

Diagnostic approach to drug hypersensitivity in children

Skin tests and in vitro testing

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Hello!

I am Luis Moral

I work in Alicante (Spain)
and this is (part of) my team



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PENICILLIN
ALLERG





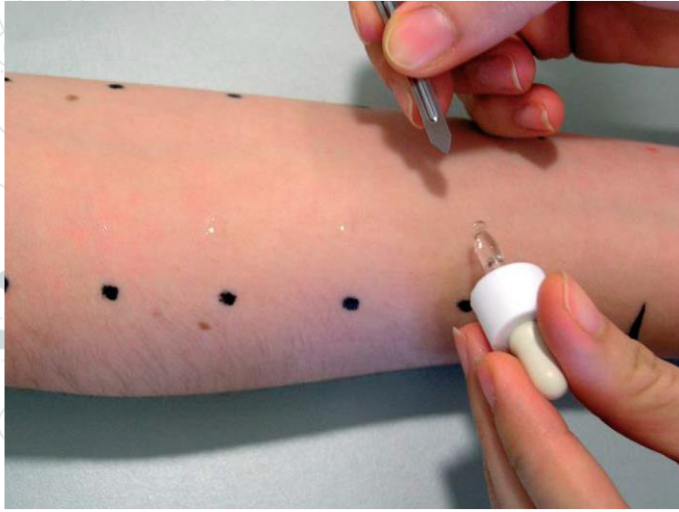
ANXIETY & PHOBIAS

**Increased use of alternative antibiotics
Increased length of hospitalization**

Objectives

- ◎ To know how skin tests work and how to use it
- ◎ To know how in vitro tests work and how to use it
- ◎ To know the limitations of skin and in vitro testing
- ◎ Specific issues in pediatrics

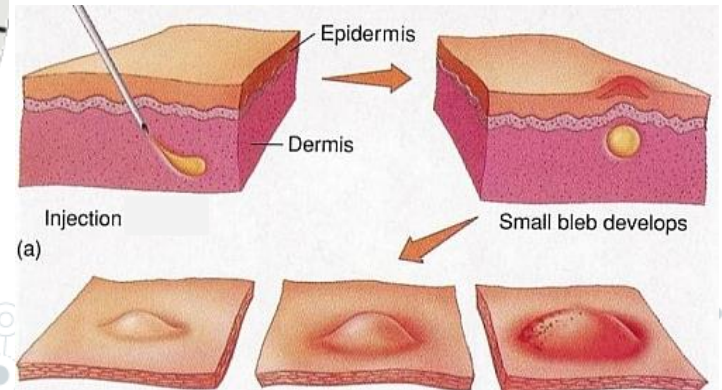
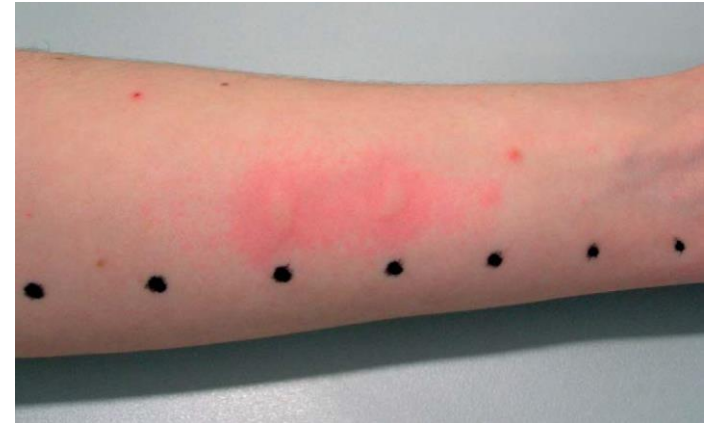
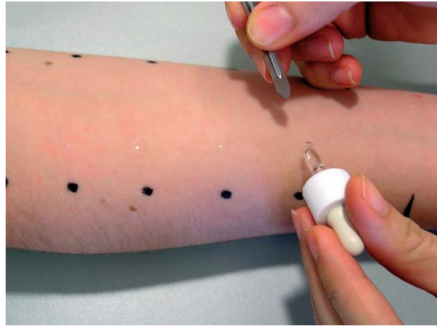
Specific issues with betalactams and NSAIDs



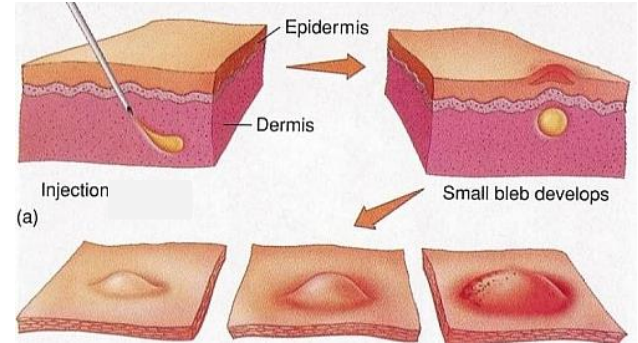
Skin testing



Skin testing: immediate response



Skin testing: late response



Skin testing: factors to consider

- ◎ Type of skin testing
- ◎ Device used
- ◎ Placement of tests (location and adjacent testing)
- ◎ Particular extracts being used
- ◎ Potential confounder of medications that may suppress the test response

Time elapsed

Skin testing: safety and risks



Skin testing: safety and risks

Dermatologica 136: 489–496 (1968)

From the Ospedale civile di Saluzzo, Ambulatorio Dermatovenerologico
(Dir.: Prof. Dr. *Marco Dogliotti*), Torino

An Instance of Fatal Reaction to the Penicillin Scratch-Test

By **M. DOGLIOTTI**

Severe Anaphylaxis With Cardiac Arrest Caused by Prick Test With Cefuroxime

Fernandes RA¹, Regateiro FS^{1,2}, Pita J¹, Ribeiro C¹, Carrapatoso I¹,
Todo-Bom A¹, Faria E¹

¹*Allergy and Clinical Immunology Unit, Hospitais da Universidade
de Coimbra, Centro Hospitalar e Universitário de Coimbra,
Coimbra, Portugal*

²*Instituto de Imunologia, Faculdade de Medicina, Universidade
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J Investig Allergol Clin Immunol 2018; Vol. 28(6): 426-428
doi: 10.18176/jiaci.0305

Ceftriaxone intradermal test-related fatal anaphylactic shock: a medico-legal nightmare

ALLERGY 2010: 65: 130–139

I. Riezzo, S. Bello, M. Neri, E. Turillazzi,
V. Fineschi*

Skin testing: availability

Table 2 Level of certainty to recommend skin tests in children with suspected drug hypersensitivity

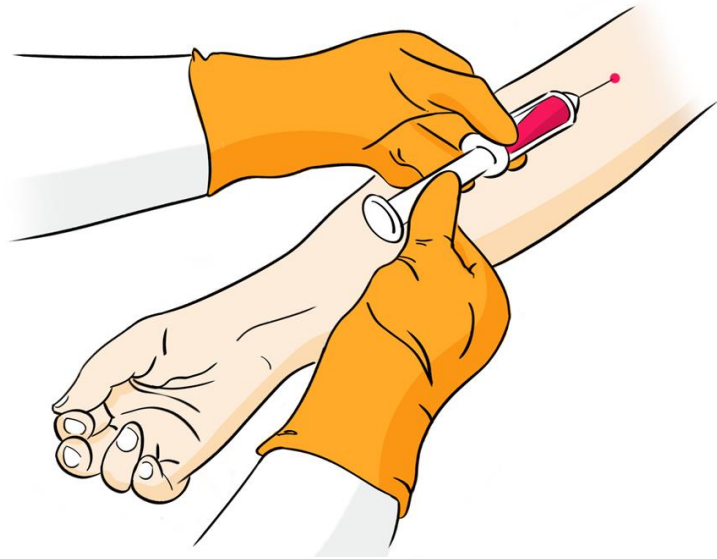
Higher evidence	Lower evidence
Anticonvulsants	Biologicals
Betalactam antibiotics*	Local anesthetics
Chlorhexidine*	Hormones
Heparins	Insulins
Neuromuscular blocking agents*	Nonbetalactam antibiotics
Platinum salts	Nonpyrazolone NSAIDs
Radiocontrast media	Opioids
Blue dyes	
Proton pump inhibitors	

*In addition, specific IgE determinations are available and recommended for these drugs.

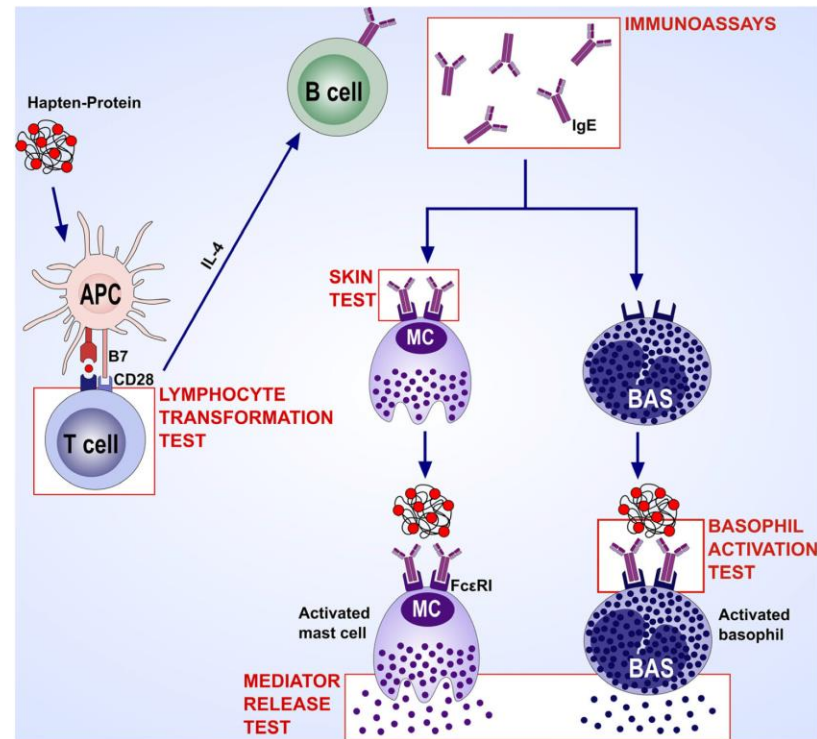
Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group

E. R. Gomes¹, K. Brockow², S. Kuyucu³, F. Saretta⁴, F. Mori⁵, N. Blanca-Lopez⁶, H. Ott⁷, M. Atanaskovic-Markovic⁸, M. Kidon⁹, J.-C. Caubet¹⁰ & I. Terreehorst¹¹ on behalf of the ENDA/EAACI Drug Allergy Interest Group

Allergy 2016; 71: 149–161



In vitro testing



In vitro testing: modalities

- ⊙ Markers for severity and type of reaction at the acute phase:
tryptase, histamine
 - ⊙ Identifying the relevant drug or drugs for immediate reactions:
 - sIgE by using an immunoassay
 - Basophil activation test (BAT)
 - ⊙ Identifying the relevant drug or drugs for non-immediate reactions:
 - Lymphocyte transformation test (LTT)
 - Cytokine determination
- Combined cytokine and cytotoxicity assays

HLA markers

J ALLERGY CLIN IMMUNOL
JANUARY 2019

Controversies in drug allergy: *In vitro* testing



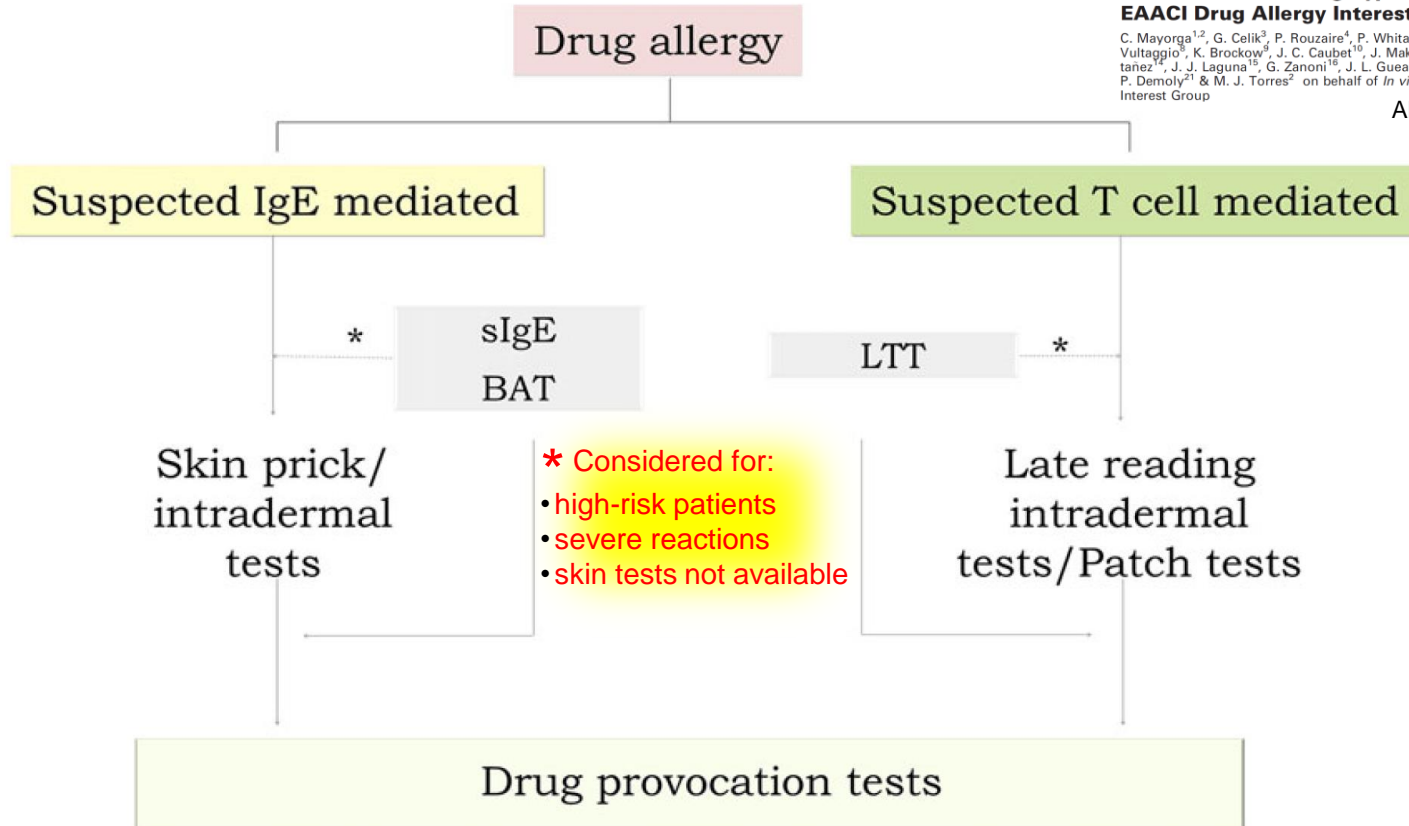
Cristobalina Mayorga, PhD,^{a,b,c} Didier G. Ebo, MD, PhD,^c David M. Lang, MD,^d Werner J. Pichler, MD,^e
Vito Sabato, MD, PhD,^c Miguel A. Park, MD,^f Joanna Makowska, MD, PhD,^g Marina Atanaskovic-Markovic, MD, PhD,^h
Patrizia Bonadonna, MD,ⁱ and Edgardo Jares, MD^a
^aMalaga, Spain, ^bAntwerp, Belgium, ^cCleveland, Ohio, ^dBern, Switzerland,
^eRochester, Minn, ^fLodz, Poland, ^gBelgrade, Serbia, ^hVerona, Italy, and ⁱBuenos Aires, Argentina

In vitro testing: present use

***In vitro* tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper**

C. Mayorga^{1,2}, G. Celik³, P. Rouzairi⁴, P. Whitaker⁵, P. Bonadonna⁶, J. Rodrigues-Cernadas⁷, A. Vultaggio⁸, K. Brockow⁹, J. C. Caubet¹⁰, J. Makowska¹¹, A. Nakonechna¹², A. Romão¹³, M. I. Montañez¹⁴, J. J. Laguna¹⁵, G. Zanoni¹⁶, J. L. Gueant¹⁷, H. Oude Elberink¹⁸, J. Fernandez¹⁹, S. Vlieg²⁰, P. Demoly²¹ & M. J. Torres² on behalf of *In vitro* tests for Drug Allergy Task Force of EAACI Drug Allergy Interest Group

Allergy 2016; 71: 1103–1134.



In vitro testing: future





History & Tests

Patients with positive skin test results to penicillin should not undergo penicillin or amoxicillin challenge

To the Editor:

Miguel A. Park, MD^a

Roland Solensky, MD^a

David A. Khan, MD^b

Mariana C. Castells, MD, PhD^c

Eric M. Macy, MD^e

David M. Lang, MD^d

J ALLERGY CLIN IMMUNOL

MARCH 2015



**Positive tests are
not confirmed**

**Accuracy can not
be determined**

Drug hypersensitivity tests: accuracy

You need to know these equations for boards!

2x2 Table

	Disease Present	No Disease	
Positive Test	a (true positive)	b (false positive, Type 1 error)	PPV = $a/(a+b)$
Negative Test	c (false negative, Type 2 error)	d (true negative)	NPV = $d/(d+c)$

$$\text{Sensitivity} = a/(a+c)$$

$$\text{Specificity} = d/(d+b)$$

$$\text{PPV} = \frac{\text{true positives} \times 100\%}{(\text{true positives} + \text{false positives})}$$

$$\text{NPV} = \frac{\text{true negatives} \times 100\%}{(\text{true negatives} + \text{false negatives})}$$

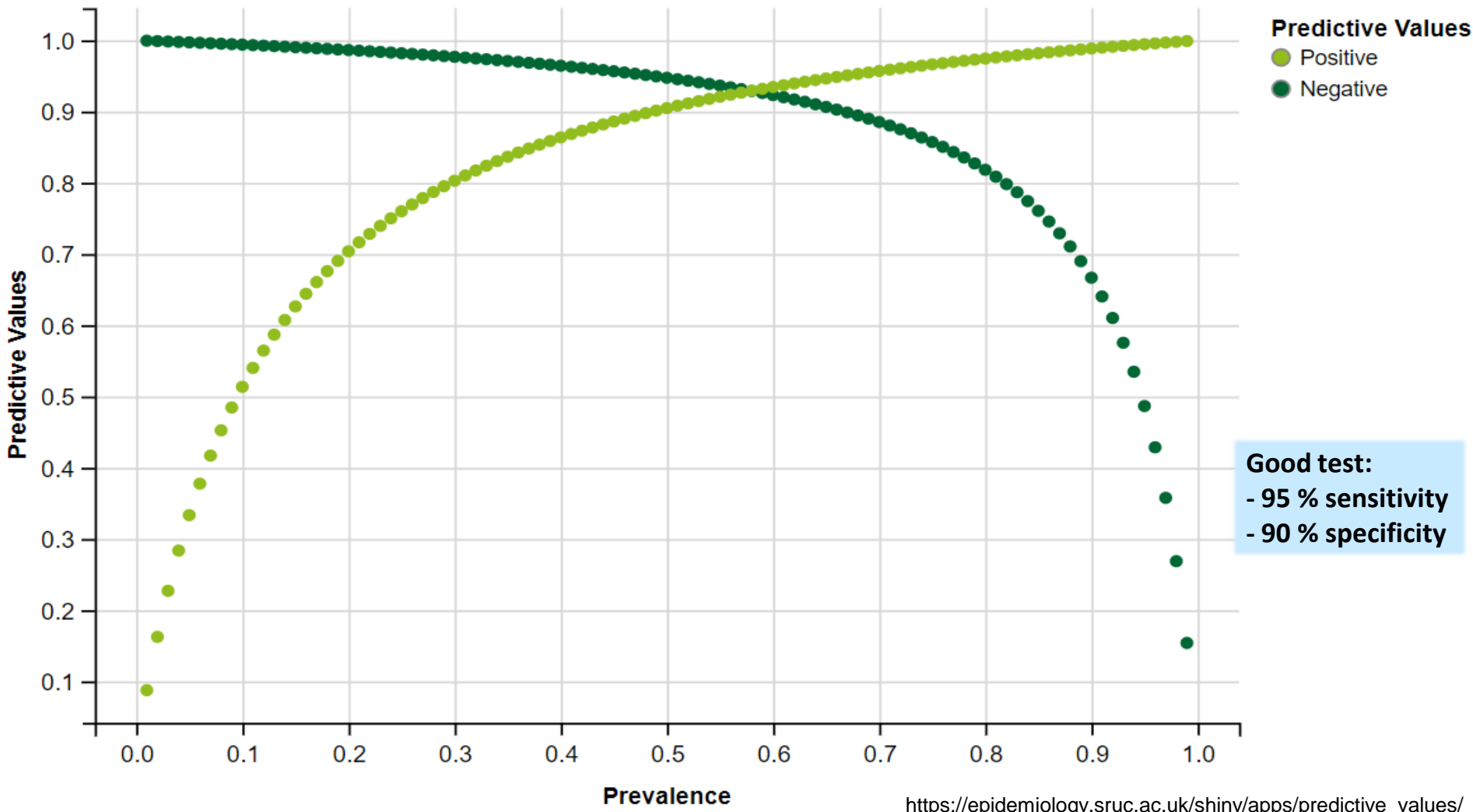


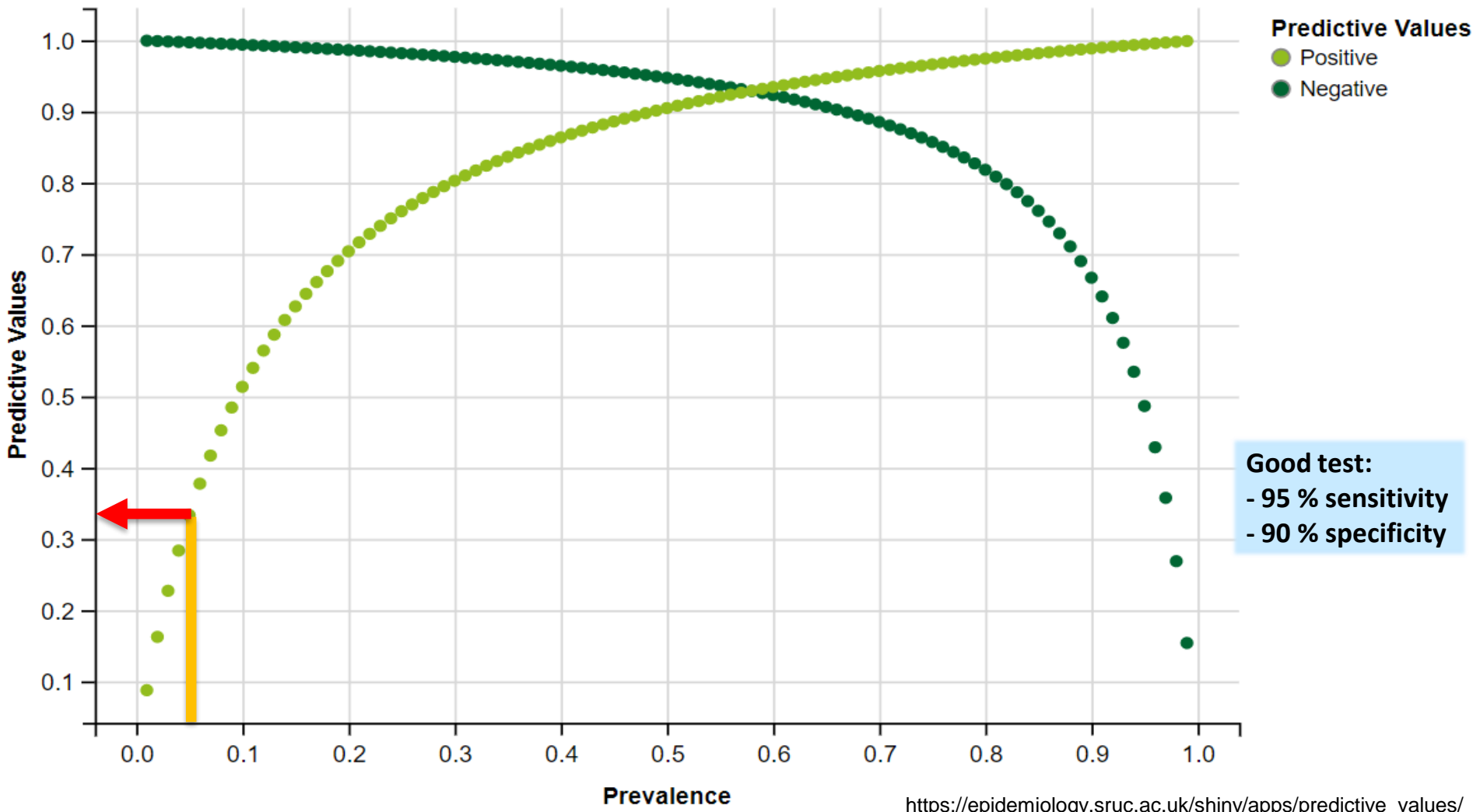
Is the predictive value always the same?

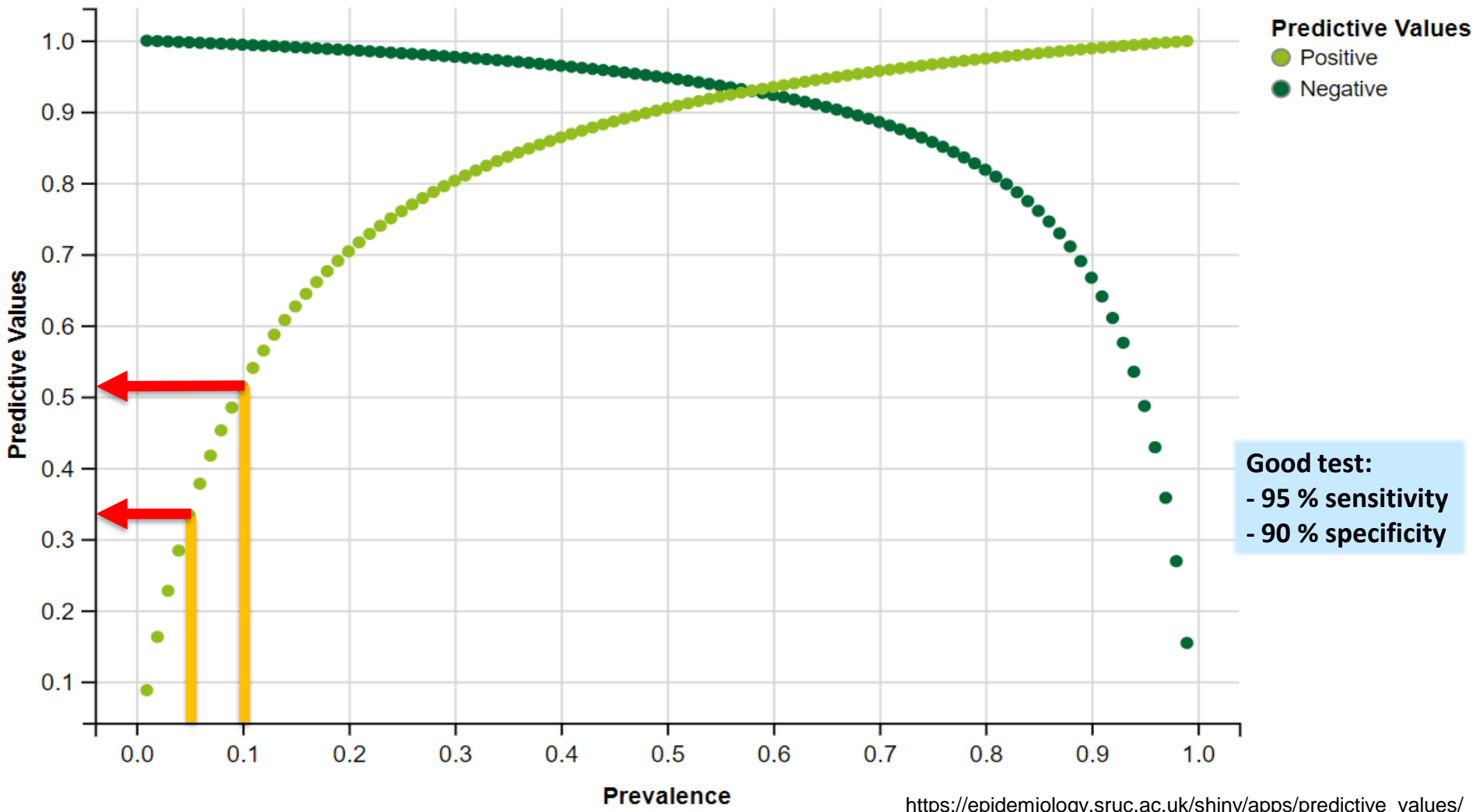
Great question!

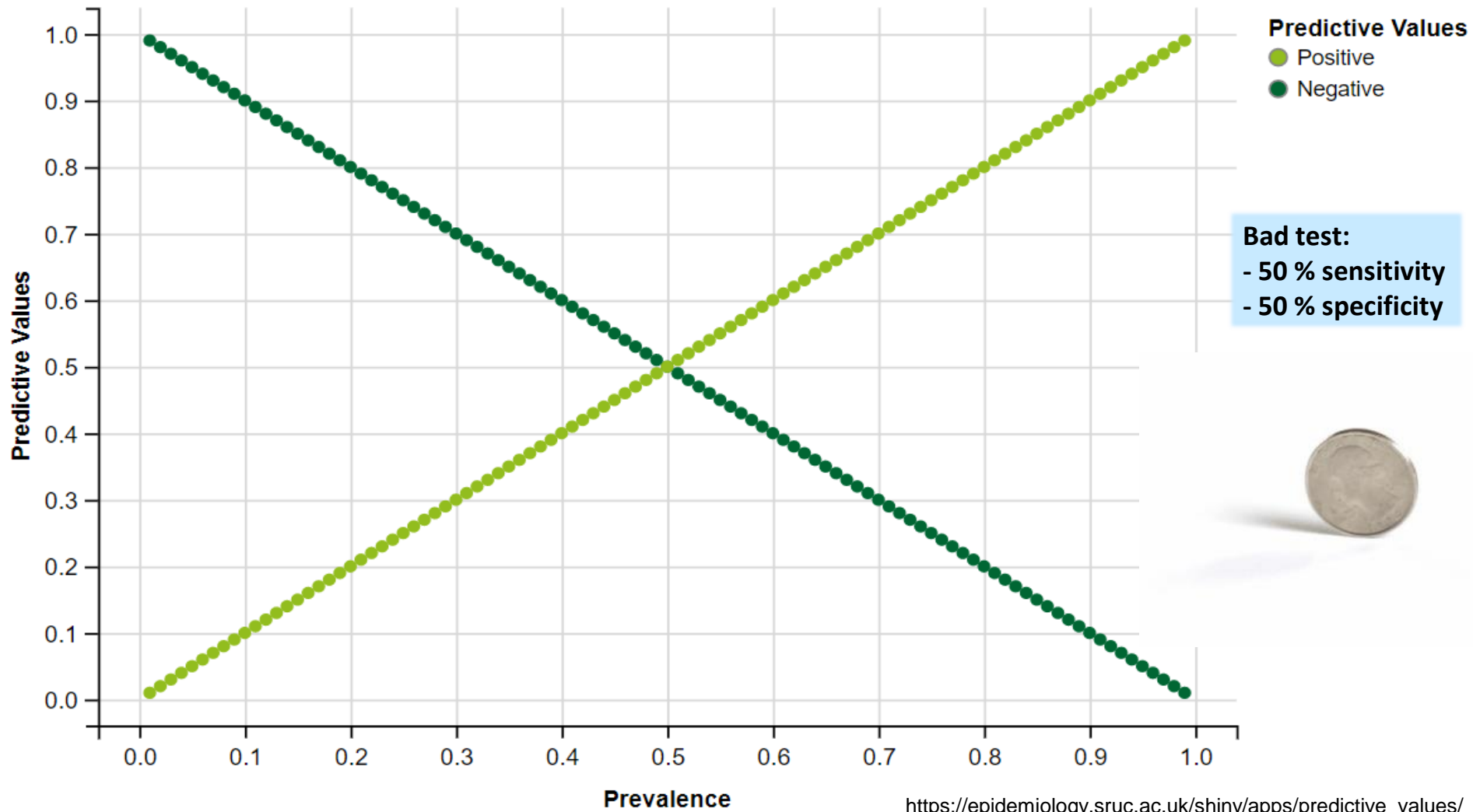


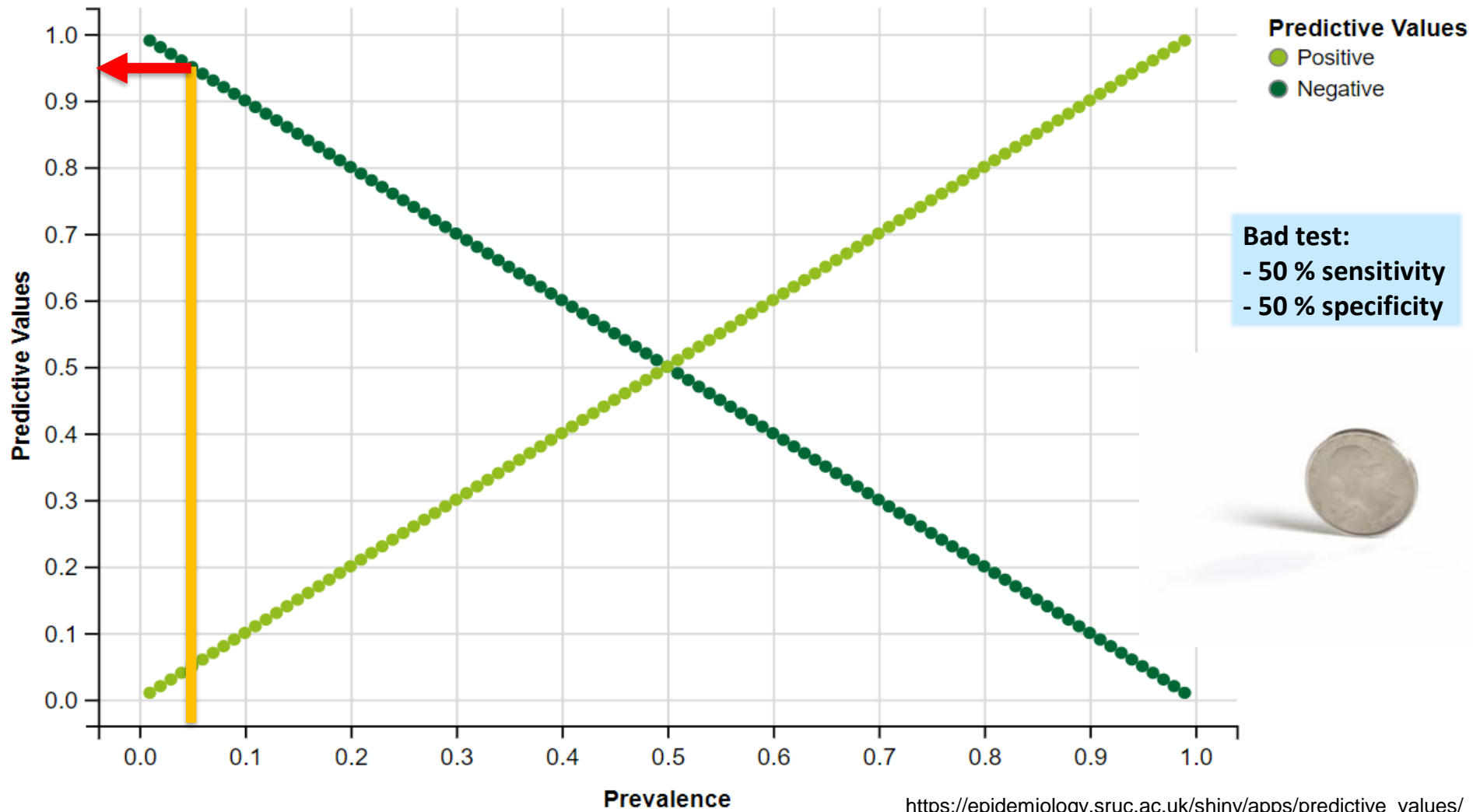
*Sensitivity & Specificity
+
Prevalence!*











Are skin or in vitro tests useful in drug hypersensitivity?

In favor:

- ⊙ Easy to perform and minimally invasive
- ⊙ Safety, specially when challenges may be dangerous
- ⊙ High negative predictive values
- ⊙ Investigation of the underlying pathomechanisms (in vitro tests)

Against:

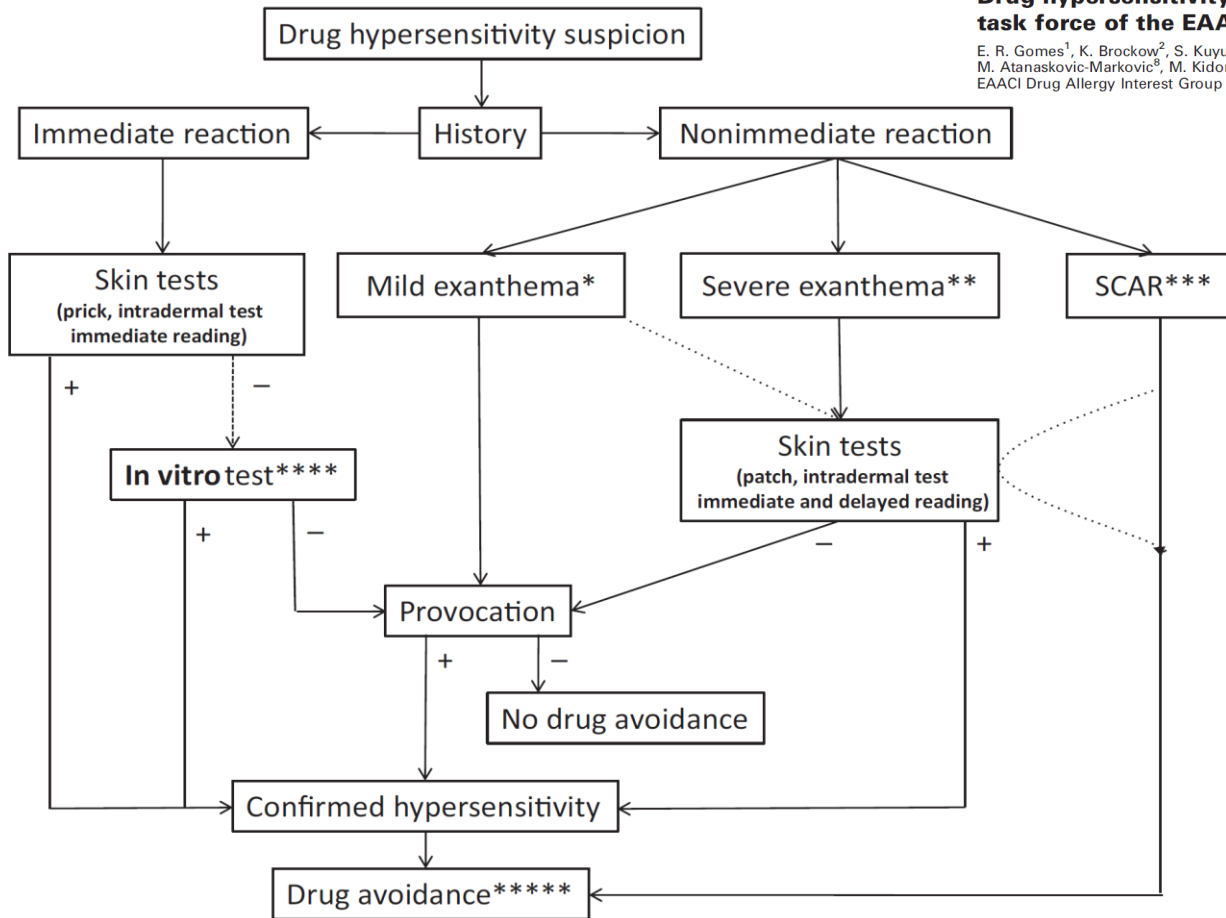
- ⊙ Time and resources-consuming
- ⊙ Painful
- ⊙ Not completely safe (skin tests)
- ⊙ Unknown but probably low positive predictive values (overdiagnosis)

Algorithm for drug hypersensitivity in children

Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group

E. R. Gomes¹, K. Brockow², S. Kuyucu³, F. Saretta⁴, F. Mori⁵, N. Blanca-Lopez⁶, H. Ott⁷, M. Atanaskovic-Markovic⁸, M. Kidon⁹, J.-C. Caubet¹⁰ & I. Terreehorst¹¹ on behalf of the ENDA/EAACI Drug Allergy Interest Group

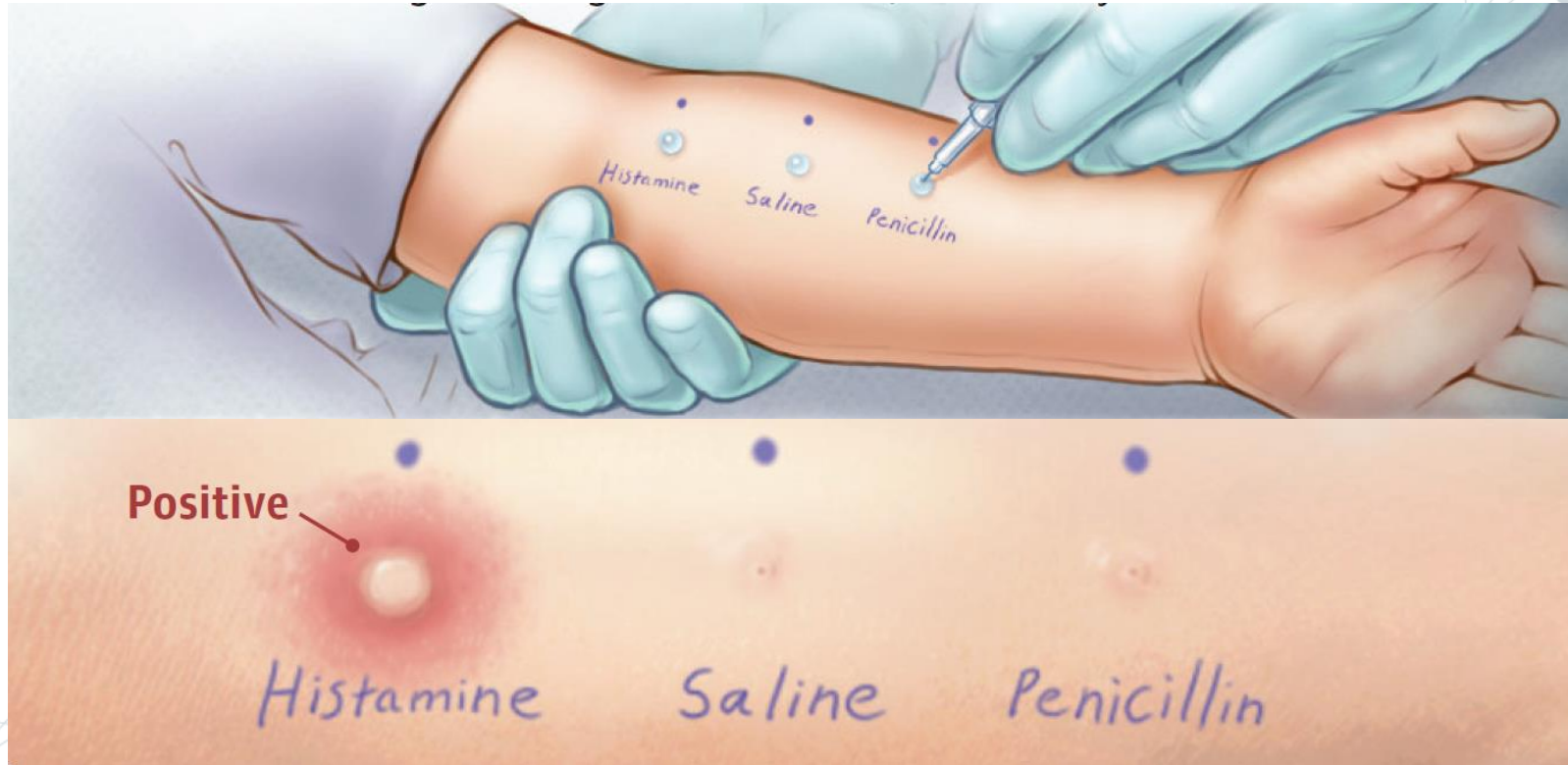
Allergy 2016; 71: 149–161



Specific issues in pediatrics

- ◎ Much less experience and research in children than in adults.
- ◎ Prevalence of hypersensitivity much lower in children than adults, lowering positive predictive values.
- ◎ A far less range of drugs implicated: mainly (but not only) antibiotics (betalactams) and NSAIDs
- ◎ The pain of intradermal tests (and of blood sampling) may limit their use in young children.

Is My Child Allergic to Penicillin?



Skin testing: non irritating test concentrations

Table 1 Nonirritating test concentrations for betalactam antibiotics

DRUG	SPT	IDT	PT
Penicilloyl-poly-L-lysine	5×10^{-5} mM	5×10^{-5} mM	NA
Minor determinant mixture	2×10^{-2} mM	2×10^{-2} mM	NA
Benzylpenicillin	10.000 UI	10.000 UI	5%
Amoxicillin	20 mg/ml	20 mg/ml	5%
Ampicillin	20 mg/ml	20 mg/ml	5%
Cephalosporins	2 mg/ml	2 mg/ml	5%

REVIEW

Immediate hypersensitivity reactions to penicillin and related antibiotics

M. E. WEISS and N. F. ADKINSON

Johns Hopkins University, School of Medicine,
Baltimore, Maryland, U.S.A.

Table 5. Incidence of allergic reactions to penicillin among patients who were skin tested

Reference	Skin-test reagents	Subjects evaluated	% with reactions	Comments (unless otherwise stated all subjects had positive histories of penicillin allergy)
<i>Positive skin tests</i>				
Parker <i>et al.</i> (1962) [89]	PPL	23	39%	All with negative histories of penicillin allergy
Rytel <i>et al.</i> (1963) [90]	PPL	55	5.2%	Only these with negative histories treated. See comments from Table 4
Brown <i>et al.</i> (1964) [91]	PPL	33	27.3%	Positive history of penicillin allergy
Brown <i>et al.</i> (1964) [91]	PPL	206	10.2%	Negative history of penicillin allergy
Levine and Zolov (1969) [42]	PPL	11	73%	All immediate or accelerated reactions
	MDM			
Adkinson <i>et al.</i> (1971) [94]	PPL	1	100%	Accelerated urticarial reaction
	MDM			
Green <i>et al.</i> (1977) [95]	PPL	9	67%	Some reacted to intradermal dose during desensitization (many with immediate type reactions)
	Pen G			
Chandra <i>et al.</i> (1980) [32]	PPL	8	100%	All with accelerated reactions
	MDM			
Solley <i>et al.</i> (1982) [46]	PPL	8	50%	
	MDM			

The role of penicillin in benign skin rashes in childhood: A prospective study based on drug rechallenge

Jean-Christoph Caubet, MD,^a Laurent Kaiser, MD,^b Barbara Lemaître, MS,^b Benoît Fellay, PhD,^c Alain Gervaix, MD,^a
and Philippe A. Eigenmann, MD^a *Geneva and Fribourg, Switzerland*

J ALLERGY CLIN IMMUNOL
JANUARY 2011

Culprit drug	Intradermal test (+)	Oral challenge (culprit drug)
Amoxicillin + clavulanic acid	MDM & PPL	Delayed skin rash
Amoxicillin	PPL	Delayed skin rash
Amoxicillin (± clavulanic acid)	MDM & PPL	No reaction
Amoxicillin (± clavulanic acid)	MDM & PPL	No reaction
Amoxicillin (± clavulanic acid)	MDM & PPL	No reaction
Amoxicillin (± clavulanic acid)	PPL	No reaction
Amoxicillin (± clavulanic acid)	MDM & PPL & Amoxicillin	No reaction
Amoxicillin (± clavulanic acid)	Amoxicillin	No reaction
Cefaclor	Cefuroxime	Immediate skin rash
Cefprozil	Cefuroxime	Delayed skin rash
Cephalosporin	PPL	No reaction

PPV
36%

11 children with immediate reading positive intradermal test



Drug Allergy

Theme Coordinators: Pascal Demoly and James Li

AN OFFICIAL JOURNAL OF



American Academy of
Allergy Asthma
& Immunology

CLINICAL MANAGEMENT REVIEW
Cephalosporin Allergy: Current Understanding
and Future Challenges

CLINICAL COMMENTARY REVIEWS
Sulfonamide Hypersensitivity: Fact and Fiction

Innovations in Health Care Delivery:
Drug Allergy

SPECIAL ARTICLE
Large Health System Databases and Drug
Hypersensitivity

GRAND ROUNDS REVIEW
Identification and Management of Perioperative
Anaphylaxis

THEME EDITORIAL
The Changing World of Drug Allergies

To challenge or not to challenge: Literature data on the positive predictive value of skin tests to beta- lactams

Anca Mirela Chiriac, MD, PhD^{a,b},

Maria-Joao Vasconcelos, MD^{a,c}, Lisa Izquierdo, MD^a,

Laetitia Ferrando, MS^a, Olga Nahas, MD^a, and

Pascal Demoly, MD, PhD^{a,b}

Number of patients	Type of reaction	Drug reexposure	Positive predictive value
15	Anaphylaxis	Culprit	100%
11	Immediate non-anaphylactic	Culprit	55%
37	Non-immediate	Culprit	84%
56	Mostly immediate	Cross-reactive	16%

Lack of uniformity in the investigation and management of suspected β -lactam allergy in children










Ru-Xin Melanie Foong¹, Kirsty Logan¹, Michael Richard Perkin² & George du Toit^{1,3}

¹Department of Paediatric Allergy, Guys and St. Thomas' Hospitals NHS Foundation Trust, London, UK; ²Population Health Research Institute, St. George's University of London, London, UK; ³Division of Asthma, Allergy and Lung Biology, Department of Allergy, King's College London, St. Thomas' Hospital, London, UK

Pediatr Allergy Immunol 2016; **27**: 527–532.

There is **lack of consistency** amongst clinicians in different countries in the diagnosis and management of suspected beta-lactam allergy


A EAACI drug allergy interest group survey on how European allergy specialists deal with β -lactam allergy

Maria Jose Torres¹  | Gulfem Elif Celik²  | Paul Whitaker³ |
Marina Atanaskovic-Markovic⁴  | Annick Barbaud⁵ | Andreas Bircher⁶  |
Miguel Blanca⁷ | Knut Brockow⁸  | Jean-Christoph Caubet⁹ |
Josefina Rodrigues Cernadas¹⁰ | Anca Chiriac^{11,12}  | Pascal Demoly¹¹  |
Lene Heise Garvey¹³  | Hans F. Merk¹⁴ | Holger Mosbech¹³ | Alla Nakonechna¹⁵  |
Antonino Romano¹⁶

Allergy. 2019;74:1052–1062

A **significant heterogeneity** exists in current practice not only among countries, but also among centres within the same country

Oral challenge without skin tests in children with non-severe beta-lactam hypersensitivity: Time to change the paradigm?

Luis Moral¹  | Jean-Christoph Caubet²

Original Article

Comparing Direct Challenge to Penicillin Skin Testing for the Outpatient Evaluation of Penicillin Allergy: A Randomized Controlled Trial



S. Shahzad Mustafa, MD^{a,b}, Kelly Conn, PhD, MPH^c, and Allison Ramsey, MD^{a,b} *Rochester, NY*

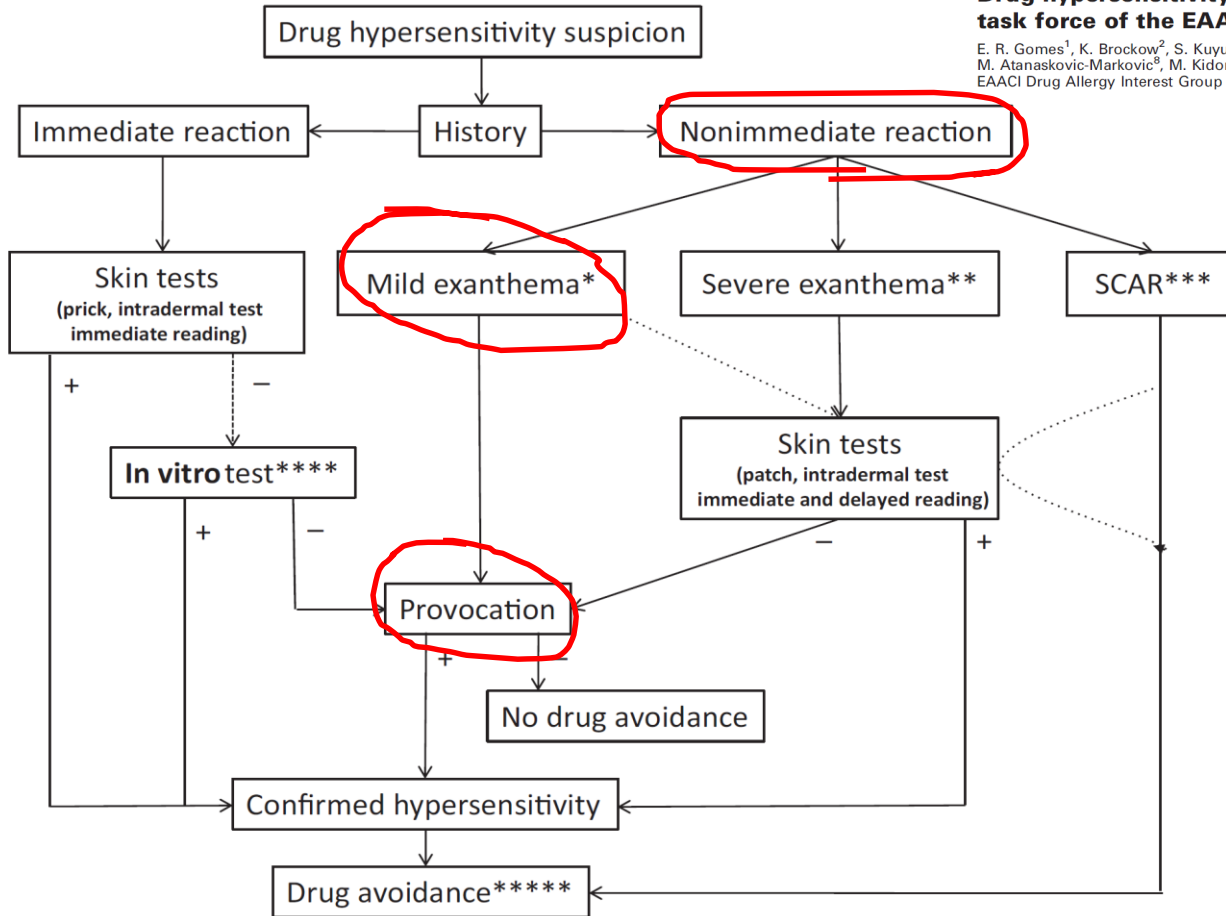
Farah Farid, MD^b, PhD, MPH^c, and Nabiyat Haque, MD^b, PhD^c *London, UK, and Hong Kong, China*

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Allergy 2016; 71: 149–161



Non
Steroidal
Anti
Inflammatory
Drugs



EAACI/ENDA Position Paper: Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents

Mona Kidon¹  | Natalia Blanca-Lopez² | Eva Gomes³ | Ingrid Terreehorst⁴ |
Luciana Tanno^{5,6,7} | Claude Ponvert⁸  | Chiang Wen Chin⁹ | Jean Christoph Caubet¹⁰ |
Ozge Soyer¹¹ | Francesca Mori¹² | Miguel Blanca¹³ | Marina Atanaskovic-Markovic¹⁴ 

Pediatr Allergy Immunol. 2018;29:469–480.

TABLE 3 Test concentrations and formulations of metamizole and paracetamol for skin and intradermal testing

	Formulation	Skin test	Intradermal test
Acetaminophen	Perfalgan [®]	10 mg/mL	1 mg/mL
Metamizole sodium	Novalgin [®]	40-400 mg/mL 400 mg/mL	0.4-4 mg/mL 40 mg/mL





*Take
home message

So, what?



**Take
home message*

In vitro tests...



Potentially dangerous
reaction (immediate,
severe...)

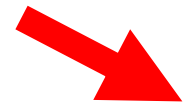
Mild late reaction

**Skin
tests**

Drug
challenge



**Take
home message*



Factors increasing Positive Predictive Values

(M): Exanthem – Urticaria – Anaphylaxis
(T): Late – Immediate – Sudden
(D): Dissimilar – Cross reactive – Same

(M): Manifestations

(T): Timing

(D): tested Drug



**Take
home message*

Thanks!

See you anytime!



You can find me at:
lmoralg@gmail.com