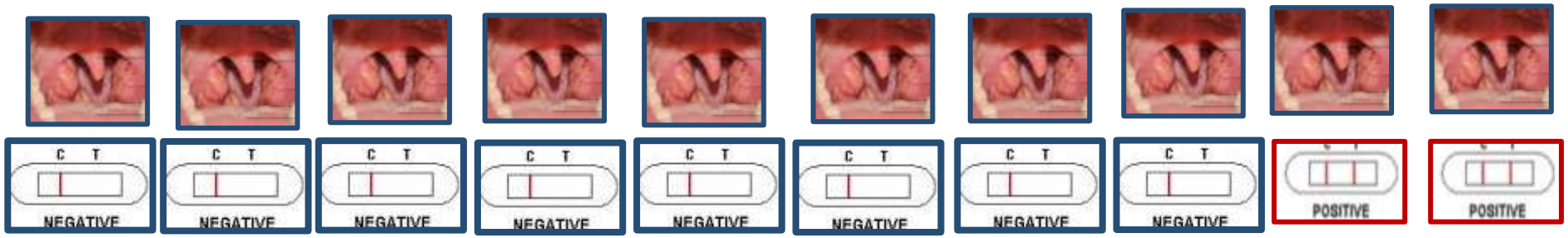
Sensibilità = 90% (10% falsi negativi)

Il **VPP** parte dalla osservazione (dal n°) di tutti coloro che hanno il test positivo e su questi verifica i veri portatori di malattia (il n° di malati). **Serve per diagnosticare la malattia nel paziente nella pratica clinica. Risente della prevalenza della malattia.**



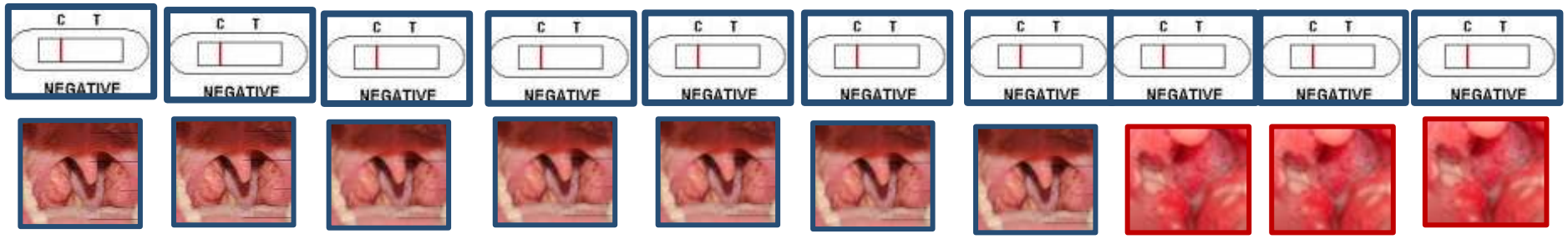
VPP = 70% (30% falsi positivi)

La **specificità** parte dalla osservazione (dal n°) di tutti coloro che sono sani e su questi verifica quanti test risultano negativi ed in che percentuale. **Valuta la performance del test su pazienti che noi già sappiamo essere sani**



Specificità = 80% (20% falsi positivi)

Il **VPN** parte dalla osservazione (dal n°) di tutti coloro che hanno il test negativo e su questi verifica i veri sani (il n° di sani) **Serve per escludere la malattia nel paziente nella pratica clinica. Risente della prevalenza della malattia.**



VPN = 70% (30% falsi negativi)

Un unico parametro per la valutazione di un test diagnostico

Per ogni test diagnostico possiamo definire più valori di validità in base alla probabilità pre-test di malattia.

Per semplificare, questi 2 parametri possono essere riuniti in 1.

Il rapporto di verosimiglianza (RV)

RV + (per il test positivo) : sens/ (1-spec) >>>> molto più grande di 1
RV- (per il test negativo) : (1-sens)/spec >>>> molto più piccolo di 1

>>>> è molto sensibile e molto specifico, quindi dà un'informazione spesso conclusiva ai fini della diagnosi

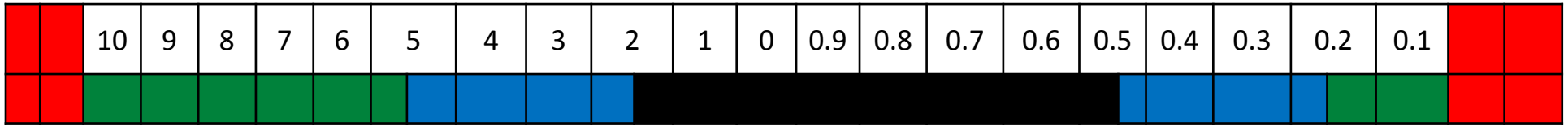
RV +/- = 1 >>> Il test non può cambiare la probabilità pre-test >>> non ci dà nessuna informazione in più >>> **non serve**

Likelihood ratios of >10 or < 0.1 generate large and often conclusive changes from pre- to post-test probability;

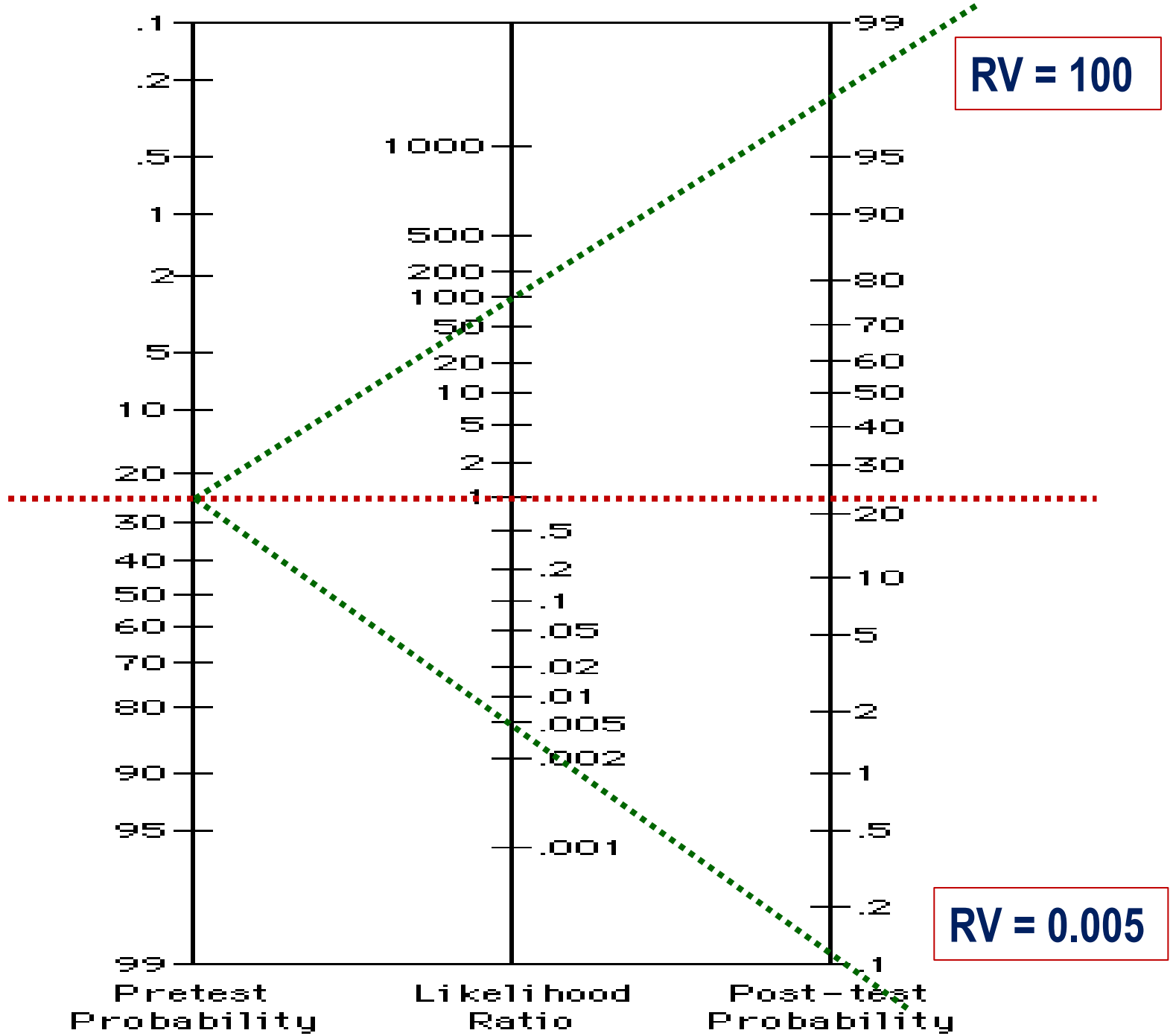
Likelihood ratios of 5–10 and 0.1–0.2 generate moderate shifts in pre- to post-test probability;

Likelihood ratios of 2–5 and 0.5–0.2 generate small (but sometimes important) changes in probability; and

Likelihood ratios of 1–2 and 0.5–1 alter probability to a small (and rarely important) degree.



Il nomogramma di Fagan



Affidabilità e validità di un test

Affidabilità di un test

capacità del test di offrire sempre lo stesso risultato nel corso di misurazioni ripetute

Validità di un test

capacità del test di distinguere in una popolazione i soggetti sani da quelli malati

Diagnostic Test Calculator

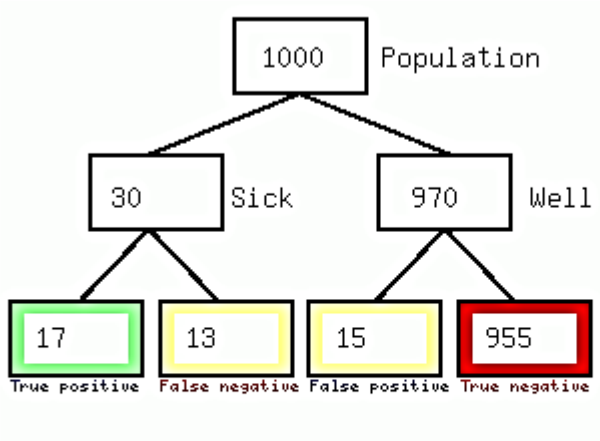
http://araw.mede.uic.edu/cgi-bin/testcalc.pl

disease after a positive or negative test.

Numbers of patients with and without the disease who test positive and negative:

	Disease present	Disease absent	Total
Test positive	17	15	32
Test negative	13	955	968
Total	30	970	1000

Compute



or
disease prevalence, test sensitivity, and test specificity (and, optionally, sample size):

Prevalence (e.g. 0.10)	0.030000
Sensitivity (e.g. 0.80):	0.557
Specificity (e.g. 0.80):	0.984
Total sample size:	

Compute

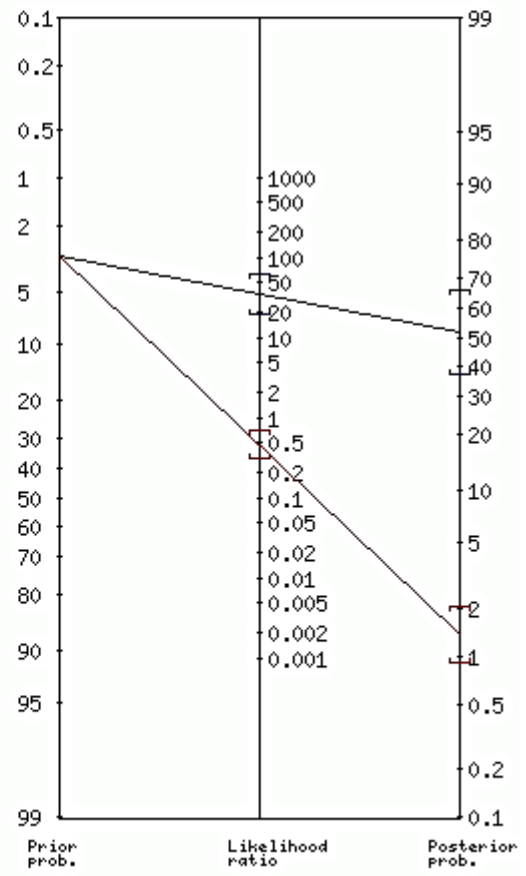
or
disease prevalence, positive likelihood ratio, and negative likelihood ratio (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.030000
+LR (e.g. 4):	35
-LR (e.g. 0.01):	0.45
Total sample size:	

Compute

Optional information:

Your local prevalence (e.g. 0.10):	0.03000(

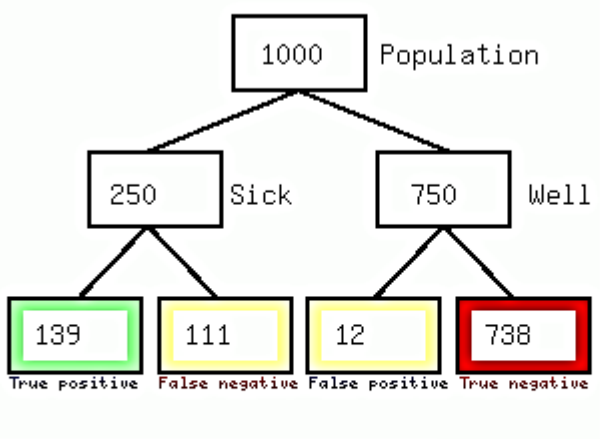


disease after a positive or negative test.

Numbers of patients with and without the disease who test positive and negative:

	Disease present	Disease absent	Total
Test positive	139	12	151
Test negative	111	738	849
Total	250	750	1000

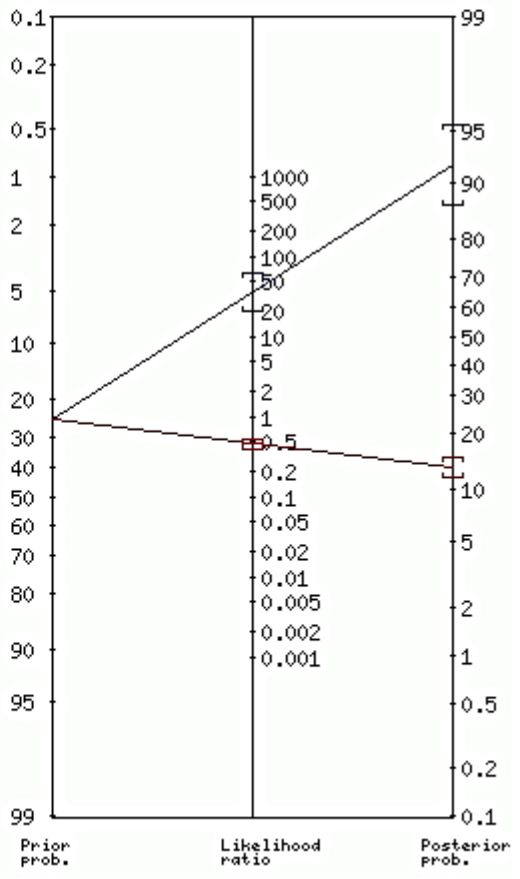
Compute



or
disease prevalence, test sensitivity, and test specificity (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.250000
Sensitivity (e.g. 0.80):	0.557
Specificity (e.g. 0.80):	0.984
Total sample size:	

Compute



or
disease prevalence, positive likelihood ratio, and negative likelihood ratio (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.250000
+LR (e.g. 4):	35
-LR (e.g. 0.01):	0.45
Total sample size:	

Compute

Optional information:

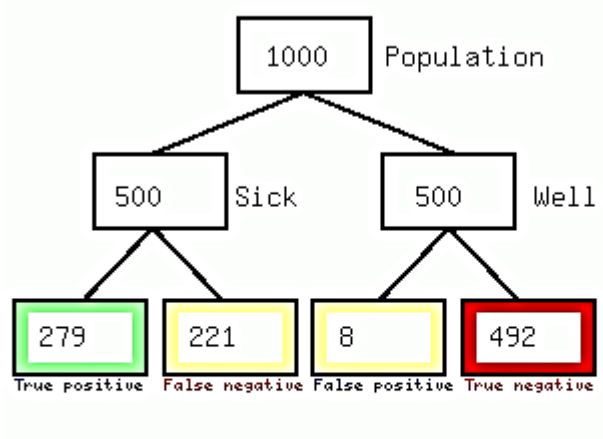
Your local prevalence (e.g. 0.10):	0.25000(

disease after a positive or negative test.

Numbers of patients with and without the disease who test positive and negative:

	Disease present	Disease absent	Total
Test positive	279	8	287
Test negative	221	492	713
Total	500	500	1000

Compute



or
disease prevalence, test sensitivity, and test specificity (and, optionally, sample size):

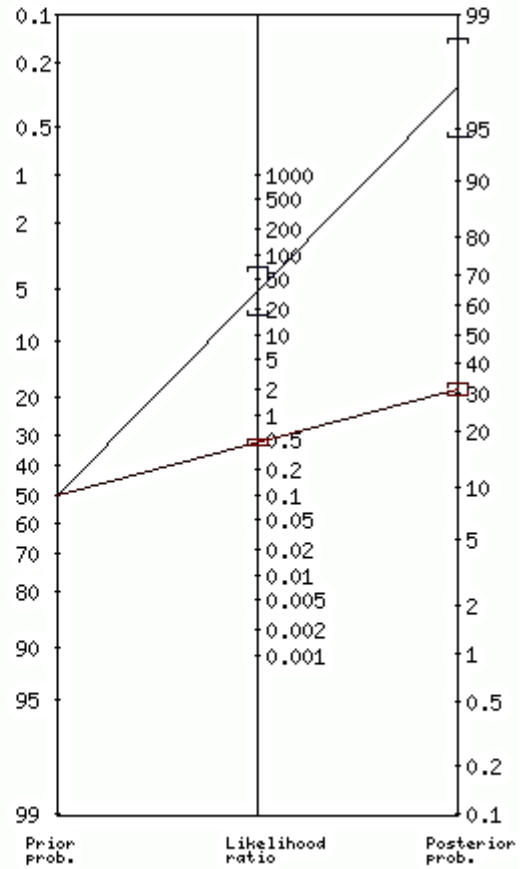
Prevalence (e.g. 0.10):	0.500000
Sensitivity (e.g. 0.80):	0.557
Specificity (e.g. 0.80):	0.984
Total sample size:	

Compute

or
disease prevalence, positive likelihood ratio, and negative likelihood ratio (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.500000
+LR (e.g. 4):	35
-LR (e.g. 0.01):	0.45
Total sample size:	

Compute



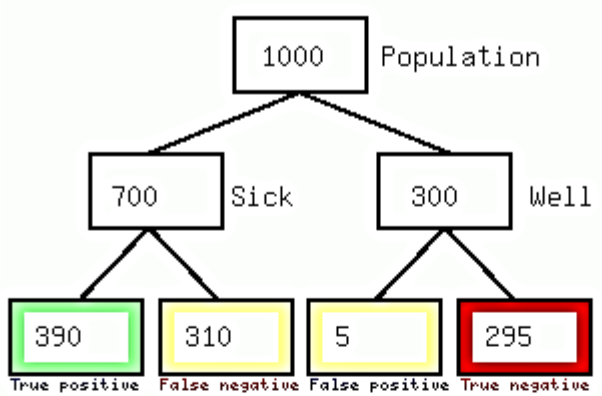
Optional information:

Your local prevalence (e.g. 0.10):	0.50000(

Numbers of patients with and without the disease who test positive and negative:

	Disease present	Disease absent	Total
Test positive	390	5	395
Test negative	310	295	605
Total	700	300	1000

Compute



or
disease prevalence, test sensitivity, and test specificity (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.700000
Sensitivity (e.g. 0.80):	0.557
Specificity (e.g. 0.80):	0.984
Total sample size:	

Compute

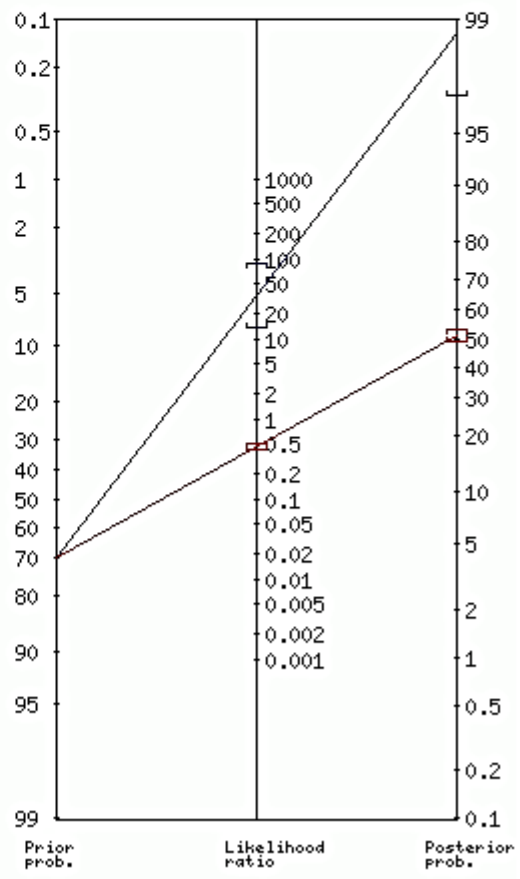
or
disease prevalence, positive likelihood ratio, and negative likelihood ratio (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.700000
+LR (e.g. 4):	35
-LR (e.g. 0.01):	0.45
Total sample size:	

Compute

Optional information:

Your local prevalence (e.g. 0.10):	0.70000(



Dall'intuizione…

Caso n° 5

Mese di febbraio.

Bambino di 5 anni, moderatamente febbrile (t= 38°C), tonsille iperemiche aumentate di volume ma senza essudato, assenza di linfoadenopatia satellite, assenza di tosse.

E' in corso una piccola epidemia di infezioni streptococciche. Il bambino frequenta l'asilo, alcuni suoi compagni sono assenti da qualche giorno perché affetti da tonsillite streptococcica o scarlattina

Test Rapido: Negativo

MA…

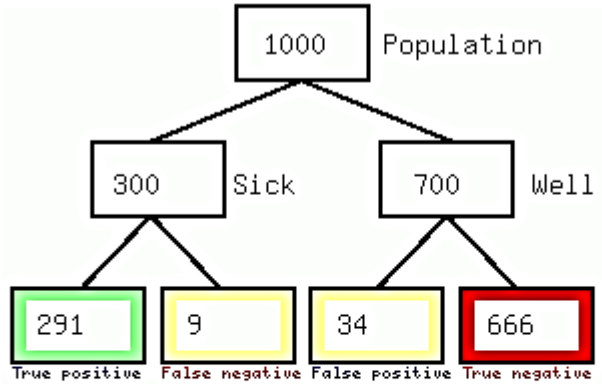
Se la probabilità pre-test è così alta, non sarà un falso negativo?

Dovrei confermare la negatività con l'esame colturale.

Numbers of patients with and without the disease who test positive and negative:

	Disease present	Disease absent	Total
Test positive	291	34	325
Test negative	9	666	675
Total	300	700	1000

Compute

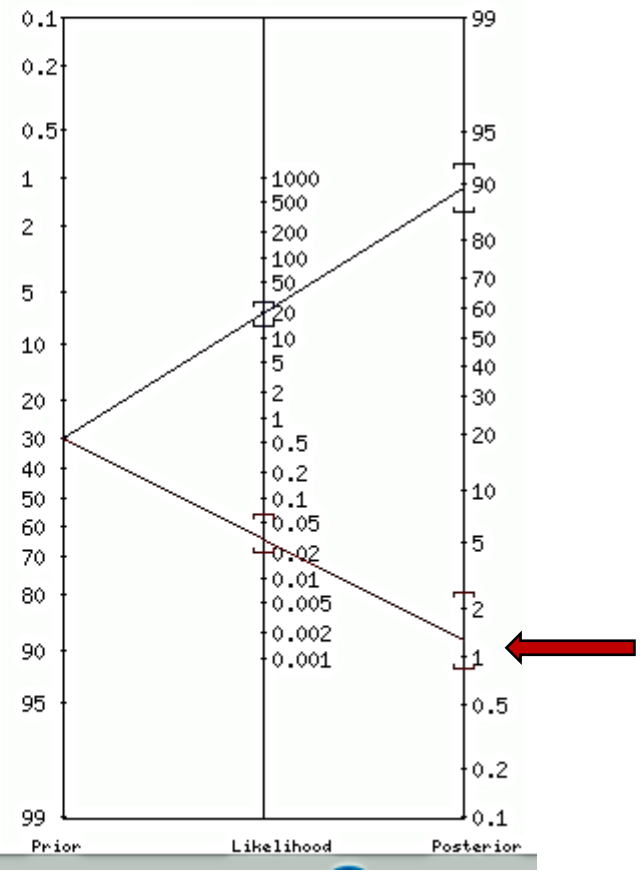


or
disease prevalence, test sensitivity, and test specificity (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.300000
Sensitivity (e.g. 0.80):	0.971
Specificity (e.g. 0.80):	0.951
Total sample size:	

Compute

Score 3
Prob. Pre-test 30%
RADT positivo e negativo



or
disease prevalence, positive likelihood ratio, and negative likelihood ratio (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.300000
+LR (e.g. 4):	20
-LR (e.g. 0.01):	0.03
Total sample size:	

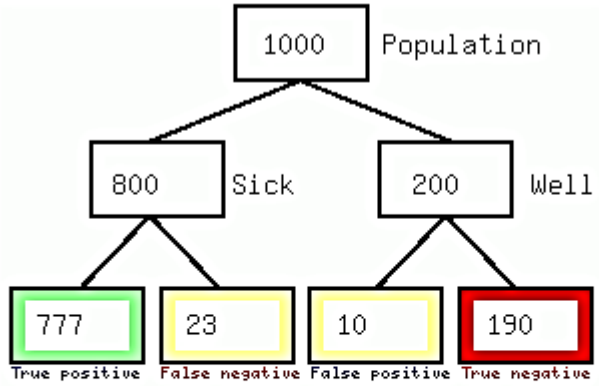
Compute

Optional information:

Numbers of patients with and without the disease who test positive and negative:

	Disease present	Disease absent	Total
Test positive	777	10	787
Test negative	23	190	213
Total	800	200	1000

Compute

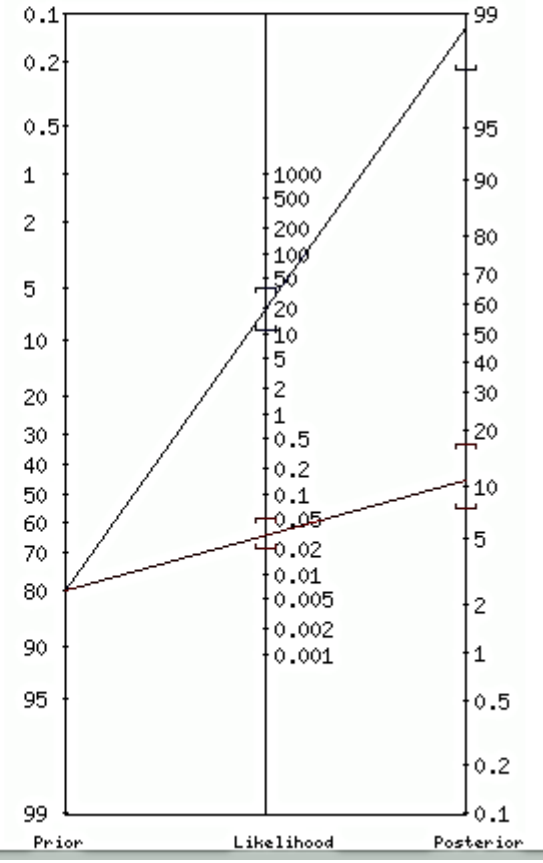


or
disease prevalence, test sensitivity, and test specificity (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.800000
Sensitivity (e.g. 0.80):	0.971
Specificity (e.g. 0.80):	0.951
Total sample size:	

Compute

Score 3
Prob. Pre-test 80%
RADT positivo e negativo



or
disease prevalence, positive likelihood ratio, and negative likelihood ratio (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.800000
+LR (e.g. 4):	20
-LR (e.g. 0.01):	0.03
Total sample size:	

Compute

Optional information:

Il valore di cut-off

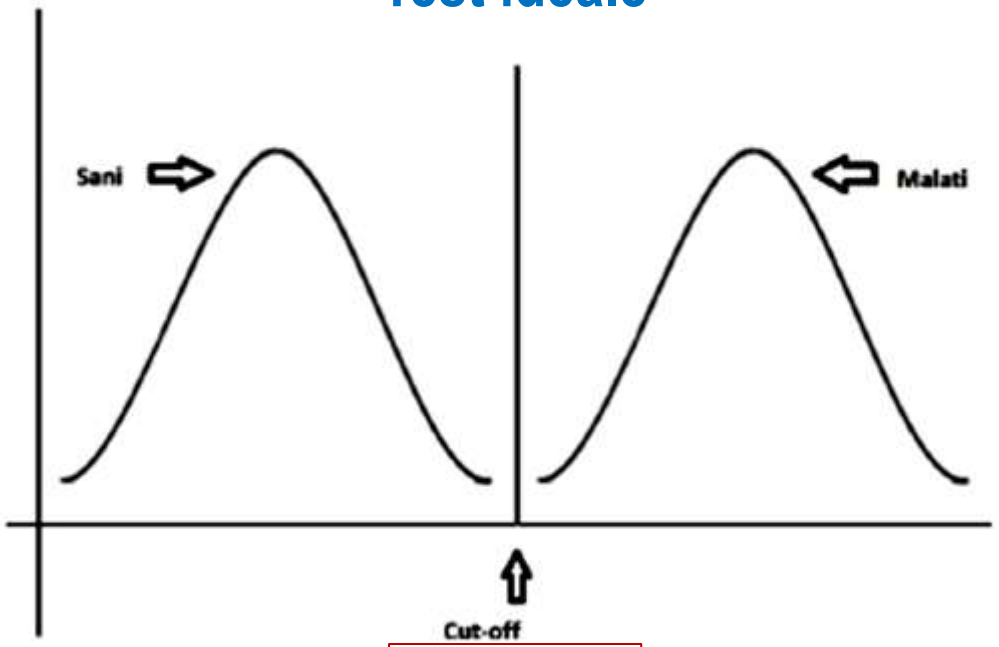


La diagnosi è un processo imperfetto

Dosaggio proteina x (mg/l) per la diagnosi di tumore Y

Sani	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9								
Malati										1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9

Test ideale

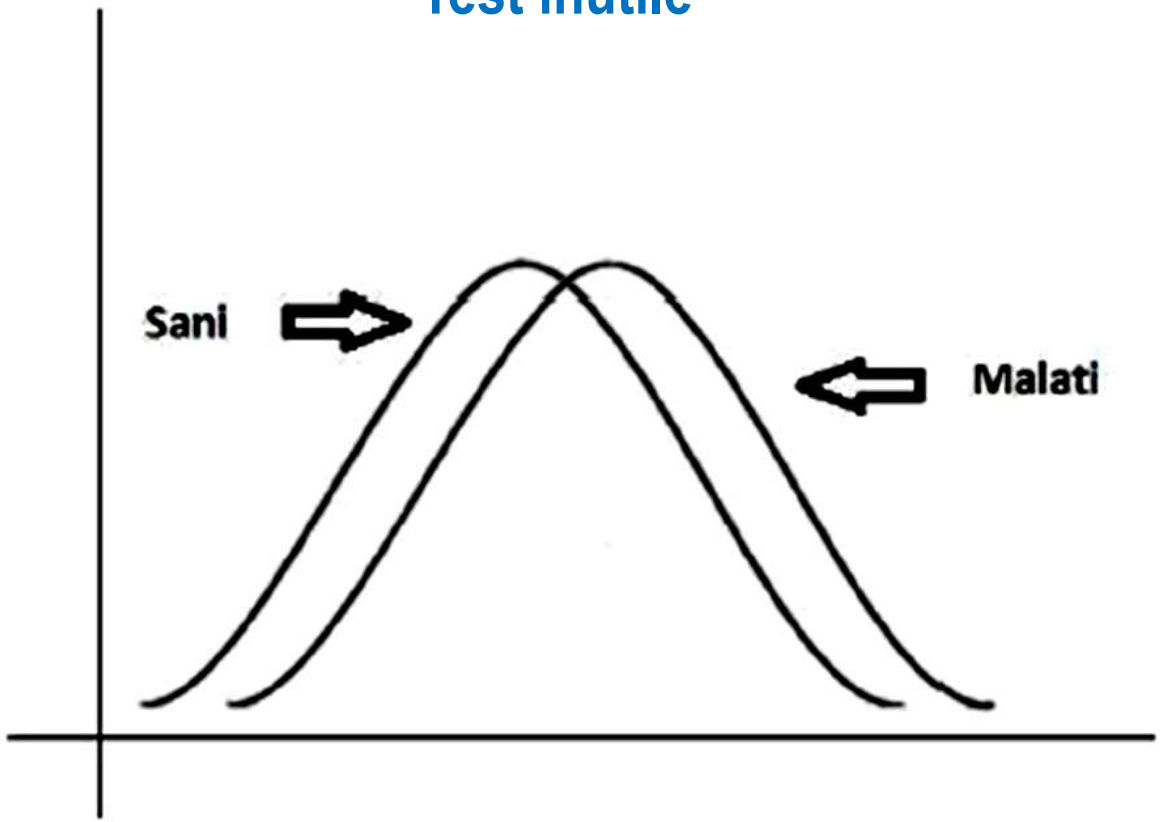


1.0 mg/l

Dosaggio proteina x (mg/l) per la diagnosi di tumore Y

Sani	0.1	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	
Malati		**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	1.9

Test inutile



Dosaggio proteina x (mg/l) per la diagnosi di tumore Y

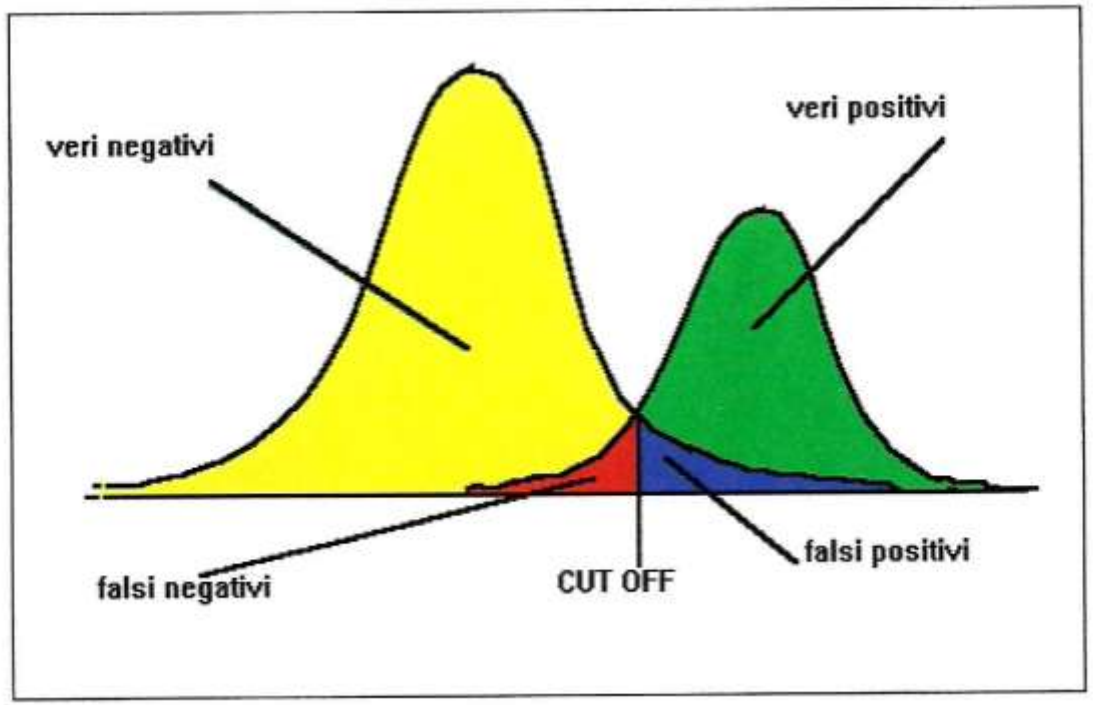
1.0 mg/l

Falsi positivi

Sani	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	**1.1**	**1.2**	**1.3**						
Malati							**0.7**	**0.8**	**0.9**	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9

Falsi negativi

Test reale



Roberto Buzzetti

In base alla scelta del valore di cut-off si può ottenere uno dei seguenti effetti:

1. Aumento della sensibilità e diminuzione della specificità
2. Aumento della specificità e diminuzione della sensibilità

La scelta non è fatta secondo criteri statistici

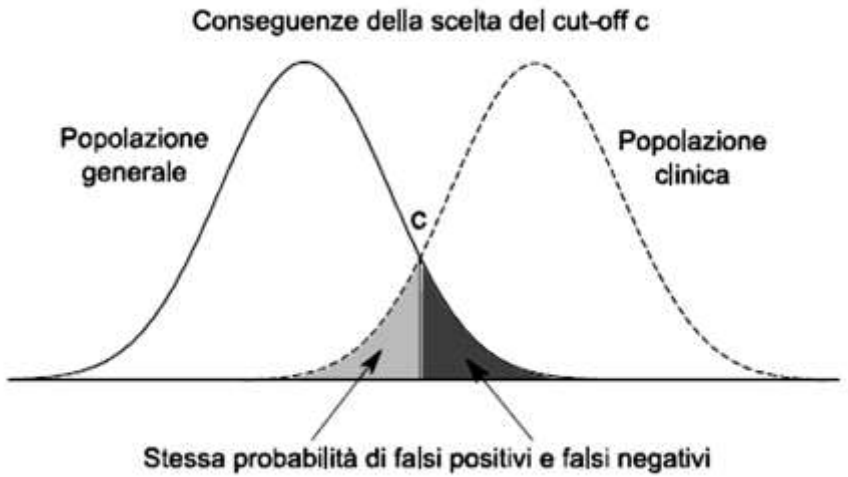
In caso di malattia molto grave o contagiosa sarà opportuno minimizzare la quota di falsi negativi e privilegiare la sensibilità a scapito della specificità

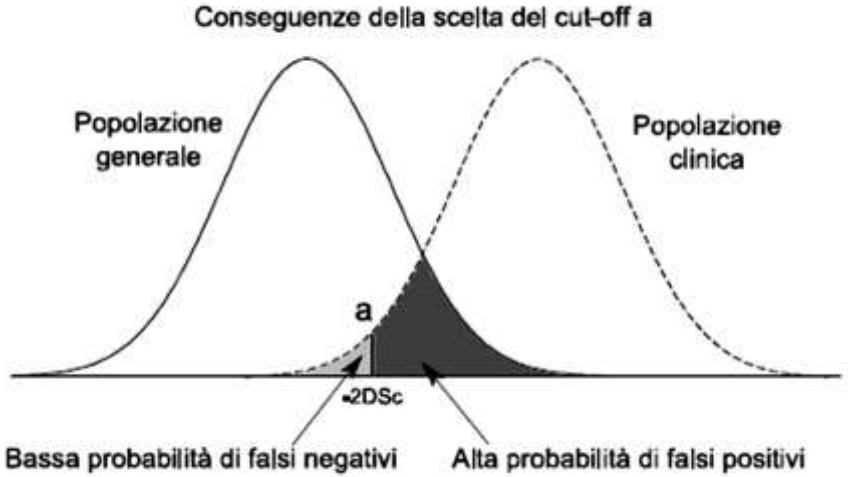
+ Falsi positivi
- specificità

Sani	0.1	0.2	0.3	0.4	0.5	0.6	0.7	**0.8**	**0.9**	**1.1**	**1.2**	**1.3**						
Malati							**0.7**	0.8	0.9	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9

- Falsi negativi
+ sensibilità

0.75 mg/l





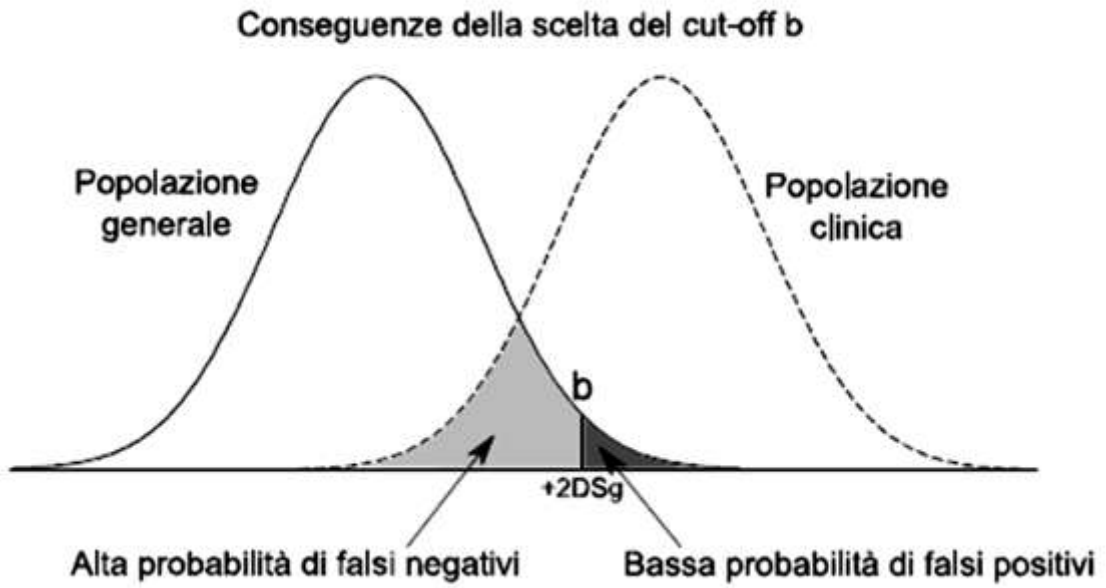
Se, per esempio, si volesse utilizzare il test in sostituzione di un Gold Standard molto invasivo o costoso, sarebbe opportuno minimizzare la quota di falsi positivi e privilegiare la specificità a scapito della sensibilità

- Falsi positivi
+ specificità

Sani	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.1	1.2	**1.3**						
Malati							**0.7**	**0.8**	**0.9**	**1.1**	**1.2**	1.3	1.4	1.5	1.6	1.7	1.8	1.9

+ Falsi negativi
- sensibilità

1.25 mg/l



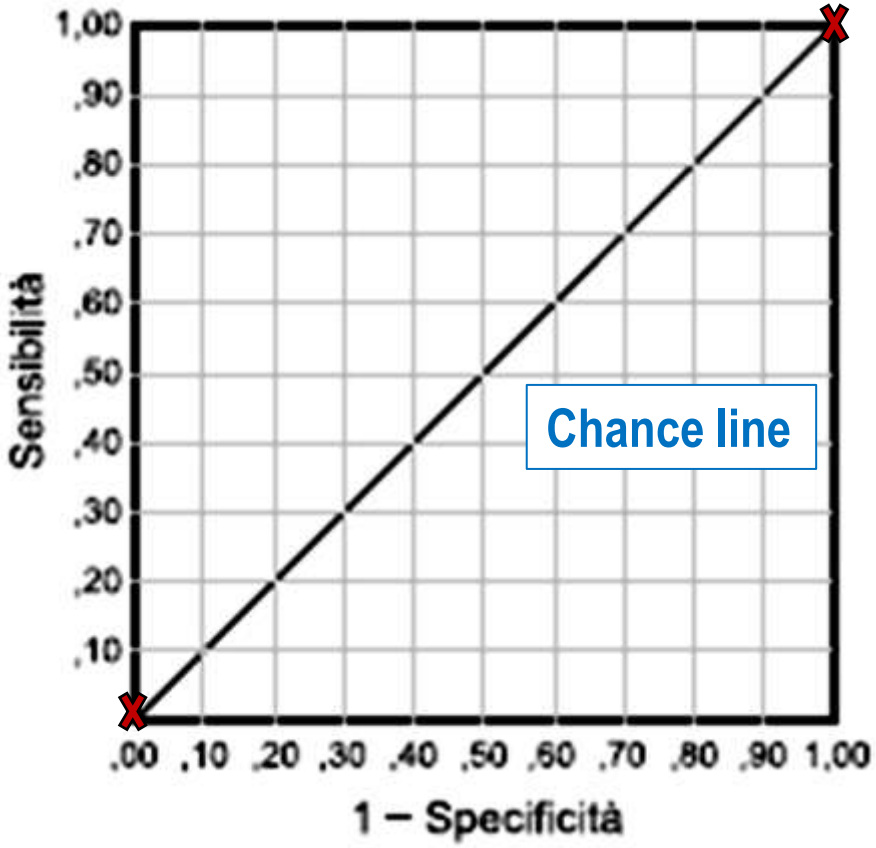
Le curve ROC

Receiver Operator Characteristic curve

Decidere il punteggio di cut-off ottimale

Può essere utile avere a disposizione una tabella con i dati e un grafico che ci permettano di visualizzare, per ogni possibile punteggio al test, quale sarebbe la sensibilità e la specificità del test se lo specifico punteggio venisse scelto come cut-off.

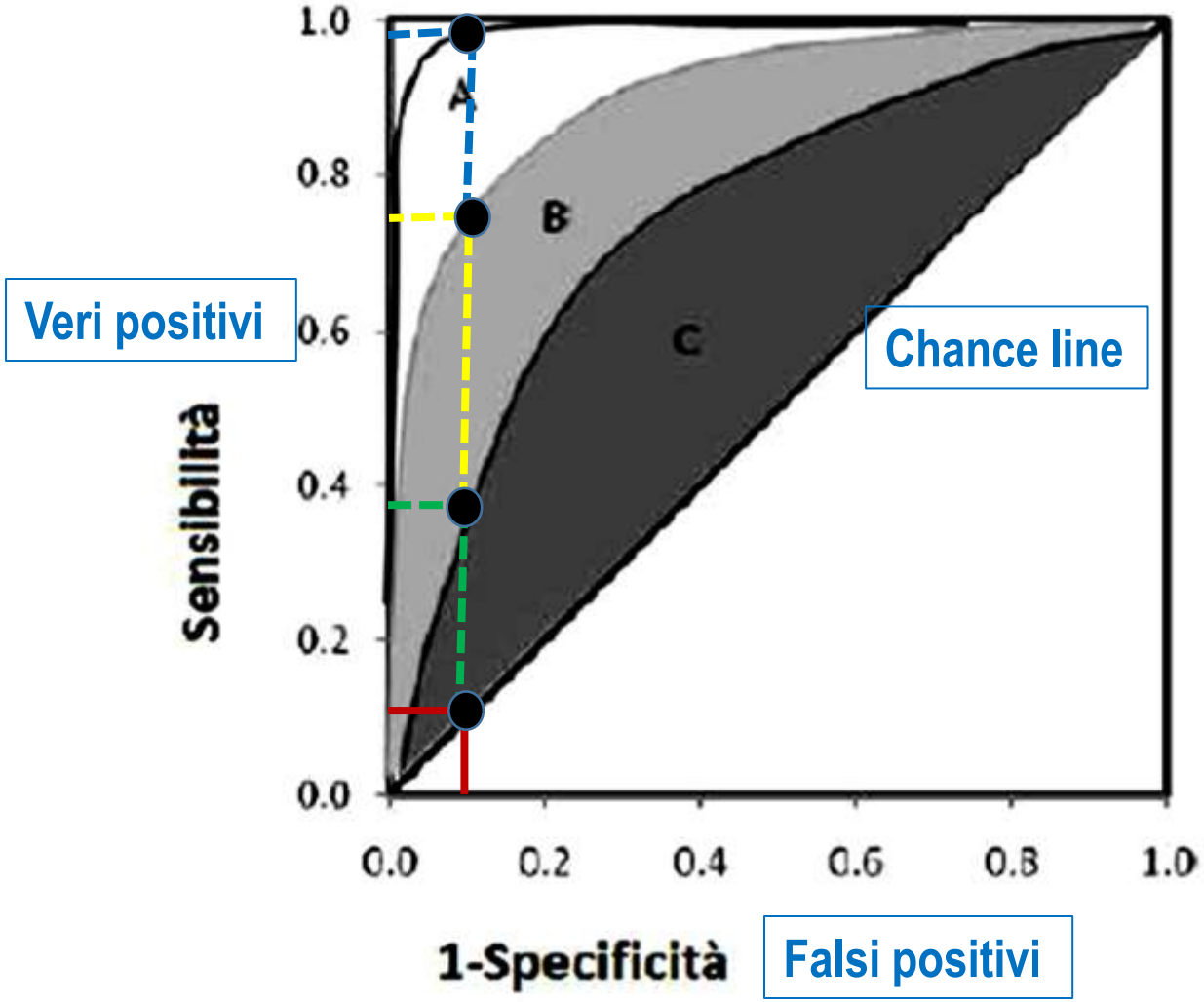
Al vertice opposto del quadrato
Test con **perfetta sensibilità = 1,** ma **specificità nulla = 0,** ossia il test che considera tutti i casi come positivi.



La diagonale che unisce questi due punti è detta **linea del caso**, che corrisponde alla retta sulla quale si trovano i punti di quei test che discriminano in modo causale, con il 50% di veri positivi ed il 50% di falsi positivi **>>>> il lancio della monetina**.

Origine degli assi
Test con **perfetta specificità** (**1**, da cui 1 − Specificità = 0) ma **sensibilità nulla = 0**.
In pratica, è il test che considera tutti i casi come negativi.

Tre test a confronto



E’ possibile identificare un valore di cut-off per le IgEs e/o gli SPT che consenta di fare diagnosi di allergia all’uovo senza praticare il TPO?

		Likelihood of clinical allergy from specific IgE (KU/L) or SPT (mm) results		
		Low (<0.35 or <3)	**Intermediate** (0.35 to <15 or 3 to <8)	**High** (≥15 or ≥8)
Likelihood of clinical allergy from history	**High** eg urticaria and wheeze on 2 exposures	Possible allergy	Probable allergy	Allergy
	Intermediate eg urticaria on a single exposure	Possible allergy	Possible allergy	Probable allergy
	Low eg non-IgE symptoms	No allergy	Possible allergy	Possible allergy

Children and adolescents in the possible allergy box require an OFC for a definitive diagnosis. Specific IgE and SPT values are specific for peanuts. Values associated with a high likelihood of clinical allergy are lower for egg, milk and fish Modified from Stiefel G, Roberts G. How to use serum specific IgE measurements in diagnosing and monitoring food allergy. Arch Dis Child Educ Pract Ed 2012; 97: 29–36.

Due tipi di cut-off

1. quelli basati su una elevata specificità del test (cut-off con il 95% della specificità).
2. quelli basati su un elevato (in letteratura, 95%) valore predittivo positivo (VPP)

I **cut-off basati sul 95% della specificità** invece sono generati di solito mediante la curva ROC.

Poiché la specificità indica la probabilità di ottenere un test negativo in un soggetto sano, un cut-off con la specificità del 95% indica che solo il 5% dei soggetti sani risulterà falsamente positivo al test.

Non variano con la prevalenza della malattia nella popolazione, non ci dicono nulla su quanto frequentemente il TPO risulterà positivo nei malati, ma ci permettono di selezionare meglio i bambini da sottoporre a TPO, in quanto ad alto rischio di averlo positivo

In pratica ci consente di sottoporre al TPO i positivi al test con una maggiore probabilità che risulti positivo, evitando TPO inutili, perché negativi, in bambini sani.

Il **cut-off con 95% PPV** è un buon surrogato di un TPO

In pratica ci consente di <u>NON SOTTOPORRE al TPO i bambini con quel valore di SPT o IgEs</u> perché solo il 5% di essi sarebbe falsamente positivo, quindi allergico.

E' quello relativo al nostro quesito.

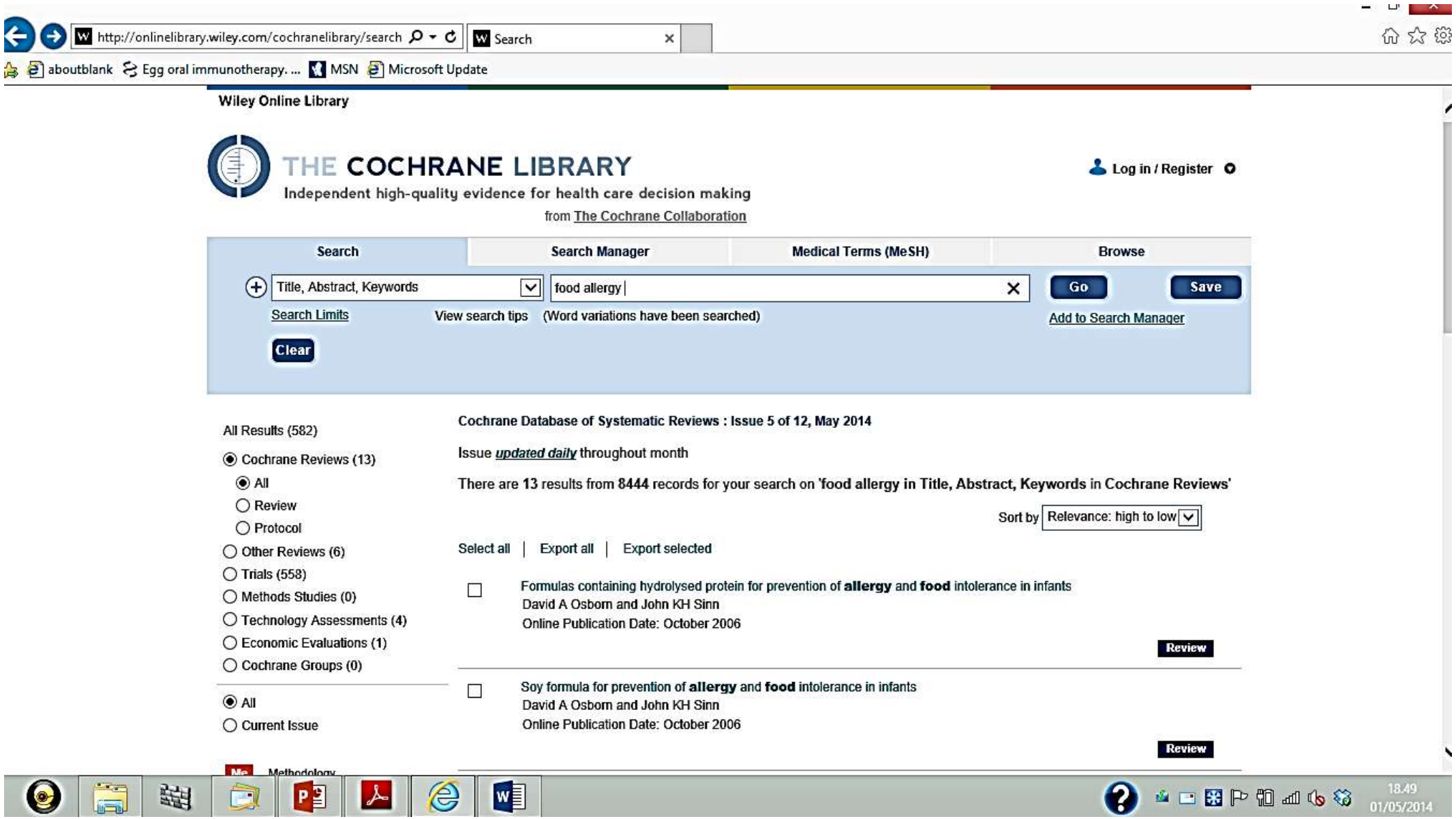
Questi cut-off però, essendo basati sul valore predittivo, **dipendono dalla prevalenza dell'allergia nella popolazione studiata** e quindi sono applicabili solo in centri allergologici in cui si presume che la prevalenza dell'allergia alimentare sia simile a quella riscontrata negli studi che li hanno prodotti.

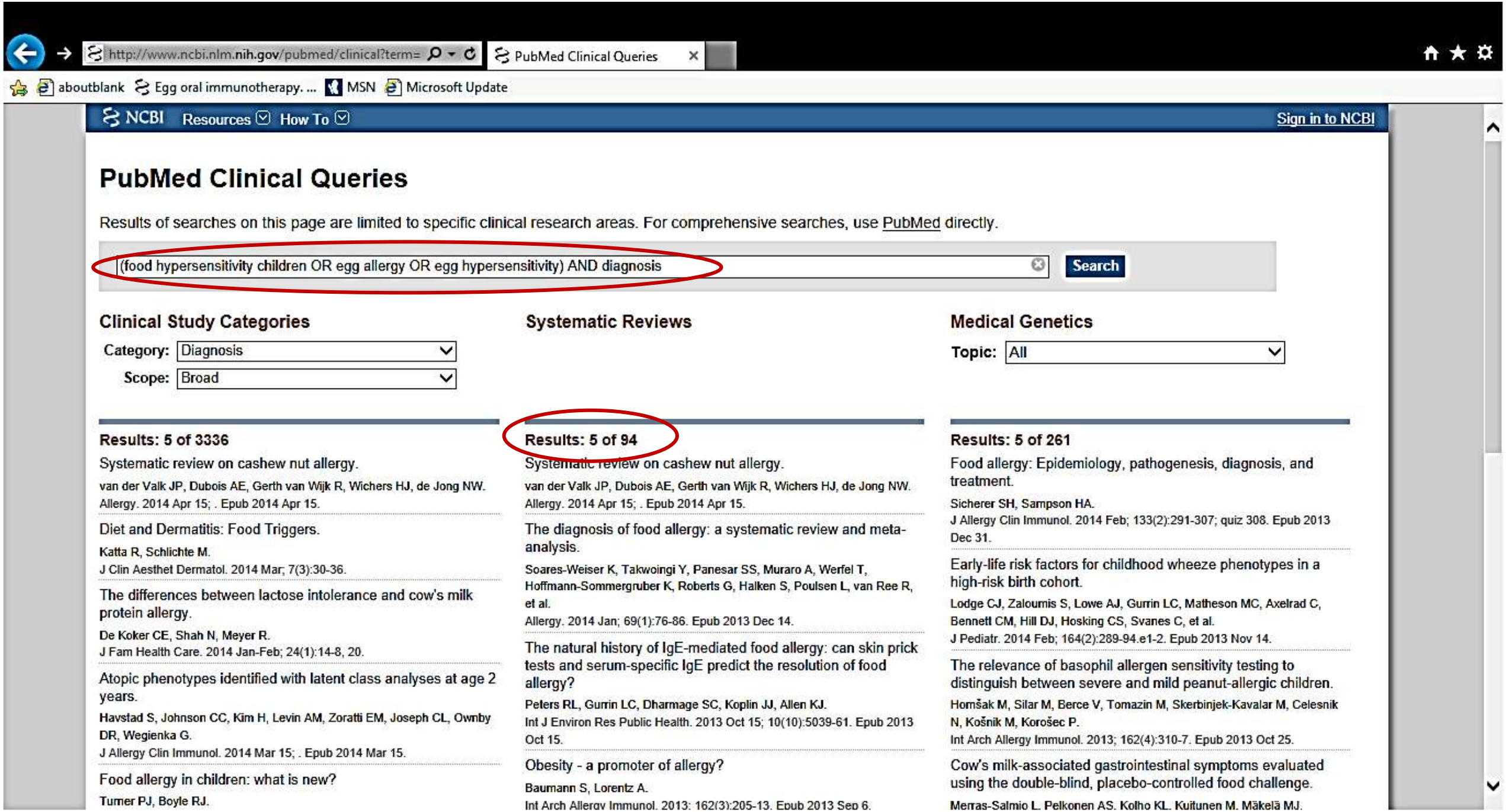
<u>N.B. Un cut-off con il 100% di specificità ha un PPV = 100%, quindi consentirebbe di non sottoporre il bambino a TPO</u>

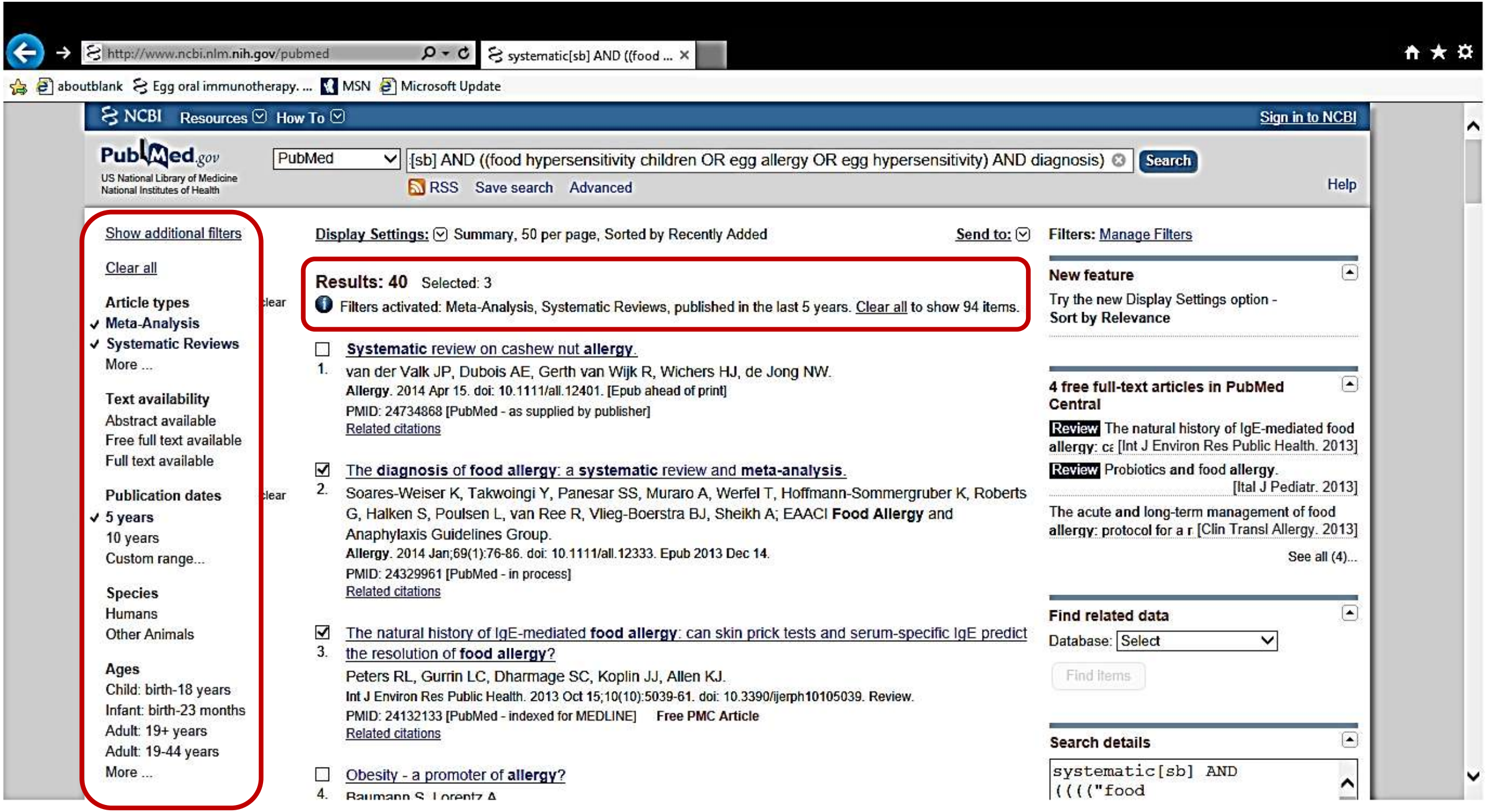

LINEE GUIDA
La Piramide delle evidenze
Revisioni sistematiche e metanalisi
Studi clinici con gruppo di controllo randomizzato (RCT)
Studi clinici con gruppo di controllo
Consensus conference
Studi di coorte
Studi caso-controllo
Studi osservazionali trasversali
Serie di casi
Case report,
Opinione di esperti
?

Ricerca delle Revisioni Sistematiche

Cochrane Library: 13 risultati, nessuno pertinente




http://www.ncbi.nlm.nih.gov/pubmed/clinical?term=
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NCBI
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How To
Sign in to NCBI
PubMed Clinical Queries
Results of searches on this page are limited to specific clinical research areas. For comprehensive searches, use PubMed directly.
(food hypersensitivity children OR egg allergy OR egg hypersensitivity) AND diagnosis
Search
Clinical Study Categories
Category: Diagnosis
Scope: Broad
Systematic Reviews
Medical Genetics
Topic: All
Results: 5 of 3336
Systematic review on cashew nut allergy.
van der Valk JP, Dubois AE, Gerth van Wijk R, Wichers HJ, de Jong NW.
Allergy. 2014 Apr 15; . Epub 2014 Apr 15.
Diet and Dermatitis: Food Triggers.
Katta R, Schlichte M.
J Clin Aesthet Dermatol. 2014 Mar; 7(3):30-36.
The differences between lactose intolerance and cow's milk protein allergy.
De Koker CE, Shah N, Meyer R.
J Fam Health Care. 2014 Jan-Feb; 24(1):14-8, 20.
Atopic phenotypes identified with latent class analyses at age 2 years.
Havstad S, Johnson CC, Kim H, Levin AM, Zoratti EM, Joseph CL, Ownby DR, Wegienka G.
J Allergy Clin Immunol. 2014 Mar 15; . Epub 2014 Mar 15.
Food allergy in children: what is new?
Turner PJ, Boyle RJ.
Results: 5 of 94
Systematic review on cashew nut allergy.
van der Valk JP, Dubois AE, Gerth van Wijk R, Wichers HJ, de Jong NW.
Allergy. 2014 Apr 15; . Epub 2014 Apr 15.
The diagnosis of food allergy: a systematic review and meta-analysis.
Soares-Weiser K, Takwoingi Y, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Halken S, Poulsen L, van Ree R, et al.
Allergy. 2014 Jan; 69(1):76-86. Epub 2013 Dec 14.
The natural history of IgE-mediated food allergy: can skin prick tests and serum-specific IgE predict the resolution of food allergy?
Peters RL, Gurrin LC, Dharmage SC, Koplin JJ, Allen KJ.
Int J Environ Res Public Health. 2013 Oct 15; 10(10):5039-61. Epub 2013 Oct 15.
Obesity - a promoter of allergy?
Baumann S, Lorentz A.
Int Arch Allergy Immunol. 2013; 162(3):205-13. Epub 2013 Sep 6.
Results: 5 of 261
Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment.
Sicherer SH, Sampson HA.
J Allergy Clin Immunol. 2014 Feb; 133(2):291-307; quiz 308. Epub 2013 Dec 31.
Early-life risk factors for childhood wheeze phenotypes in a high-risk birth cohort.
Lodge CJ, Zaloumis S, Lowe AJ, Gurrin LC, Matheson MC, Axelrad C, Bennett CM, Hill DJ, Hosking CS, Svanes C, et al.
J Pediatr. 2014 Feb; 164(2):289-94.e1-2. Epub 2013 Nov 14.
The relevance of basophil allergen sensitivity testing to distinguish between severe and mild peanut-allergic children.
Hornšak M, Silar M, Berce V, Tomazin M, Skerbinjek-Kavalar M, Celesnik N, Košnik M, Korošec P.
Int Arch Allergy Immunol. 2013; 162(4):310-7. Epub 2013 Oct 25.
Cow's milk-associated gastrointestinal symptoms evaluated using the double-blind, placebo-controlled food challenge.
Merras-Salmio L, Pelkonen AS, Kolho KL, Kuitunen M, Mäkelä MJ.


http://www.ncbi.nlm.nih.gov/pubmed
systematic[sb] AND ((food ...
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Egg oral immunotherapy. ...
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Sign in to NCBI
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Other Animals
Ages
Child: birth-18 years
Infant: birth-23 months
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Adult: 19-44 years
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Send to:
Results: 40 Selected: 3
Filters activated: Meta-Analysis, Systematic Reviews, published in the last 5 years. Clear all to show 94 items.
Systematic review on cashew nut allergy.
1. van der Valk JP, Dubois AE, Gerth van Wijk R, Wichers HJ, de Jong NW.
Allergy. 2014 Apr 15. doi: 10.1111/all.12401. [Epub ahead of print]
PMID: 24734868 [PubMed - as supplied by publisher]
Related citations
The diagnosis of food allergy: a systematic review and meta-analysis.
2. Soares-Weiser K, Takwoingi Y, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Halken S, Poulsen L, van Ree R, Vlieg-Boerstra BJ, Sheikh A; EAACI Food Allergy and Anaphylaxis Guidelines Group.
Allergy. 2014 Jan;69(1):76-86. doi: 10.1111/all.12333. Epub 2013 Dec 14.
PMID: 24329961 [PubMed - in process]
Related citations
The natural history of IgE-mediated food allergy: can skin prick tests and serum-specific IgE predict the resolution of food allergy?
3. Peters RL, Gurrin LC, Dharmage SC, Koplin JJ, Allen KJ.
Int J Environ Res Public Health. 2013 Oct 15;10(10):5039-61. doi: 10.3390/ijerph10105039. Review.
PMID: 24132133 [PubMed - indexed for MEDLINE] Free PMC Article
Related citations
Obesity - a promoter of allergy?
4. Baumann S, Lorentz A
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Review The natural history of IgE-mediated food allergy: ca [Int J Environ Res Public Health. 2013]
Review Probiotics and food allergy. [Ital J Pediatr. 2013]
The acute and long-term management of food allergy: protocol for a r [Clin Transl Allergy. 2013]
See all (4)...
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systematic[sb] AND ((((("food

1. The diagnosis of food allergy: a systematic review and meta-analysis.
Soares-Weiser K, et al.
EAACI Food Allergy and Anaphylaxis Guidelines Group.
Allergy. 2014 Jan;69(1):76-86

2. The predictive value of skin prick testing for challenge-proven food allergy: a systematic review.
Peters RL, Gurrin LC, Allen KJ.
Pediatr Allergy Immunol. 2012 Jun;23(4):347-52

Valutazione delle RS – Checklist AMSTAR

Criteri (tradotti e parzialmente modificati)	**Soares 2014 EAACI**
1. E' stato descritto un disegno di studio "a priori"?	**SI**
2. La selezione degli studi e l'estrazione dei dati sono state eseguite "in doppio"?	**SI**
E' stata sviluppata una ricerca esaustiva della letteratura?	**SI**
4. Lo stato della pubblicazione (ad es. letteratura grigia) costituiva un criterio di inclusione?	**NO**
5. E' stato fornito un elenco degli studi inclusi ed esclusi?	**NO**
6. Sono state descritte le caratteristiche degli studi inclusi?	**SI**
7. E' stata valutata e documentata la qualità scientifica degli studi inclusi?	**SI**
8. La determinazione della qualità degli studi inclusi è stata usata in modo appropriato al fine di formulare le conclusioni della RS?	**SI**
9. Sono stati utilizzati metodi appropriati per l'accorpamento dei risultati dei vari studi?	**SI**
10. E' stata verificata la probabilità di bias di pubblicazione?	**NO**
11. E' stato dichiarato il conflitto di interessi?	**SI**
TOTALE	**8/11 Items**

The diagnosis of food allergy: a systematic review and meta-analysis.

Punteggio AMSTAR = 8/11

Soares-Weiser K, et al.
EAACI Food Allergy and Anaphylaxis Guidelines Group.
Allergy. 2014 Jan;69(1):76-86

Implications for patient care

This review has identified relevant evidence for different tests available for a range of foods most commonly implicated in suspected food allergy and highlighted both the volume and strength of evidence available to guide clinical decision-making.

Direct comparisons are difficult because of the limited body of evidence in which these tests have been compared in the same population. That said, overall, this body of work indicates that SPT and specific-IgE (and probably also component-specific-IgE) offer high sensitivity in relation to a range of allergens implicated in immediate IgE-mediated food allergy. There was, however, greater variation in the specificity of these tests, with specific-IgE tending to a higher rate of false positives.

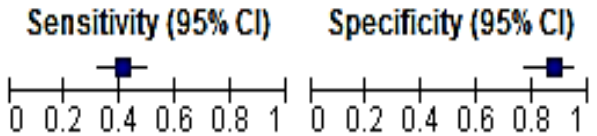
Table 2 Summary estimates of the accuracy of atopy patch test (APT), skin prick test (SPT),

Test (cut-off)	Studies	Participants	Cases	Sensitivity % (95% CI)	Specificity % (95% CI)		
Cow's milk: five prospective cohorts (8, 15, 16, 20, 44), two retrospective cohorts (37, 42), or							
APT	3	495	254	52.8 (32.6, 72.1)	88.1 (75.5, 94		
SPT (≥3 mm)	5	587	284	87.9 (75.6, 94.4)	67.5 (56.0, 77		
Specific-IgE (mixed cutoffs)	6	831	390	87.3 (75.2, 93.9)	47.7 (36.4, 59		
Ratio*				1.0 (0.93, 1.06), $P = 0.9$	0.71 (0.60, 0.8 $P < 0.01$		
Hen's egg: three prospective cohorts (4, 8, 20), one retrospective cohort (37), one prospective case–control study (38), one retrospective case–control study (31)							
SPT (mixed cutoffs)	5	448	287	92.4 (79.9, 97.4)	58.1 (49.1, 66.6)	2.30 (1.77, 2.74)	0.13 (0.05, 0.36)
Specific-IgE (mixed cutoffs)	5	572	346	93.4 (82.1, 97.8)	49.2 (40.2, 58.1)	1.84 (1.52, 2.21)	0.13 (0.05, 0.38)
Ratio				1.01 (0.70, 0.96), $P = 0.7$	0.85 (0.68, 1.05), $P = 0.1$		

Figure S3a: Individual study estimates of sensitivity and specificity for atopy patch test, skin prick test, and specific-IgE for diagnosis of hen's egg allergy

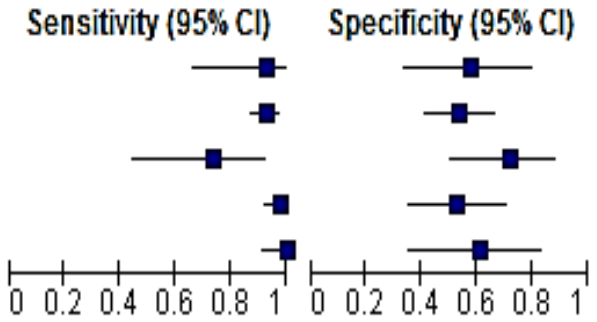
Target food: Hen's egg. Index test: APT

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Mehl 2006	52	8	76	57	NR	0.41 [0.32, 0.50]	0.88 [0.77, 0.95]



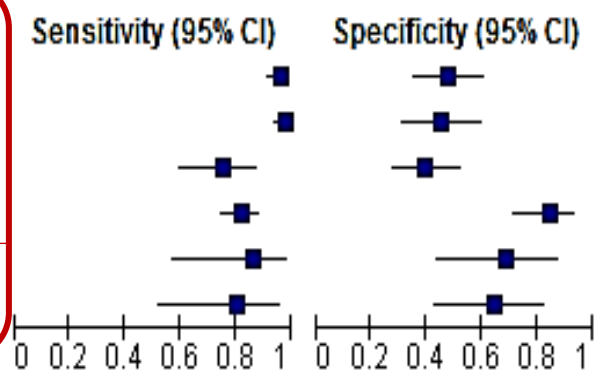
Target food: Hen's egg. Index test: SPT (mixed cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Caffarelli 1995	13	8	1	11	≥3mm	0.93 [0.66, 1.00]	0.58 [0.33, 0.80]
Mehl 2006	119	30	9	35	≥3mm	0.93 [0.87, 0.97]	0.54 [0.41, 0.66]
Sampson 1984	11	7	4	18	≥3mm	0.73 [0.45, 0.92]	0.72 [0.51, 0.88]
Sampson 1997	88	16	2	18	≥3mm	0.98 [0.92, 1.00]	0.53 [0.35, 0.70]
Eigenmann 1998	40	7	0	11	≥4mm	1.00 [0.91, 1.00]	0.61 [0.36, 0.83]



Target food: Hen's egg. Index test: Specific IgE (all cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Mehl 2006	123	34	5	31	>0.35 kU/L	0.96 [0.91, 0.99]	0.48 [0.35, 0.60]
Sampson 1997 (A)	142	28	3	23	>0.35 kU/L	0.98 [0.94, 1.00]	0.45 [0.31, 0.60]
van den 2012	33	40	11	26	>0.35 kU/L	0.75 [0.60, 0.87]	0.39 [0.28, 0.52]
Sampson 1997 (B)	119	8	26	43	≥3.4 kU/L	0.82 [0.75, 0.88]	0.84 [0.71, 0.93]
Caffarelli 1995	12	6	2	13	NR	0.86 [0.57, 0.98]	0.68 [0.43, 0.87]
Sampson 1984	12	9	3	16	NR	0.80 [0.52, 0.96]	0.64 [0.43, 0.82]



FN = false negative;

FP = false positive;

NR = not reported;

SPT = skin prick test;

TN = true negative;

TP = true positive.

The study Sampson 1997 (suffixes A and B) reported the accuracy of specific-IgE at two cut-offs.

If a study reported multiple cut-offs, only data at one cut-off was chosen for the meta-analysis.

The predictive value of skin prick testing for challenge-proven food allergy: a systematic review.

Peters RL, Gurrin LC, Allen KJ.
Pediatr Allergy Immunol. 2012 Jun;23(4):347-52

Punteggio AMSTAR = 5/11

Table 1. Published skin prick test (SPT) cutoffs in egg allergic children, stratified by age (<2 and ≥2 yrs)

Study	Sample size	Population	Outcome	Median age (range)	Allergy prevalence (%)	Method	SPT cutoff (mm)
Boyano Martinez (12)	81	Children with history of egg allergy or suspected egg allergy	64 positive OFC*	Under 2 yrs	79	93% PPV ROC curves	3
Monti (7)	107	Children with atopic dermatitis who had never ingested egg	72 positive OFCs	5 months (1–19 months)	67	94% PPV	4
Sporik (13)	39	Children referred to allergy clinic with suspected food allergy or retested after positive challenge at least 12 months prior	29 positive OFC (subgroup of below)	Under 2 yrs	74	100% specificity ROC curves	5
Tripodi (15)	47	Children attending allergy clinic with suspected egg allergy (39) or recent positive OFC to egg (8)	20 positive OFC	Mean 6.2 yr (1.1–15.7 yr)	43	100% PPV ROC curves 2 × 2 tables	6
Sporik (13)	121	Children referred to allergy clinic with suspected food allergy or retested after positive challenge at least 12 months prior	93 positive OFC	36 months (1–154 months)	77	100% specificity ROC curves	7
Dieguez (8)	157	Children previously diagnosed egg allergic, examining persistence of allergy	100 positive DBPCFC	2.5 yr (15 months–16 yr)	63	95% PPV ROC curves	9
Verstege (14)	160	Children referred to hospital with suspected food allergy (SPT fresh food allergens)	101 positive OFC (75% DBPCFC and 25% open OFC)	22 months (3 months–14.5 yr)	63	95% PPV Logistic regression	13
Mehl (9)	193	Children with suspected food allergy	128 positive OFC	13 months (3 months–14 yr)	66	95% PPV Logistic regression	14

Completiamo la ricerca per eventuali studi non inclusi nelle RS.

In questo caso la ricerca degli studi, per essere sufficientemente sensibile, richiede una stringa generica e nessun altro limite se non quello temporale degli ultimi 2 anni

«Egg hypersensitivity»

Filters activated: **Publication date from 2012/01/01 to 2014/12/31**

Results: 1 to 200 of 226 Selected: 1

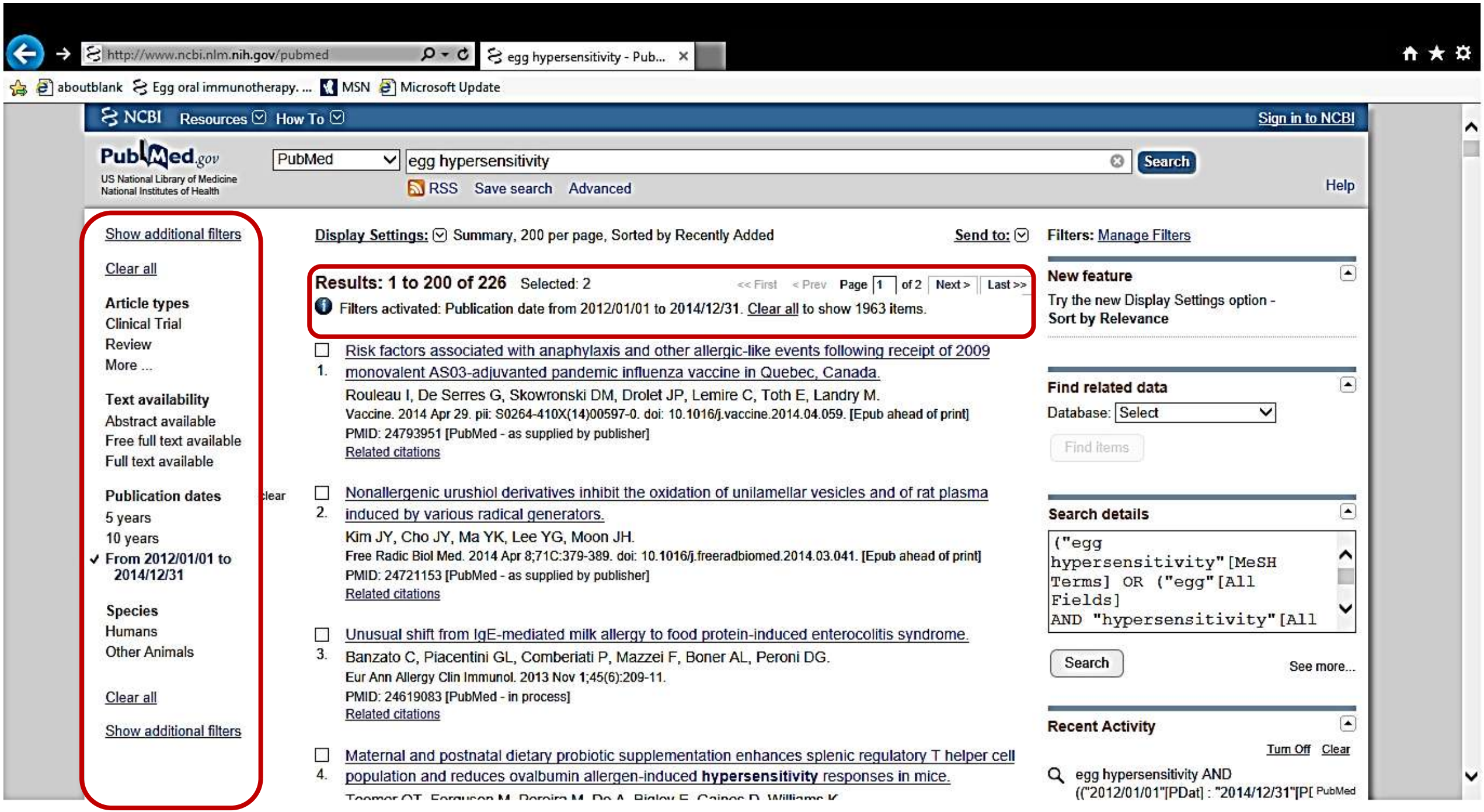
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AI n° 39

Skin prick test responses and allergen-specific IgE levels as predictors of peanut, **egg**, and sesame allergy in infants.

Peters RL, Allen KJ, Dharmage SC, Tang ML, Koplin JJ, Ponsonby AL, Lowe AJ, Hill D, Gurrin LC; HealthNuts Study.

J Allergy Clin Immunol. 2013 Oct;132(4):874-80. doi: 10.1016/j.jaci.2013.05.038. Epub 2013 Jul 24


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Filters activated: Publication date from 2012/01/01 to 2014/12/31. Clear all to show 1963 items.
1. Risk factors associated with anaphylaxis and other allergic-like events following receipt of 2009 monovalent AS03-adjuvanted pandemic influenza vaccine in Quebec, Canada.
Rouleau I, De Serres G, Skowronski DM, Drolet JP, Lemire C, Toth E, Landry M.
Vaccine. 2014 Apr 29. pii: S0264-410X(14)00597-0. doi: 10.1016/j.vaccine.2014.04.059. [Epub ahead of print]
PMID: 24793951 [PubMed - as supplied by publisher]
Related citations
2. Nonallergenic urushiol derivatives inhibit the oxidation of unilamellar vesicles and of rat plasma induced by various radical generators.
Kim JY, Cho JY, Ma YK, Lee YG, Moon JH.
Free Radic Biol Med. 2014 Apr 8;71C:379-389. doi: 10.1016/j.freeradbiomed.2014.03.041. [Epub ahead of print]
PMID: 24721153 [PubMed - as supplied by publisher]
Related citations
3. Unusual shift from IgE-mediated milk allergy to food protein-induced enterocolitis syndrome.
Banzato C, Piacentini GL, Comberiati P, Mazzei F, Boner AL, Peroni DG.
Eur Ann Allergy Clin Immunol. 2013 Nov 1;45(6):209-11.
PMID: 24619083 [PubMed - in process]
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4. Maternal and postnatal dietary probiotic supplementation enhances splenic regulatory T helper cell population and reduces ovalbumin allergen-induced hypersensitivity responses in mice.
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PubMed

Skin prick test responses and allergen-specific IgE levels as predictors of peanut, **egg**, and sesame allergy in infants.

Peters RL, Allen KJ, Dharmage SC, Tang ML, Koplin JJ, Ponsonby AL, Lowe AJ, Hill D, Gurrin LC; HealthNuts Study.

J Allergy Clin Immunol. 2013 Oct;132(4):874-80. doi: 10.1016/j.jaci.2013.05.038. Epub 2013 Jul 24

Studio di accuratezza diagnostica, trasversale, *cross-sectional*



QUADAS-2

Fase 1

Pazienti

5276 bambini di 11-15 mesi, sensibilizzati (+ 200 controlli randomizzati non sensibilizzati)

Test(s) indice

SPT e IgEs (ImmunoCap) per 4 alimenti

(Egg SPT N= 650 IgEs N= 557)

Reference standard e condizione target

TPO. Allergia all'uovo (albume)

study in Melbourne, Australia. The study methods have been described in detail previously.[7] In brief, 5276 infants aged 11 to 15 months were recruited through 131 council-run immunization sessions from September 2007 to August 2011. Infants underwent SPTs to 4 common food allergens, and infants with detectable SPT responses were invited to Melbourne's Royal Children's Hospital for a formal OFC to test for food allergy. Infants with a negative SPT

QUADAS-2

Fase 2

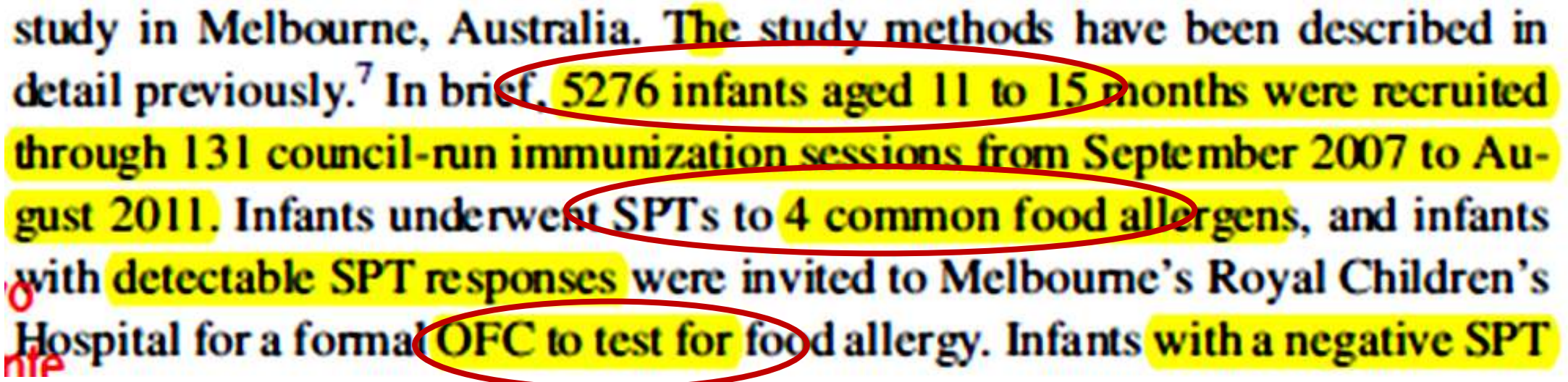
Criteri specifici di revisione e concordanza tra i revisori

Fase 3

Dominio 1: Selezione dei pazienti

Selezione consecutiva o randomizzata. Studio cross-sectional e non caso-controllo. Assenza di esclusioni inappropriate.

RISK OF BIAS: LOW / HIGH / UNCLEAR



study in Melbourne, Australia. The study methods have been described in detail previously.[7] In brief, 5276 infants aged 11 to 15 months were recruited through 131 council-run immunization sessions from September 2007 to August 2011. Infants underwent SPTs to 4 common food allergens, and infants with detectable SPT responses were invited to Melbourne's Royal Children's Hospital for a formal OFC to test for food allergy. Infants with a negative SPT

Dominio 2: Test(s) indice

Descrizione del test indice, della sua conduzione e della sua interpretazione. Interpretazione del test indice in cieco rispetto al GS. Valore soglia pre-specificato

RISK OF BIAS: LOW / HIGH / UNCLEAR

SPT

SPTs were administered with a single-tine lancet (Stallergenes, Antony, France) on the infant's back. Tests were performed to 4 foods, peanut, hen's egg, sesame, and either cow's milk or shrimp (ALK-Abelló, Madrid, Spain), along with a positive control (10 mg/mL histamine) and a negative control (saline). Wheal size was measured after 15 minutes and calculated as the average of the longest diameter and the diameter perpendicular to it after subtracting the negative control.

Serum-specific IgE testing

Blood samples were collected and plasma was isolated for sIgE assays on the same day. Serum specific IgE antibodies to whole peanut, egg white, and sesame were analyzed by using the ImmunoCAP System FEIA (Phadia AB, Uppsala, Sweden).

Definitions

Sensitization was defined as an SPT response of 2 mm or greater or an sIgE levels of 0.35 kU_A/L or greater.

A positive OFC result was defined as at least 1 of the following: 3 concurrent non–contact urticaria reactions lasting at least 5 minutes, severe persistent vomiting, perioral or periorbital angioedema, or anaphylaxis (evidence of circulatory or respiratory involvement) within 2 hours of the last challenge dose in the presence of a positive test result for sensitization.

from this analysis. Nurses were blinded to wheal size and previous history of ingestion.

Dominio 3: Reference Standard (RS)

A. Validità del RS nel classificare correttamente la condizione d'interesse. Interpretazione del test RS in cieco rispetto al test indice.

RISK OF BIAS: LOW / HIGH / UNCLEAR

B. Dubbi sull'applicabilità

CONCERN: LOW / HIGH / UNCLEAR

from this analysis. Nurses were blinded to wheal size and previous history of ingestion.

Dominio 4: Flusso e timing

Descrivere ogni paziente che non riceve il test indice e/o il RS (< 20%) e/o che venga escluso dalla tab. 2*2

Descrivere l'intervallo di tempo e qualunque intervento tra test indice e RS

RISK OF BIAS: LOW / HIGH / UNCLEAR

OFCs

Eighty-three percent of infants with detectable SPT responses at community recruitment accepted the invitation to undergo an OFC. SPTs were repeated on the day of the OFC and used for this analysis; OFCs were conducted as previously described.[7] OFC results were deemed positive if they met the predefined criteria (see definitions) within 2 hours of the last challenge dose. To capture late reactions, parents were instructed to administer a single serving of the challenge food for 7 days and observe for a reaction. The food

TABLE I. Demographic characteristics of infants who participated in OFCs*

	Peanut tolerance (n = 290)	Peanut allergy (n = 148)	Egg tolerance (n = 207)	Egg allergy (n = 445)	Sesame tolerance (n = 72)	Sesame allergy (n = 31)
Age at recruitment (mo), mean (SD)	12.6 (0.65)	12.8 (0.88)	12.6 (0.72)	12.6 (0.69)	12.5 (0.47)	12.9 (0.92)
Sex (male)	158/289 (55%)	98/148 (66%)	101/206 (49%)	250/444 (56%)	46/72 (64%)	26/31 (84%)
Eczema diagnosis†	132/261 (51%)	99/138 (72%)	66/176 (38%)	250/408 (61%)	42/67 (63%)	28/31 (90%)
Previous reaction to food‡	8/276 (3%)	20/139 (14%)	24/196 (12%)	116/424 (27%)	0	2/31 (6%)
Infant previously consumed food	83/257 (32%)	30/126 (24%)	186/195 (95%)	375/421 (89%)	33/66 (50%)	13/31 (42%)
Family history of allergic disease§	214/290 (74%)	111/148 (75%)	150/207 (72%)	344/445 (78%)	51/71 (71%)	22/31 (71%)
Family history of food allergy	36/288 (13%)	16/146 (11%)	24/202 (12%)	61/437 (14%)	6/72 (8%)	5/31 (16%)
SPT‖ (mm)	2 (0-3)	8 (6-10)	0 (0-2)	3.5 (2.5-5)	1 (0-2.5)	7 (4-10)
sIgE‖ (kU_A/L)	0.37 (0.06-1.6)	3.89 (1.1-12.4)	0.19 (0.09-0.49)	1.53 (0.51-4.91)	0.93 (0.27-2.85)	6.75 (1.63-14.3)

*The denominators are not always the same because questionnaire data on demographic factors were missing for some infants.

TABLE II. Diagnostic capacity of SPTs to challenge-confirmed food allergy

Allergen	No.	95% PPV (mm [95% CI])	NPV (% [95% CI])	Sensitivity (% [95% CI])	Specificity (% [95% CI])	Positive LR (95% CI)	Negative LR (95% CI)	AUC (95% CI)
Peanut	435	8 (7.2-9.3)	80 (76-84)	54 (46-62)	98 (95-99)	22.2 (10.5-46.8)	0.47 (0.40-0.56)	0.93 (0.90-0.96)
Egg	650	4 (3.3-5.0)	44 (40-49)	46 (41-50)	93 (89-96)	6.7 (4.0-11.3)	0.58 (0.53-0.64)	0.87 (0.84-0.90)
Baked egg	167	11 (82% PPV)*	82 (75-87)	0 (0-12)	99 (96-100)	-	1.01 (0.93-1.02)	0.65 (0.54-0.77)
Sesame	103	8 (4.6-9.4)	82 (72-89)	48 (30-67)	99 (93-100)	34.8 (4.8-252)	0.52 (0.37-0.74)	0.92 (0.86-0.98)

*Ninety-five percent PPV could not be calculated.

TABLE III. Diagnostic capacity of sIgE measurements to challenge-confirmed IgE-mediated food allergy

Allergen	No.	95% PPV (kU_A/L [95% CI])	NPV (% [95% CI])	Sensitivity (% [95% CI])	Specificity (% [95% CI])	Positive LR (95% CI)	Negative LR (95% CI)	AUC (95% CI)
Peanut	370	34 (13.5-48.0)	69 (64-74)	14 (8-21)	99 (96-100)	11.2 (3.4-37.6)	0.87 (0.81-0.94)	0.81 (0.77-0.86)
Egg	557	1.7 (0.9-3.1)	47 (41-52)	48 (43-53)	98 (94-99)	21.2 (8.0-56.3)	0.53 (0.48-0.59)	0.85 (0.82-0.89)
Baked egg	143	50 (88% PPV)*	85 (78-90)	9 (1-28)	100 (97-100)	-	0.91 (0.80-1.04)	0.66 (0.53-0.80)
Sesame	85	50 (86% PPV)*	69 (58-78)	4 (0-19)	98 (91-100)	2.2 (0.1-33.1)	0.98 (0.90-1.06)	0.76 (0.65-0.88)

SPTs – Prevalenza 50%

or
disease prevalence, test sensitivity, and test specificity (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.500000
Sensitivity (e.g. 0.80):	0.460
Specificity (e.g. 0.80):	0.931
Total sample size:	

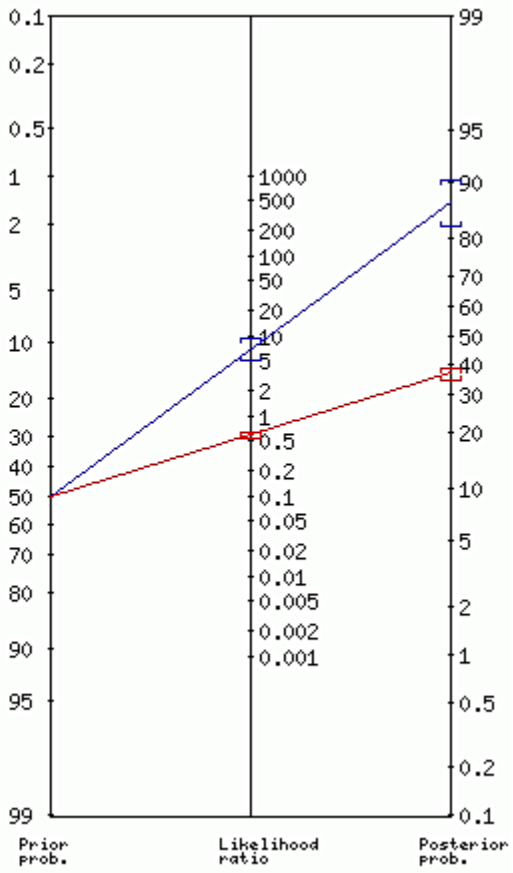
Compute

or
disease prevalence, positive likelihood ratio, and negative likelihood ratio (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.500000
+LR (e.g. 4):	6.70
-LR (e.g. 0.01):	0.58
Total sample size:	

Compute

Optional information:



IgEs – Prevalenza 50%

or
disease prevalence, test sensitivity, and test specificity (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.500000
Sensitivity (e.g. 0.80):	0.482
Specificity (e.g. 0.80):	0.977
Total sample size:	

Compute

or
disease prevalence, positive likelihood ratio, and negative likelihood ratio (and, optionally, sample size):

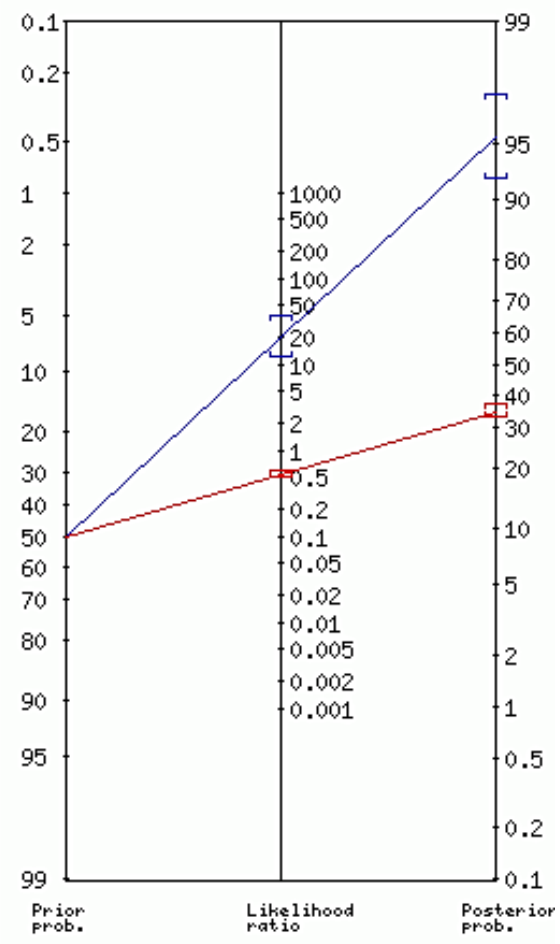
Prevalence (e.g. 0.10):	0.500000
+LR (e.g. 4):	21
-LR (e.g. 0.01):	0.53
Total sample size:	

Compute

Optional information:

Your local prevalence (e.g. 0.10):	0.500000

True positive False negative False positive True negative



SPTs – Prevalenza 0.3%

or
disease prevalence, test sensitivity, and test specificity (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.030000
Sensitivity (e.g. 0.80):	0.460
Specificity (e.g. 0.80):	0.931
Total sample size:	

Compute

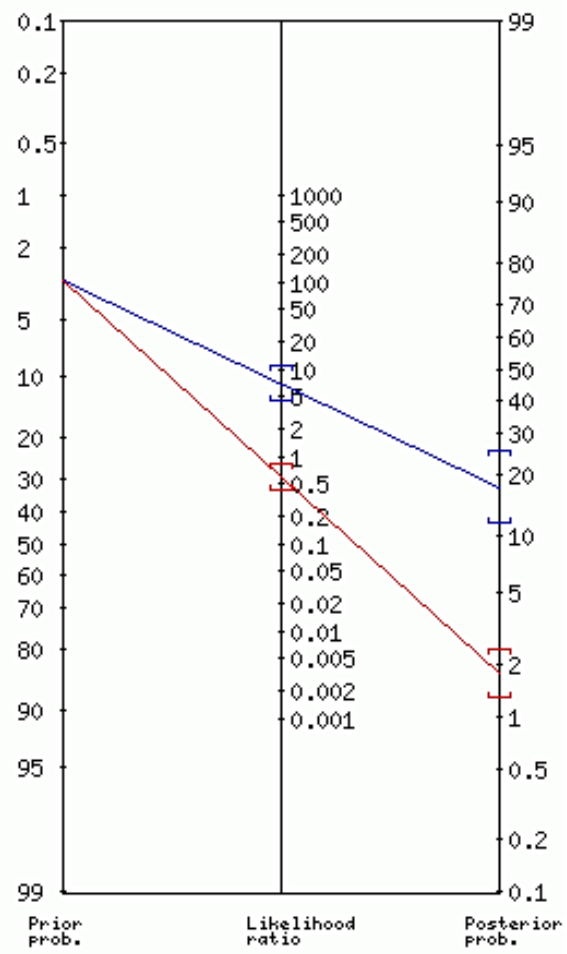
or
disease prevalence, positive likelihood ratio, and negative likelihood ratio (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.030000
+LR (e.g. 4):	6.70
-LR (e.g. 0.01):	0.58
Total sample size:	

Compute

Optional information:

Your local prevalence (e.g. 0.10):	0.030000



IgEs – Prevalenza 0.3%

or
disease prevalence, test sensitivity, and test specificity (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.030000
Sensitivity (e.g. 0.80):	0.482
Specificity (e.g. 0.80):	0.977
Total sample size:	

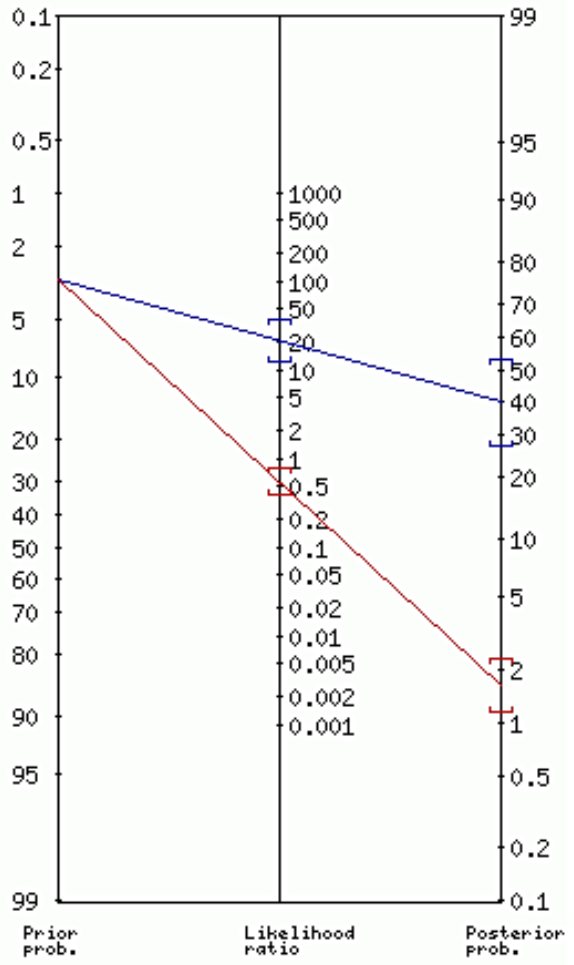
Compute

or
disease prevalence, positive likelihood ratio, and negative likelihood ratio (and, optionally, sample size):

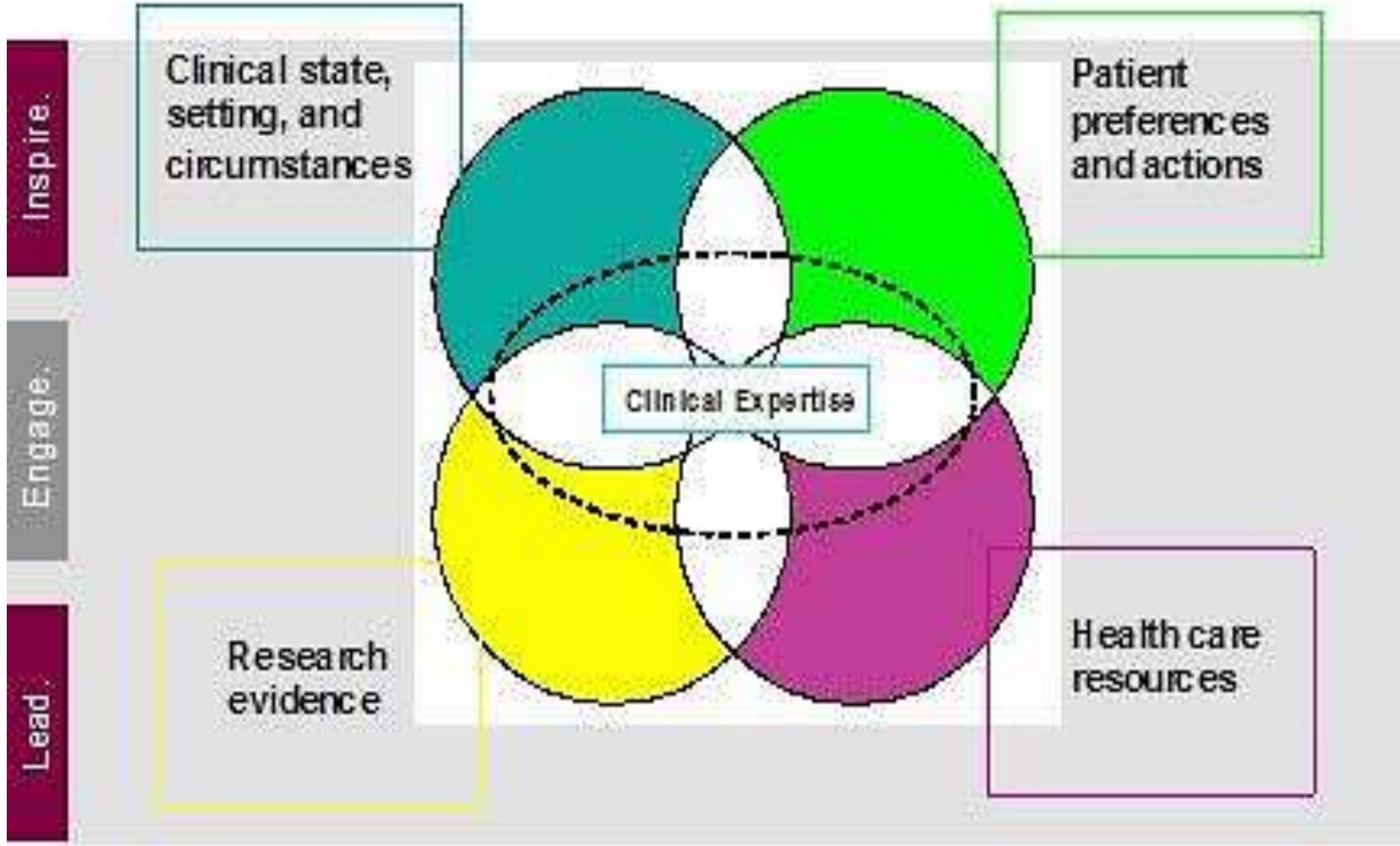
Prevalence (e.g. 0.10):	0.030000
+LR (e.g. 4):	21
-LR (e.g. 0.01):	0.53
Total sample size:	

Compute

Optional information:



Clinical Decision Making



Risoluzione dello Scenario

- 3 linee guida di buona qualità metodologica, pur indicando più o meno esplicitamente la possibilità di diagnosticare l'allergia all'uovo sulla base dell'anamnesi e della positività degli SPT e delle IgEs, riportano nelle raccomandazioni la necessità di praticare il TPO in tutti tranne che nei pazienti con pregressa reazione anafilattica
- E' convenzionalmente accettato a livello internazionale che, nei pazienti con storia suggestiva di reazione IgE-mediata all'alimento, valori di cut-off di SPT e/o IgEs con VPP = 95% consentirebbero di diagnosticare un'allergia alimentare senza praticare il TPO
- I risultati degli studi sono discordanti per la grande eterogeneità dei disegni, anche se, aggregando i dati dei bambini di età < 2 anni, i valori sono compresi tra 3 e 5 mm (SPT) e tra 1.2 KU/l e 1.7 KU/l (IgEs).
- Attualmente lo studio di Peters 2013 trova conferma (per il cut-off di SPT) solo nello studio di Sporik (su 39 bambini)
- Questi risultati, inoltre, sono relativi al VPP, quindi sono validi solo in setting con uguale prevalenza di allergia all'uovo.

- Sulla base dei RV+ riportati nello studio di Peters, i valori di cut-off di SPTs e IgEs danno una prob. post- test > 90%, quindi consentono di confermare la diagnosi senza TPO solo in setting ad alta prevalenza di patologia

- Sarebbe utile confermare i dati di RV+ ed RV- dello studio di Peters: ciò consentirebbe di valutare la validità dei cut-off in setting diversi

- Andrea non ha avuto una reazione anafilattica. I valori di SPT = 6 mm e di IgEs = 5 KU/l consentirebbero, in teoria, di diagnosticare l'allergia all'albume e di prescrivere la dieta di eliminazione. Tuttavia, a mio parere, le evidenze sarebbero state più «robuste» se i risultati di Peters fossero stati confermati da un secondo studio di pari numerosità campionaria.

- Decido di discutere con i genitori il problema, valutando sia la loro opinione, sia la maggiore o minore difficoltà di praticare un TPO in tempi relativamente brevi.

Grazie



