UMC St Radboud

Impact of prophylaxis on galactomannan, ß-D-glucan and PCR

J Peter Donnelly PhD FRC Path
Department of Haematology
Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands

Question 1

Does antifungal prophylaxis have an adverse impact on tests for galactomannan, ß-D-glucan and DNA?

- Yes
- No
- Don’t know

Question 2

Does antifungal prophylaxis have an adverse impact only on tests for **galactomannan**?

- Yes
- No
- Don’t know

Question 3

Does antifungal prophylaxis have an adverse impact only on tests for **ß-D-glucan**?

- Yes
- No
- Don’t know

Question 4

Does antifungal prophylaxis have an adverse impact only on PCR tests for **DNA**?

- Yes
- No
- Don’t know

UMC St Radboud

First things first - Google

Antifungal treatment affects the laboratory **diagnosis** of invasive - NCBI
www.ncbi.nlm.nih.gov/pubmed/22049217 - Vertaal deze pagina
door E McCulloch - 2011 - Verwante artikelen
2 Nov 2011 – **Antifungal** treatment affects the laboratory diagnosis of invasive aspergillosis. **...** to investigate the performance of non-invasive **diagnostic tests** such as **...** rat inhalation model of IA was used to examine the **effects** of an azole, **...**

Impact of **diagnostic** markers on early **antifungal** therapy.
www.ncbi.nlm.nih.gov/pubmed/14624100 - Vertaal deze pagina
door BL Jones - 2003 - Geciteerd door 39 - Verwante artikelen
Impact of **diagnostic** markers on early **antifungal** therapy. **...** on several factors including patient selection and clinical application of the **test**, and issues regarding **...**

Antifungal Therapy Decreases Sensitivity of theAspergillus **...**
cid.oxfordjournals.org/content/40/12/1762.full - Vertaal deze pagina
door KA Marr - 2005 - Geciteerd door 188 - Verwante artikelen
It follows that the utility of the **test** as a **diagnostic** aid might be impaired during **...** **impact** of mold-active **antifungal** therapy administered during **test** sampling.

Early **diagnosis** of fungal infection in immunocompromised patients
jac.oxfordjournals.org/content/61/suppl.../i3.full - Vertaal deze pagina
door RA Barnes - 2008 - Geciteerd door 28 - Verwante artikelen
Factors that influence performance of these **diagnostic tests** include underlying **....** but **impact** on **antifungal** usage was not explored.32 A randomized study of a **...**

The **effect** of **antifungal** treatments on laboratory **diagnostic** assays **...**
registration.akm.ch/einsicht.php?... - Vertaal deze pagina
9 May 2011 – The **effect** on these **diagnostic tests** and how these tests are impacted upon by the use of different classes of **antifungal** agents in this in vivo **...**

Common assertion

bjh review

Antifungal prophylaxis during treatment for haematological malignancies: are we there yet?

© 2011 Blackwell Publishing Ltd, *British Journal of Haematology* doi:10.1111/j.1365-2141.2011.08650.x

Thomas R. Rogers,[1] Monica A. Slavin[2] and J. Peter Donnelly[3]

[1]Department of Clinical Microbiology, Trinity College Dublin, St James's Hospital, Dublin 8, Ireland, [2]Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia, and [3]Department of Blood Transfusion and Transplant Immunology, Hematology, University Medical Center St. Radboud, Nijmegen, the Netherlands

…patients in most of the above studies had received different antifungal drugs for prophylaxis and, because we know this can reduce the sensitivity of galactomannan (GM) tests (Marr et al, 2005), we can assume that less cases will be recorded as probable IFD so that, according to EORTC/MSG criteria, some will be possible cases or even unclassified.

UMC St Radboud

Common assertion

Bone Marrow Transplantation (2011), 1–9
© 2011 Macmillan Publishers Limited All rights reserved 0268-3369/11
www.nature.com/bmt

ORIGINAL ARTICLE

ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients

O Marchetti[1,6], F Lamoth[1,6], M Mikulska[2], C Viscoli[2], P Verweij[3] and S Bretagne[4,5] and the European Conference on Infections in Leukemia (ECIL) Laboratory Working Groups[7]

Decreased sensitivity has been reported during exposure to mould-active antifungal agents, for instance in patients receiving posaconazole or voriconazole prophylaxis which may prevent the circulation of GM

Common assertion

Impact of diagnostic markers on early antifungal therapy

Brian L. Jones[a] and Lorna A. McLintock[b]

Current Opinion in Infectious Diseases 2003, 16:521–526

The use of empirical or prophylactic antifungal therapy may affect the release of galactomannan as may the extent or localization of the disease process. The microenvironment and availability of nutrients could have a bearing on the rate of growth and hence release of galactomannan.

Some evidence

Antifungal Therapy Decreases Sensitivity of the *Aspergillus* Galactomannan Enzyme Immunoassay

Kieren A. Marr,[1,2] Michel Laverdiere,[3] Anja Gugel,[1] and Wendy Leisenring[1,2]

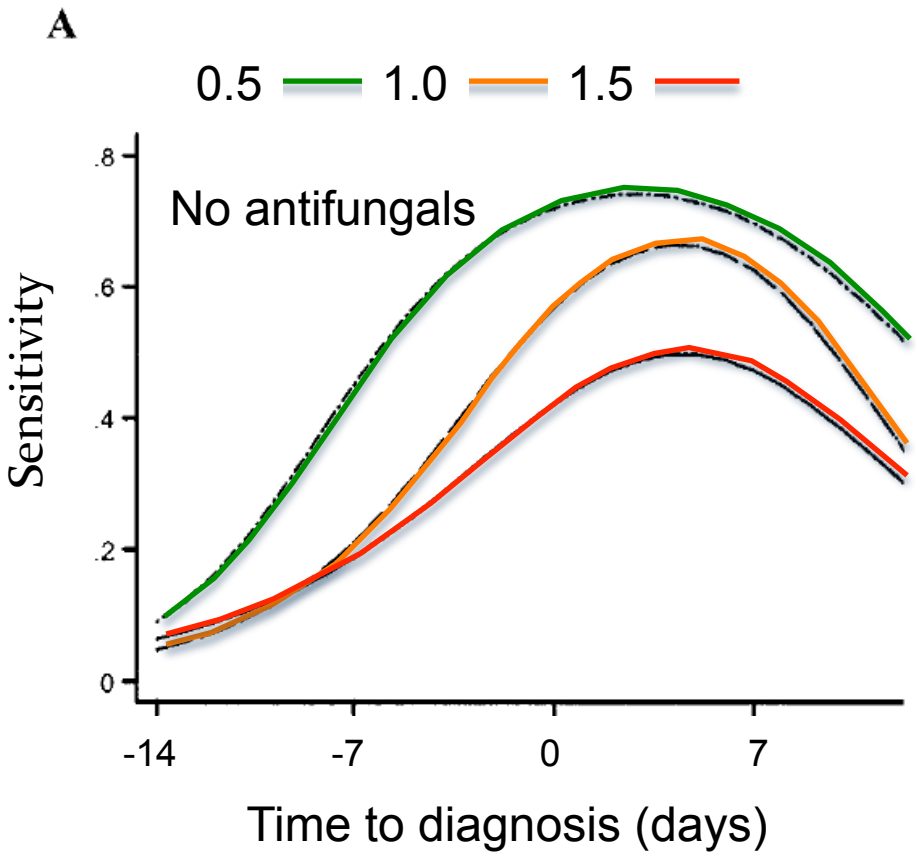
[1]Fred Hutchinson Cancer Research Center and [2]University of Washington, Seattle, Washington; and [3]Hopital Maisonneuve-Rosemont, Montreal, Canada

Clinical Infectious Diseases 2005; 40:1762–9

© 2005 by the Infectious Diseases Society of America. All rights reserved.

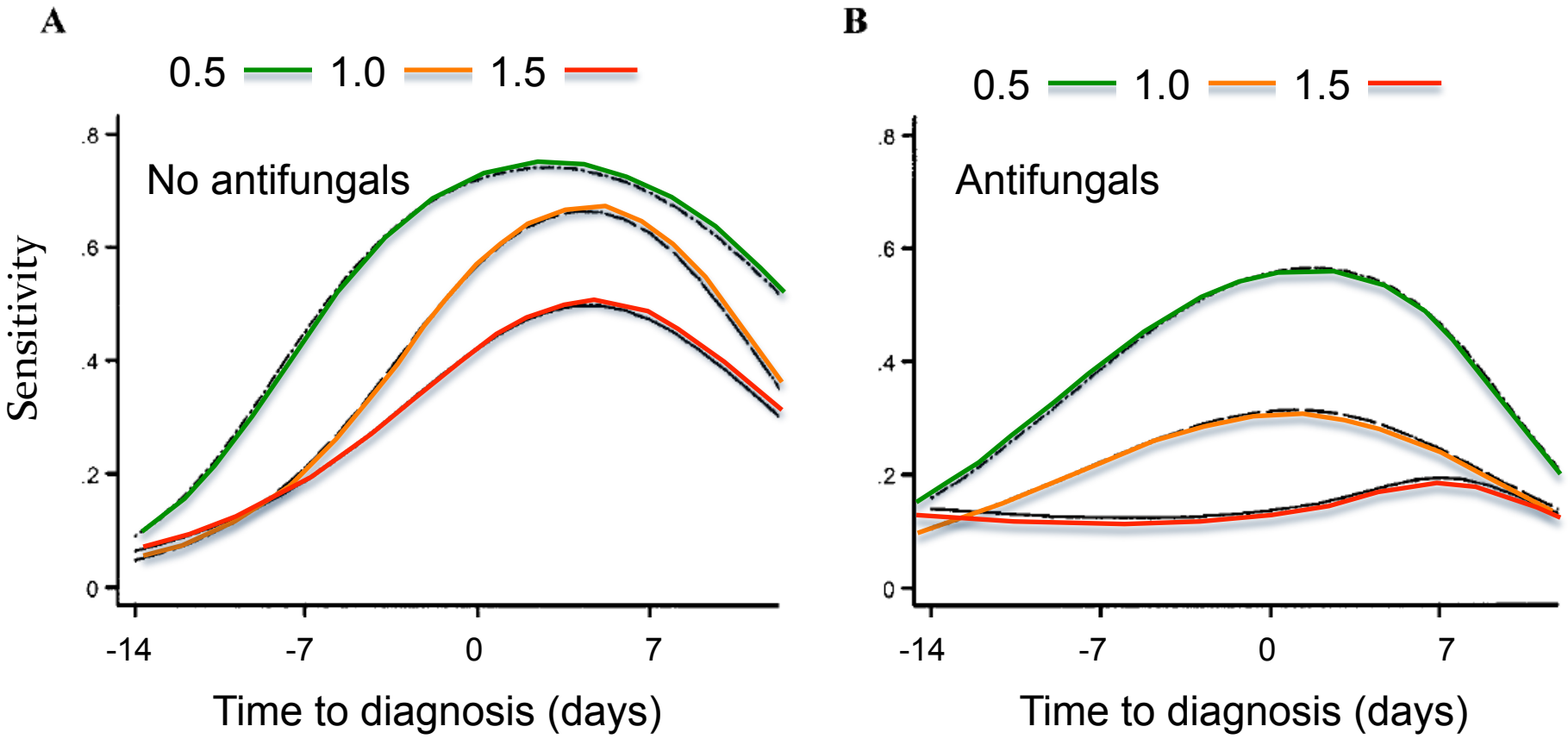
In summary, the results of this study demonstrate that the sensitivity of the GM EIA is impaired by administration of mold-active antifungal therapy. This finding has direct implications for the use of the assay as a diagnostic aid for patients receiving mold-active antifungal therapies.

Impact of antifungal drugs on GM sensitivity



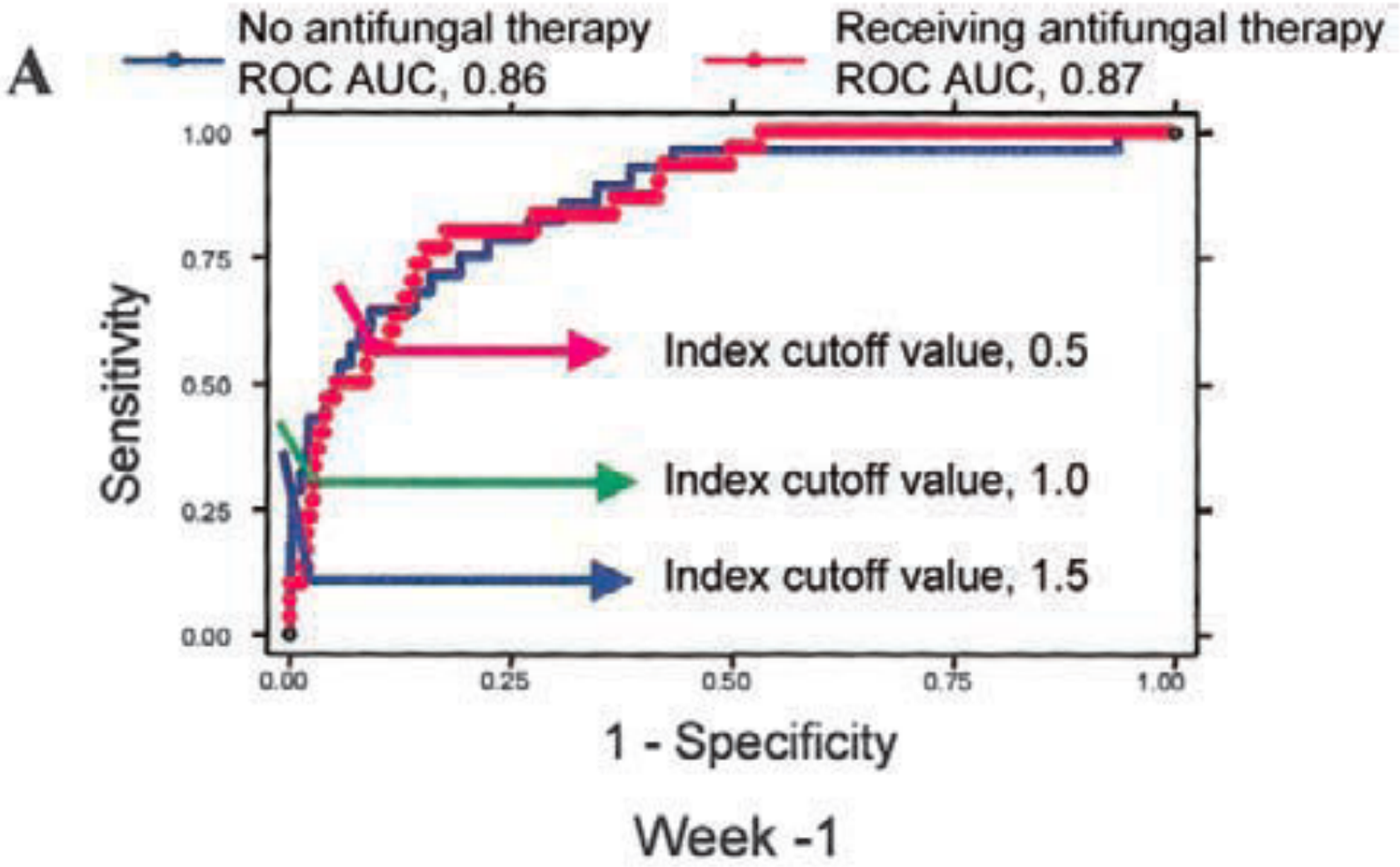
Marr et al Clin Infect Dis 2005; 40: 1762–1769.

Impact of antifungal drugs on GM sensitivity



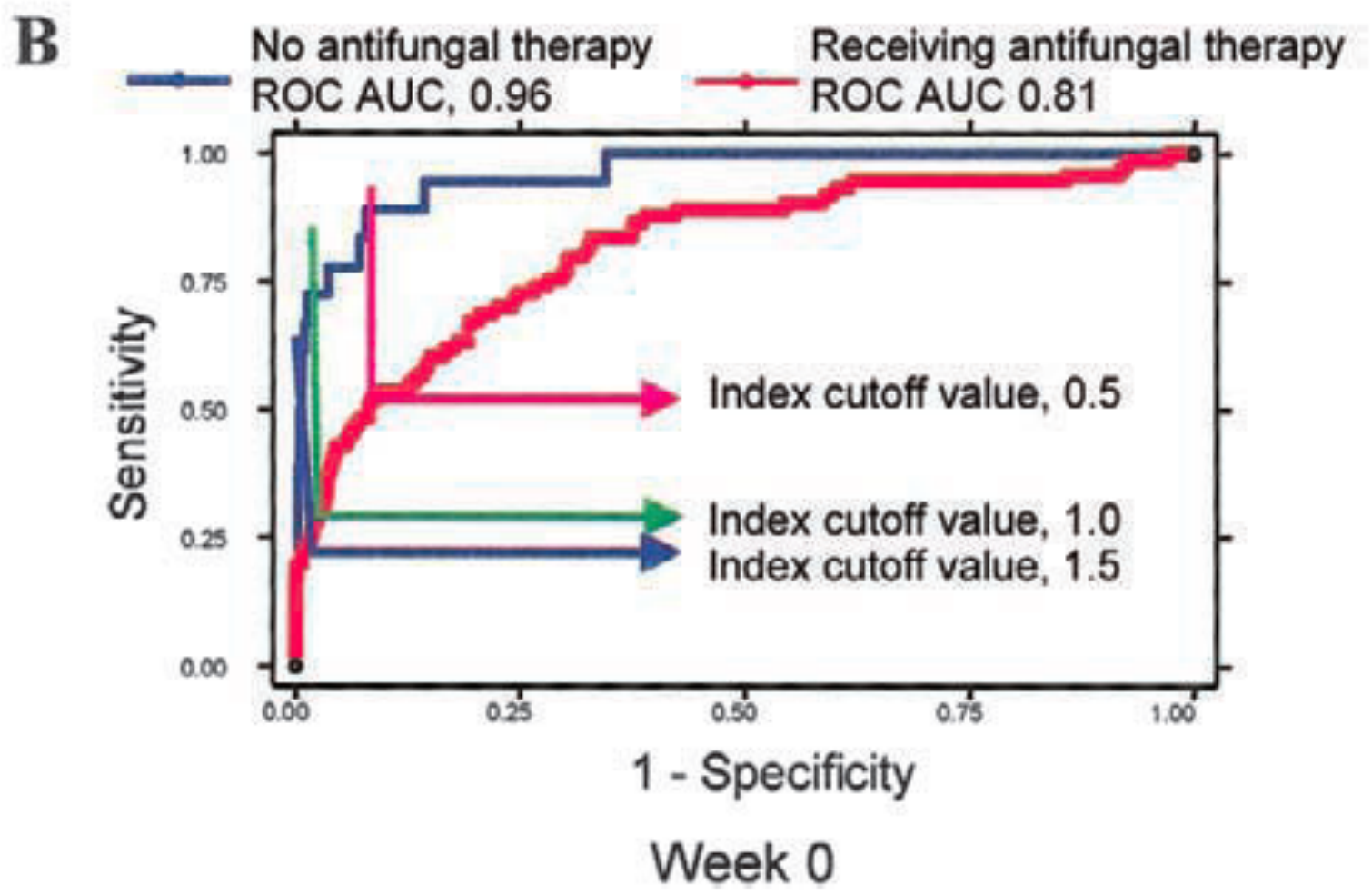
Marr et al Clin Infect Dis 2005; 40: 1762–1769.

Impact of antifungals drugs on GM test performance



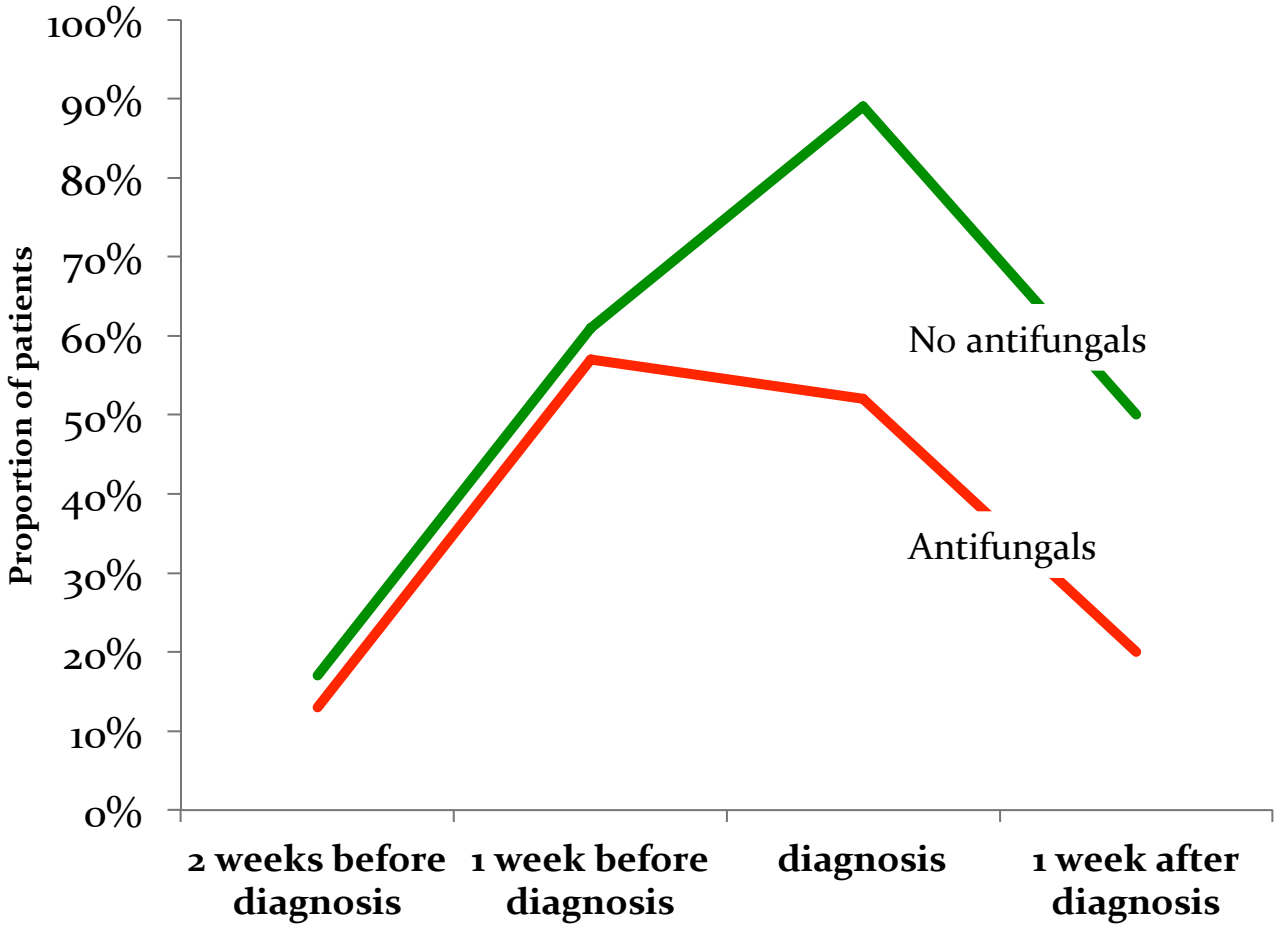
Marr et al Clin Infect Dis 2005; 40: 1762–1769.

Impact of antifungals drugs on GM test performance



Marr et al Clin Infect Dis 2005; 40: 1762–1769.

Antifungals & GM detection rates for patients



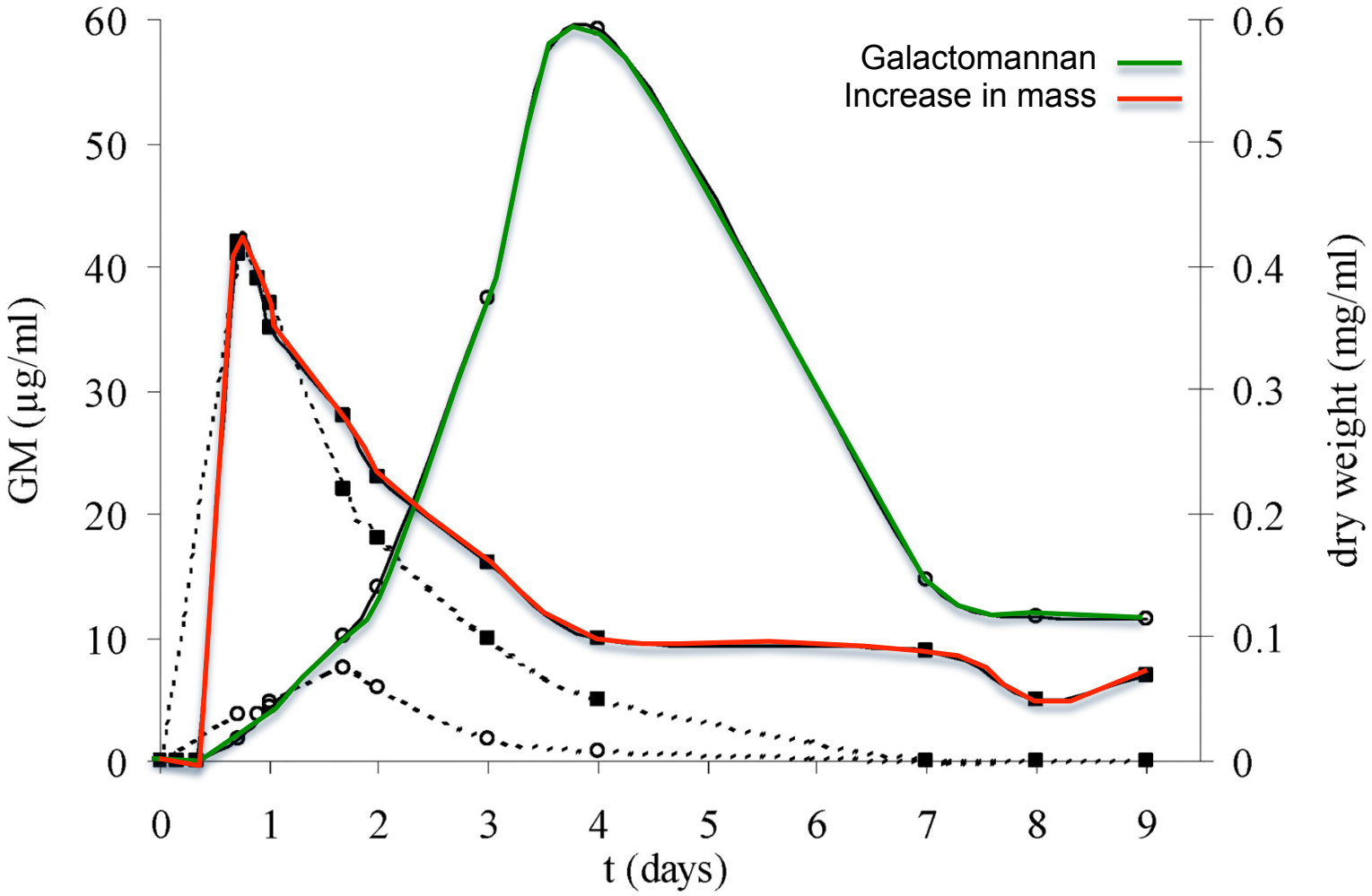
Marr et al Clin Infect Dis 2005; 40: 1762–1769.

Menu

- In-vitro data
- In-vivo data
- Patient cohort data
- Patient population data

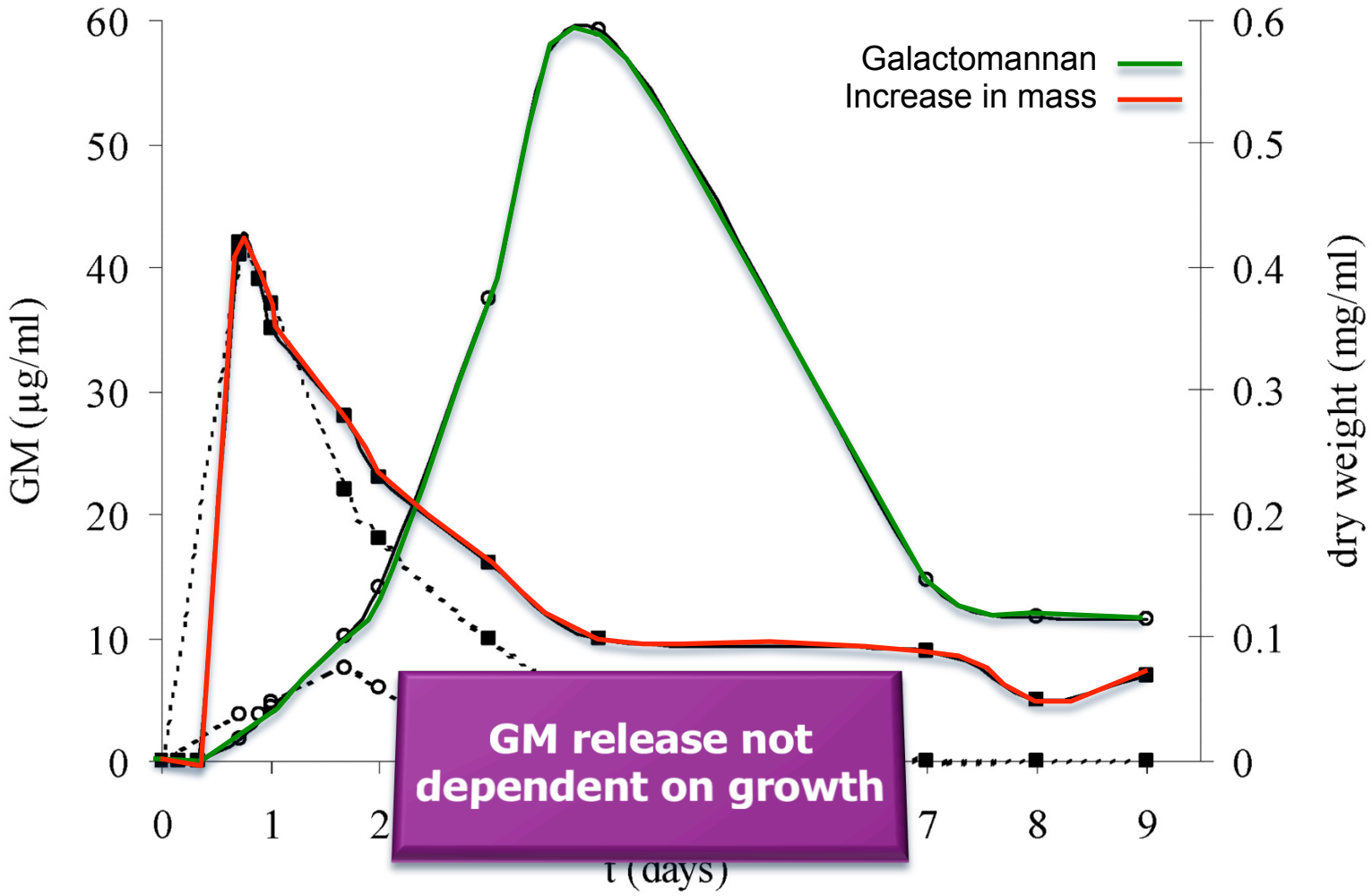
In-vitro

Release of GM from *A. fumigatus* in vitro



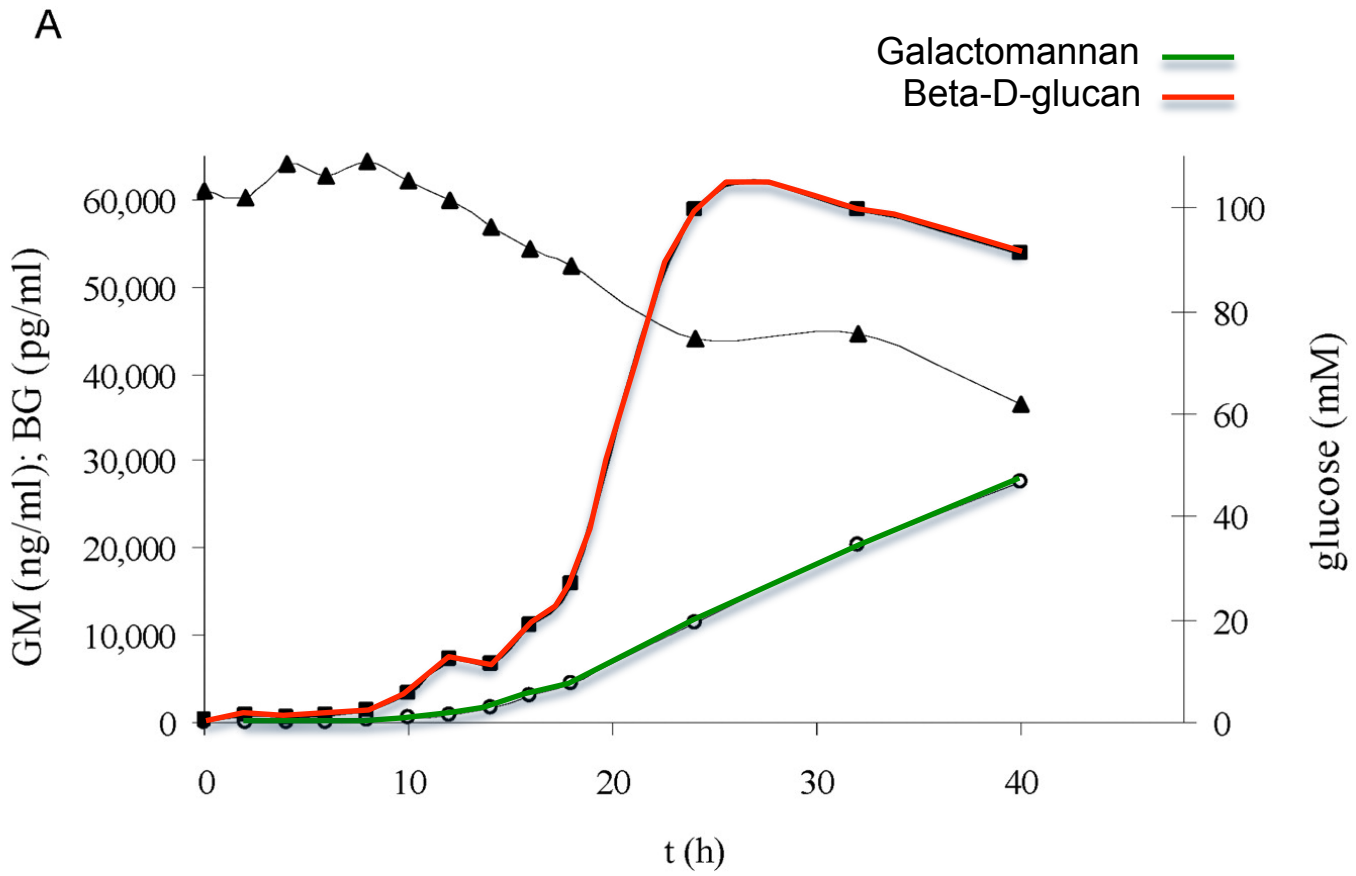
Mennink-Kersten et al. 2006 J. Clin. Microbiol. 44:1711-1718

Release of GM from *A. fumigatus* in vitro



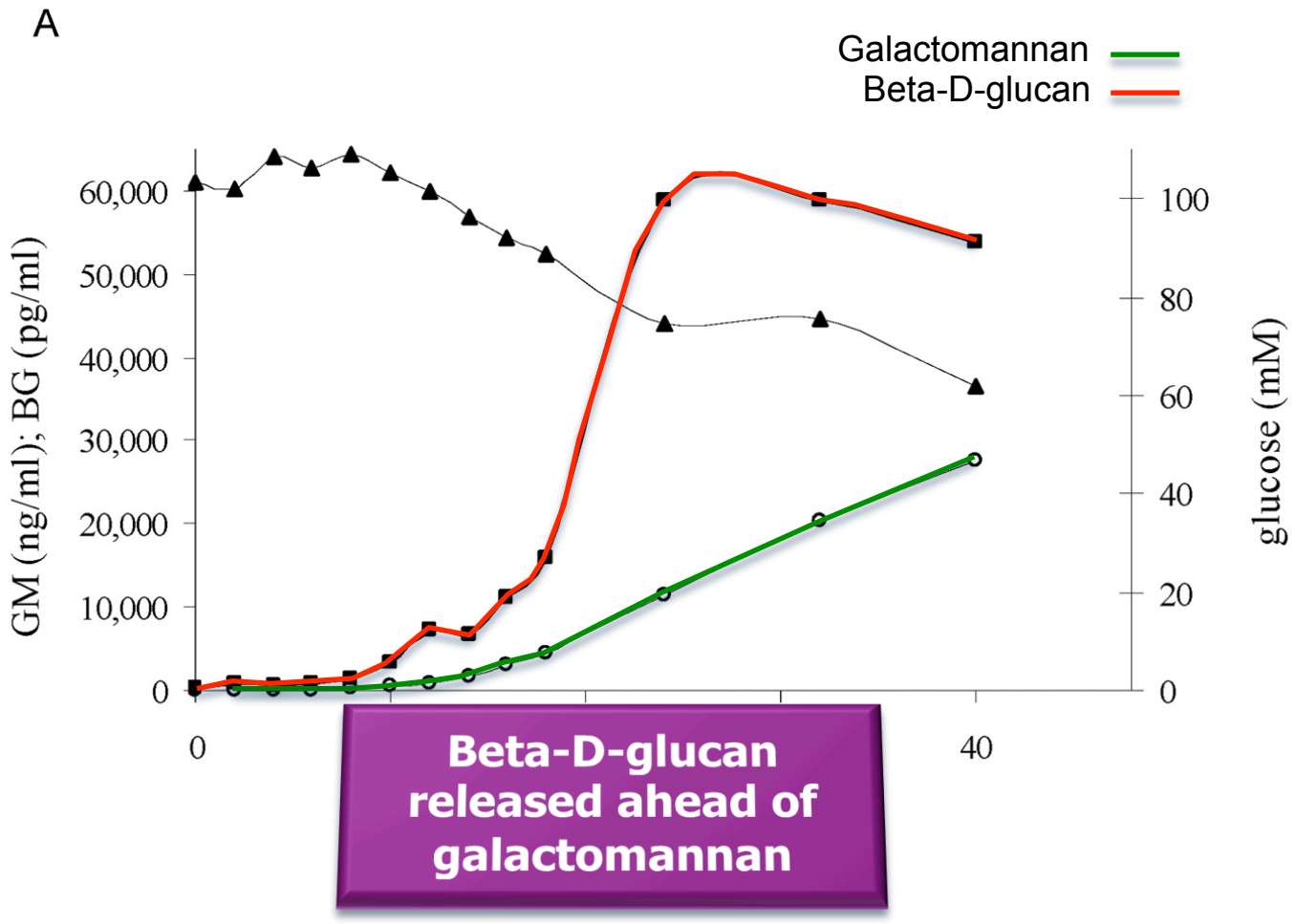
Mennink-Kersten et al. 2006 J. Clin. Microbiol. 44:1711-1718

Release of GM and BDG from *A. fumigatus* in vitro



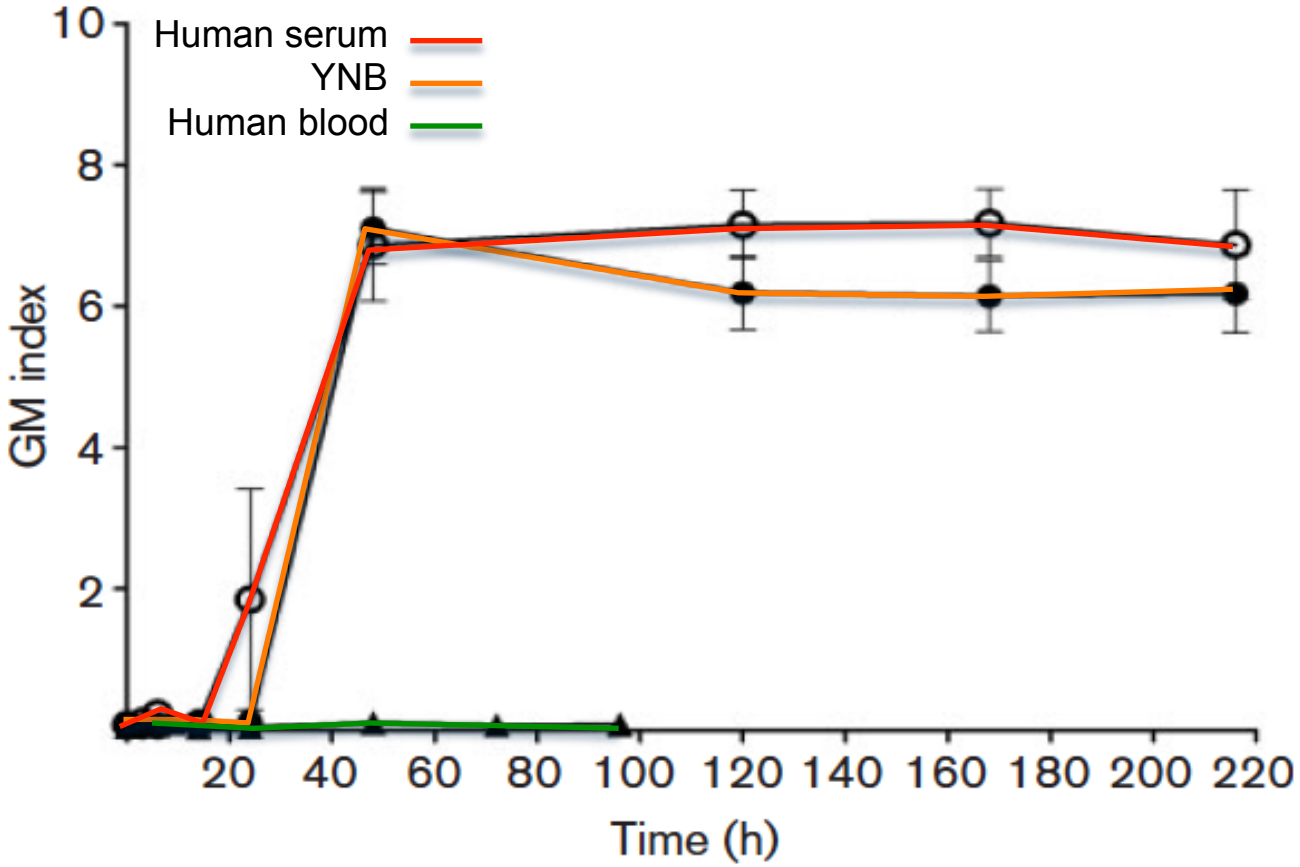
Mennink-Kersten et al. 2006 J. Clin. Microbiol. 44:1711-1718

Release of GM and BDG from *A. fumigatus* in vitro



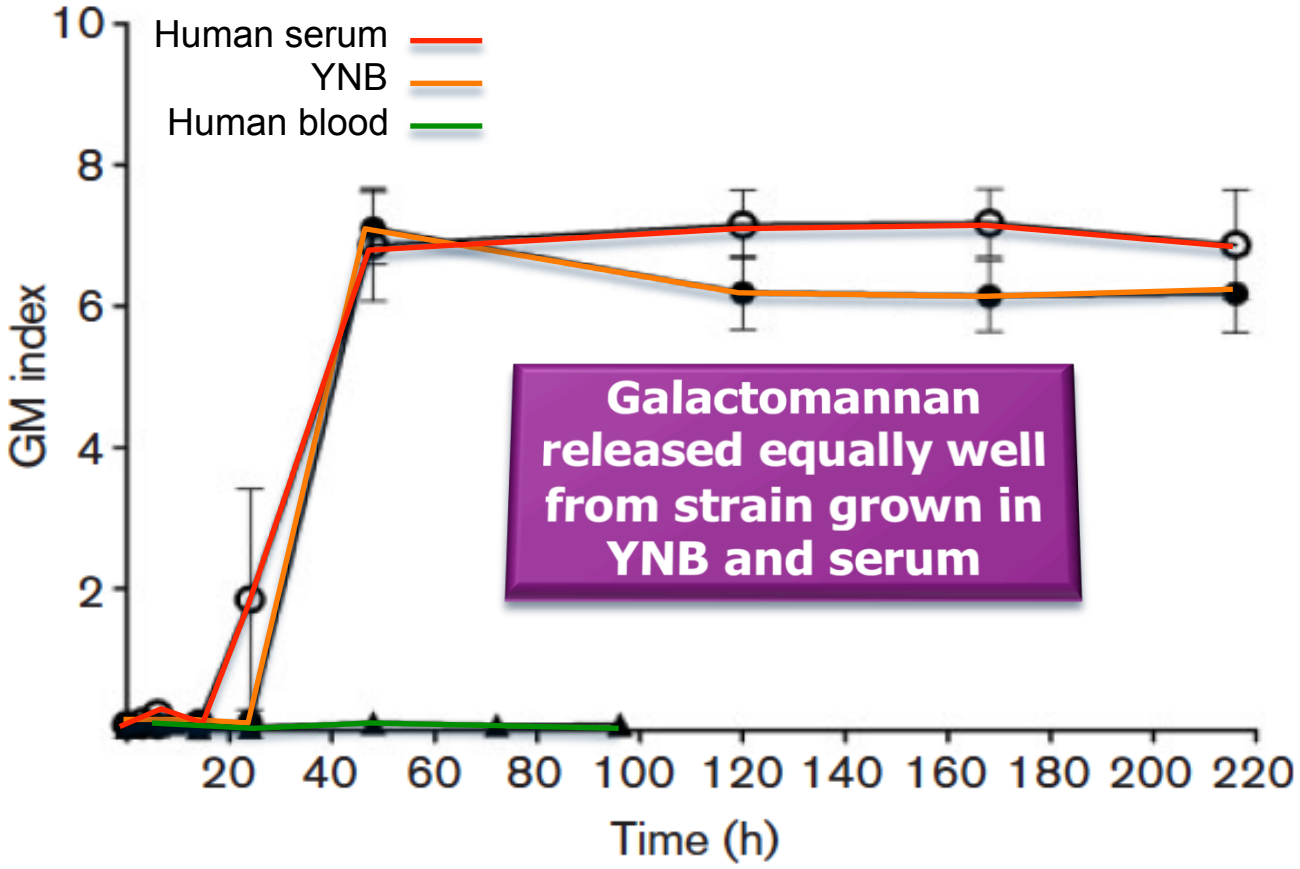
Mennink-Kersten et al. 2006 J. Clin. Microbiol. 44:1711-1718

Galactomannan release from *A. fumigatus*



Morton et al. 2010 J Med Microbiol. 2010;59:408-13

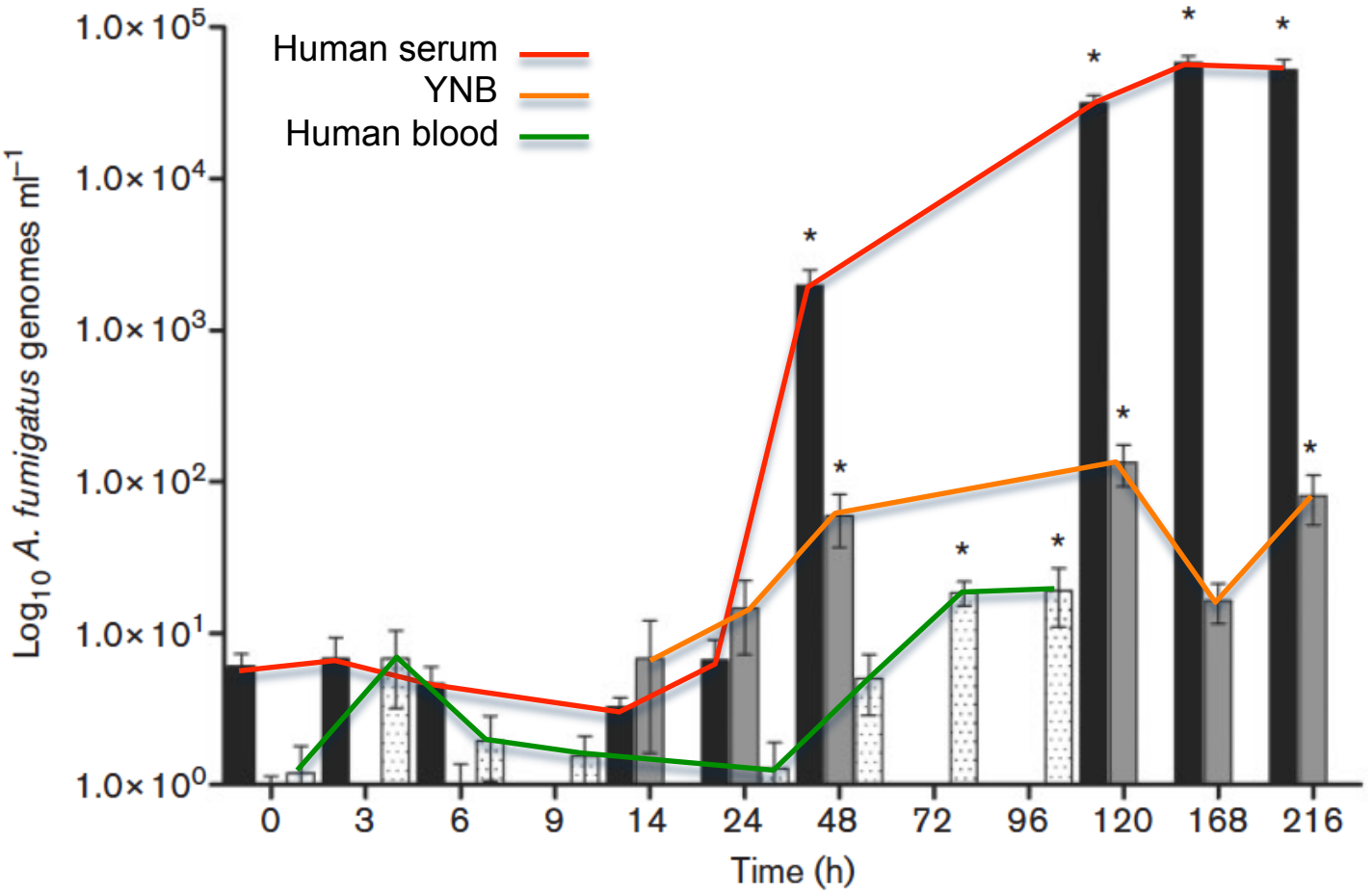
Galactomannan release from *A. fumigatus*



Morton et al. 2010 J Med Microbiol. 2010;59:408-13

DNA release from *A. fumigatus*

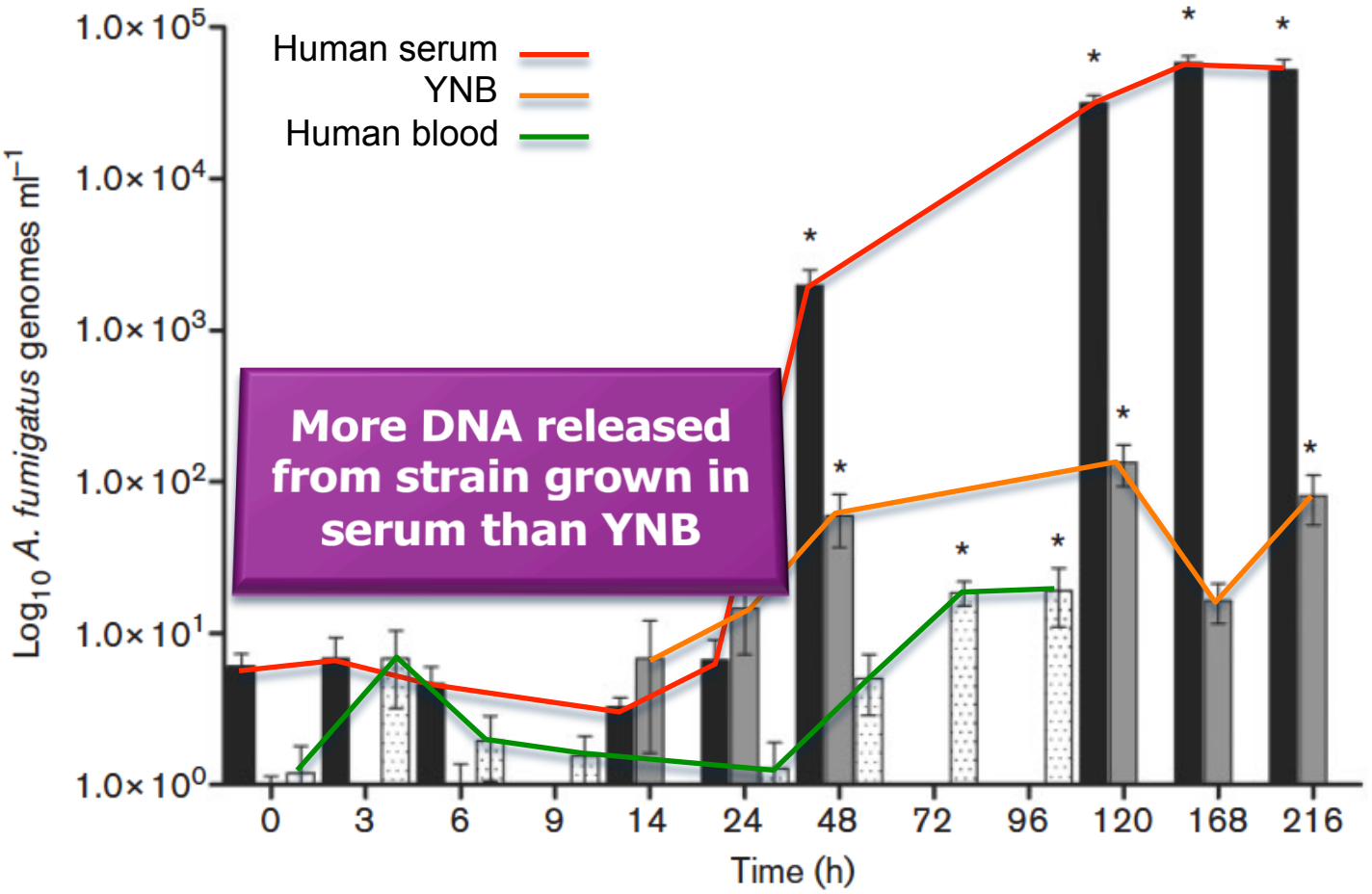
Real-time PCR targeting the ITS ribosomal region



Morton et al. 2010 J Med Microbiol. 2010;59:408-13

DNA release from *A. fumigatus*

Real-time PCR targeting the ITS ribosomal region



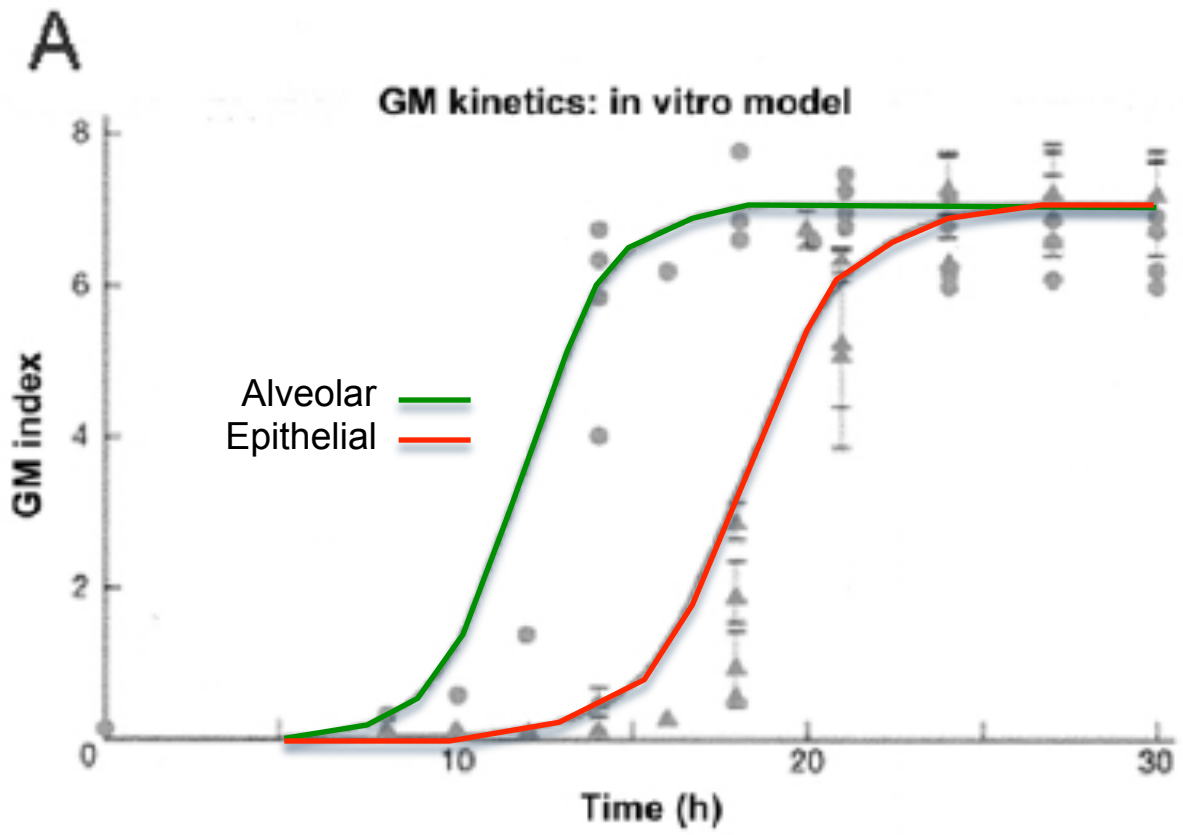
Morton et al. 2010 J Med Microbiol. 2010;59:408-13

Antifungals and in-vitro release of GM, BG and DNA

Antifungals and in-vitro release of GM, BG and DNA

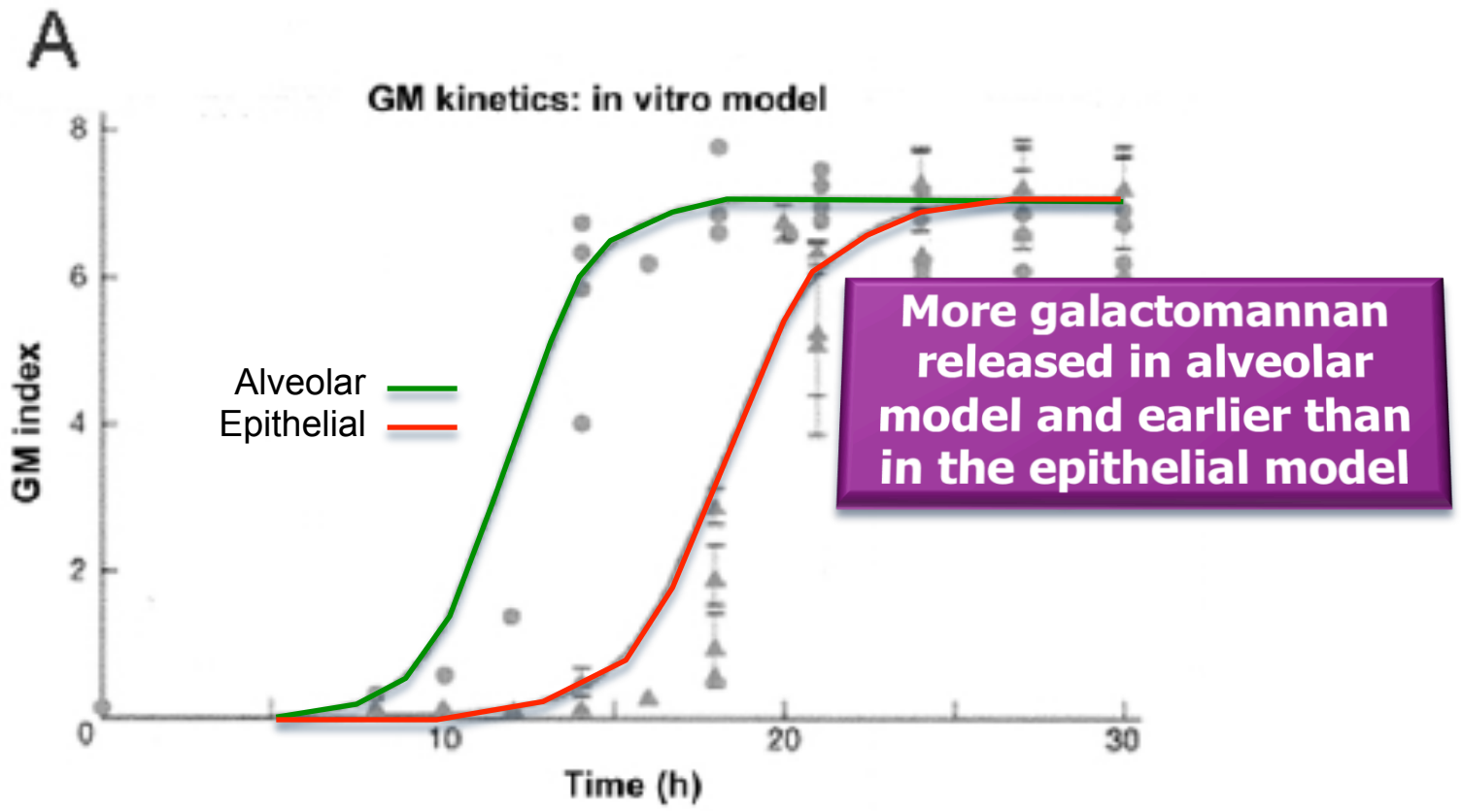
In-vivo

GM release in-vitro model



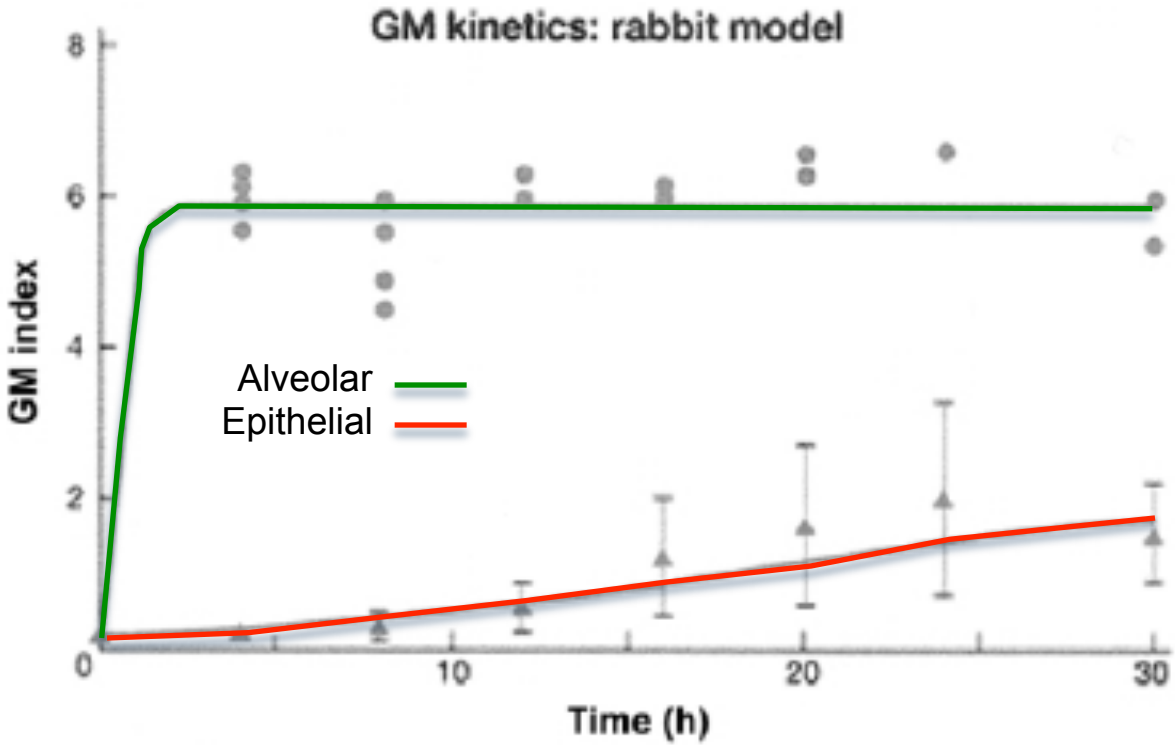
Hope et al 2007 J Infect Dis. 195:455-66.

GM release in-vitro model



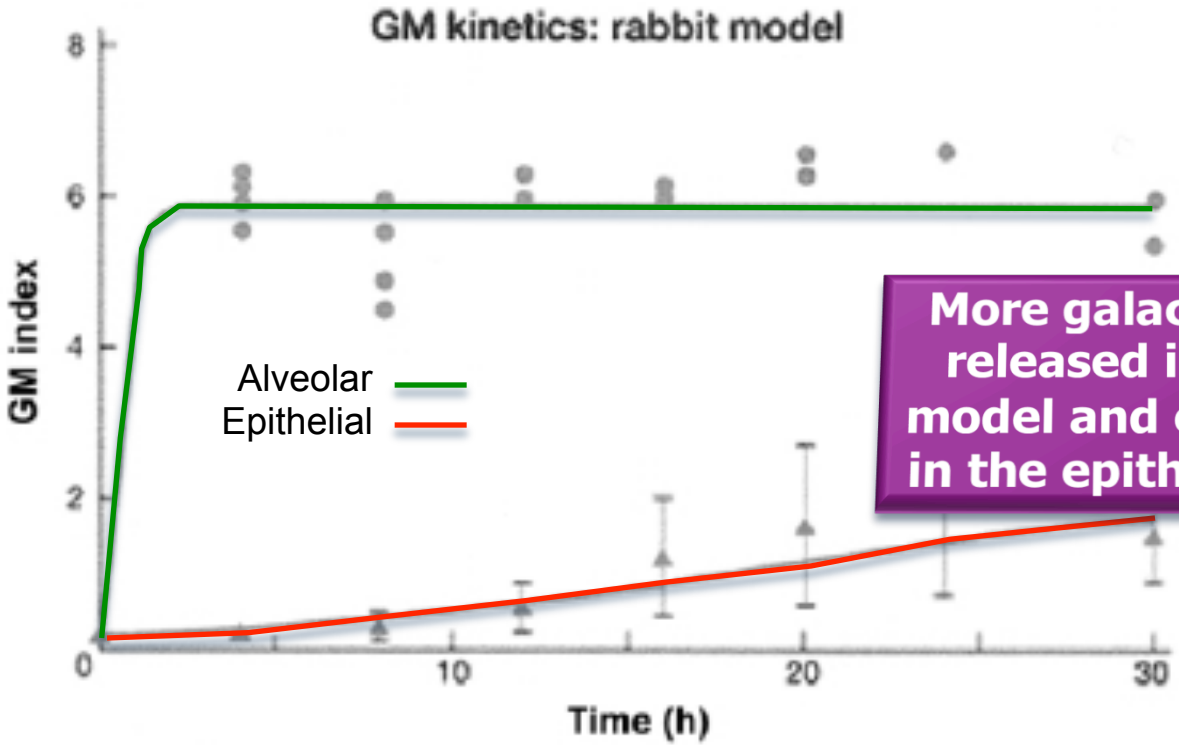
Hope et al 2007 J Infect Dis. 195:455-66.

GM release in-vivo rabbit model



Hope et al 2007 J Infect Dis. 195:455-66.

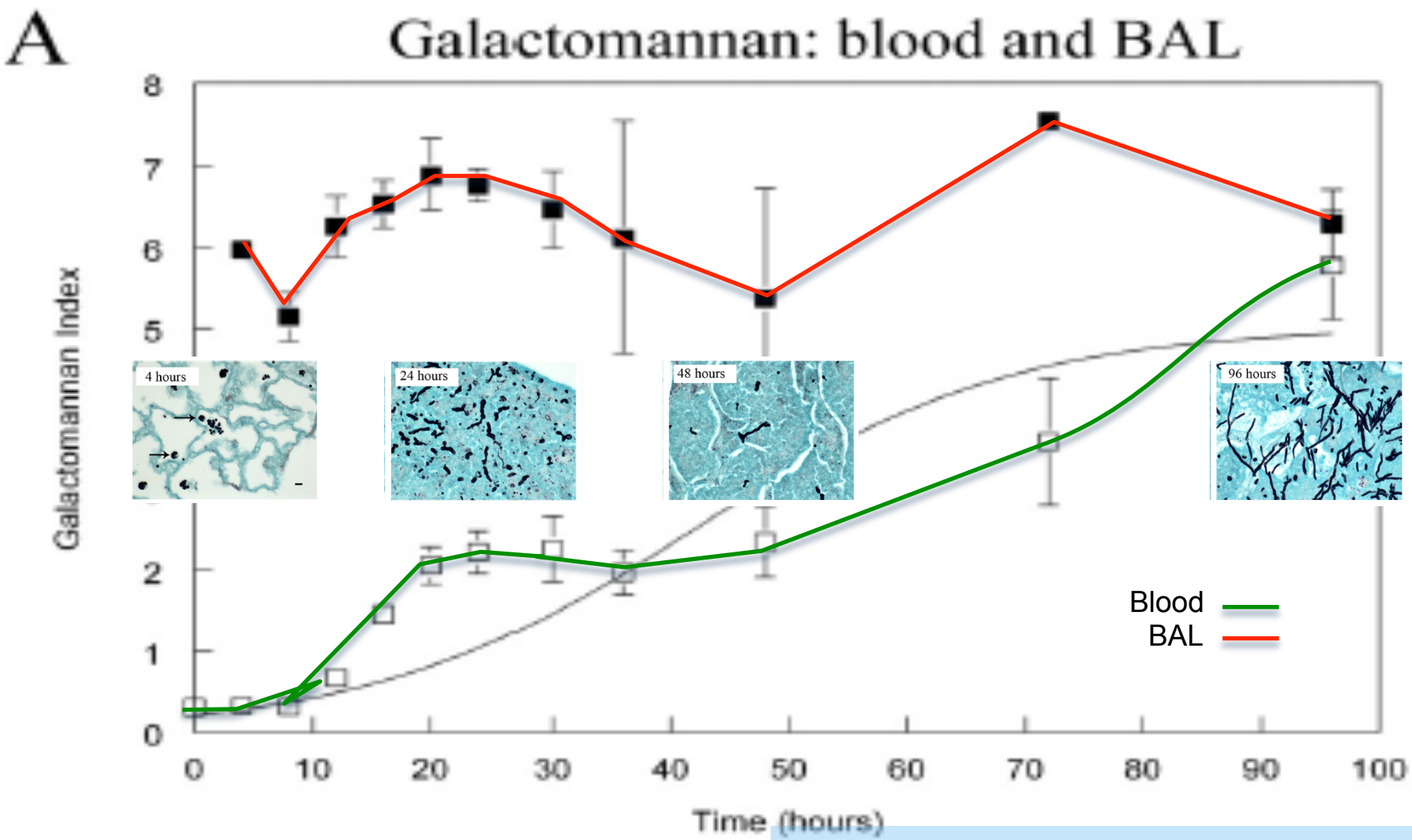
GM release in-vivo rabbit model



More galactomannan released in alveolar model and earlier than in the epithelial model

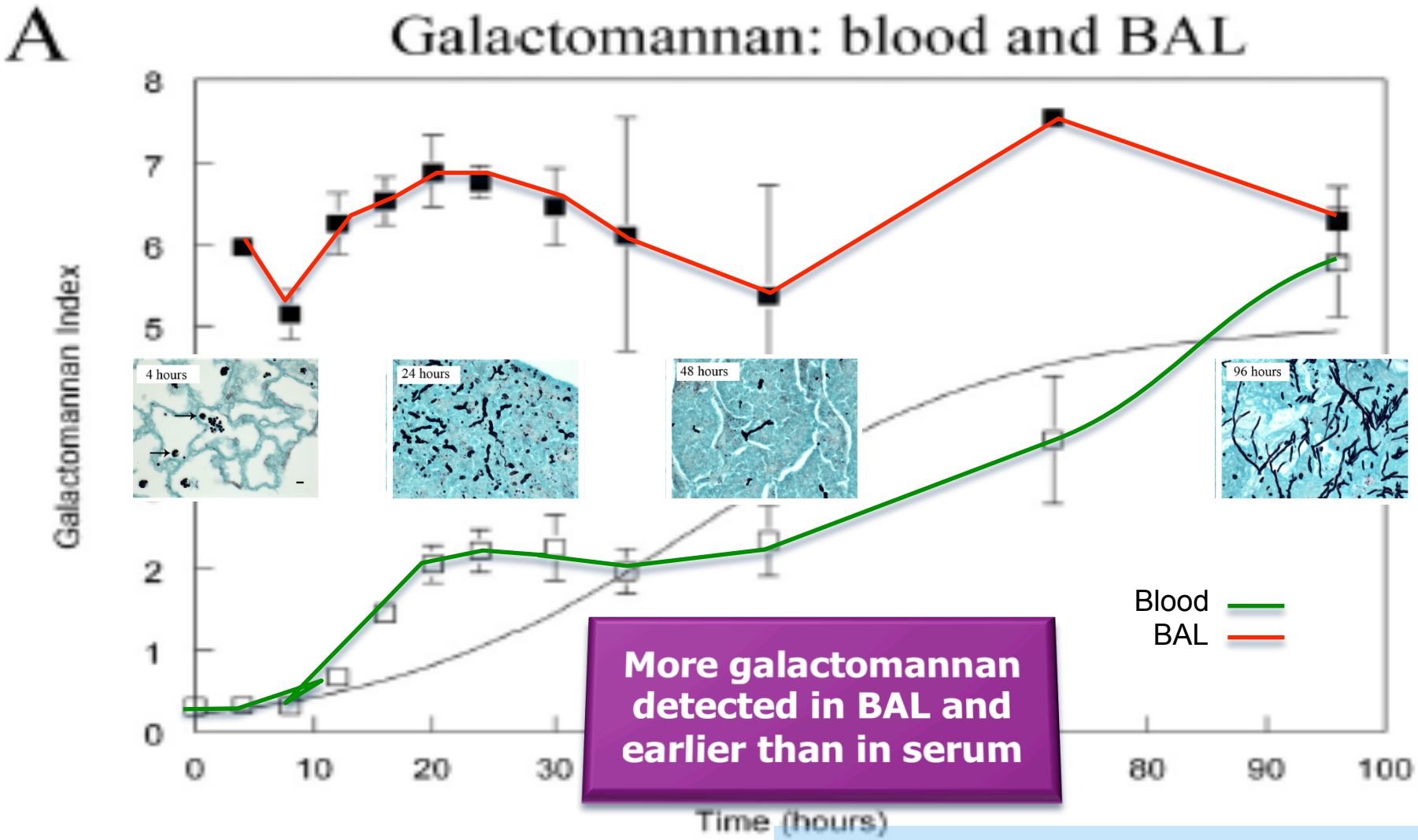
Hope et al 2007 J Infect Dis. 195:455-66.

Galactomannan release from rabbit infection



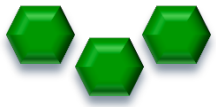
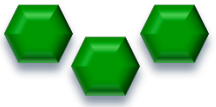
Hope et al Antimicrob Ag Chemother 2010: 54; 4879-86

Galactomannan release from rabbit infection



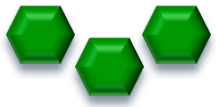
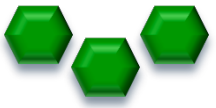
Hope et al Antimicrob Ag Chemother 2010: 54; 4879-86

Antifungals and GM detection – rats

	Day 1	Day 2	Day 3	Day 4	Day 5
Infected controls					
Amphotericin B					
Caspofungin					
Posaconazole					
Uninfected controls					

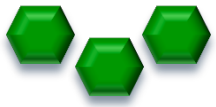
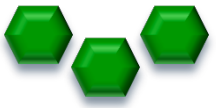
Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and GM detection – rats

	Day 1	Day 2	Day 3	Day 4	Day 5
Infected controls					
Amphotericin B					
Caspofungin					
Posaconazole					
Uninfected controls					

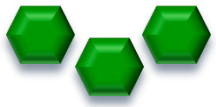
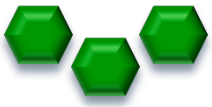
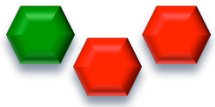
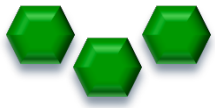
Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and GM detection – rats

	Day 1	Day 2	Day 3	Day 4	Day 5
Infected controls					
Amphotericin B					
Caspofungin					
Posaconazole					
Uninfected controls					

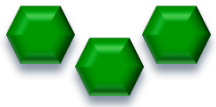
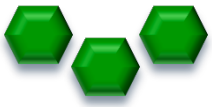
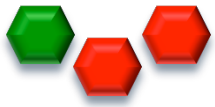
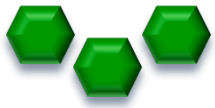
Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and GM detection – rats

	Day 1	Day 2	Day 3	Day 4	Day 5
Infected controls					
Amphotericin B					
Caspofungin					
Posaconazole					
Uninfected controls					

Mc Culloch et al 2012 J Clin Pathol 65:83-6

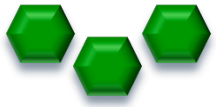
Antifungals and GM detection – rats

	Day 1	Day 2	Day 3	Day 4	Day 5
Infected controls					
Amphotericin B					
Caspofungin					
Posaconazole					
Uninfected controls					

Galactomannan detection delayed by at least posaconazole

Mc Culloch et al 2012 J Clin Pathol 65:83-6

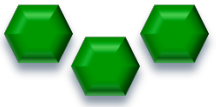
Antifungals and qPCR detection – rats

	Day 1	Day 2	Day 3	Day 4	Day 5
Infected controls					
Amphotericin B					
Caspofungin					
Posaconazole					
Uninfected controls					

Mc Culloch et al 2012 J Clin Pathol 65:83-6

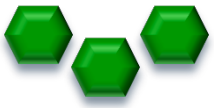
UMC St Radboud

Antifungals and qPCR detection – rats

	Day 1	Day 2	Day 3	Day 4	Day 5
Infected controls					
Amphotericin B					
Caspofungin					
Posaconazole					
Uninfected controls					

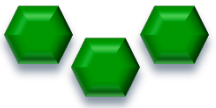
Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and qPCR detection – rats

	Day 1	Day 2	Day 3	Day 4	Day 5
Infected controls					
Amphotericin B					
Caspofungin					
Posaconazole					
Uninfected controls					

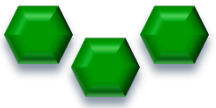
Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and qPCR detection – rats

	Day 1	Day 2	Day 3	Day 4	Day 5
Infected controls					
Amphotericin B					
Caspofungin					
Posaconazole					
Uninfected controls					

Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and qPCR detection – rats

	Day 1	Day 2	Day 3	Day 4	Day 5
Infected controls					
Amphotericin B					
Caspofungin					
Posaconazole					
Uninfected controls					

DNA detection delayed by at least a day by all antifungals

Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and qPCR detection – rats

Take-home messages

Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and qPCR detection – rats

Take-home messages

- Optimised and standardised qPCR reactions are statistically superior to galactamannan for the early detection of IA.

Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and qPCR detection – rats

Take-home messages

- Optimised and standardised qPCR reactions are statistically superior to galactamannan for the early detection of IA.
- Antifungal treatments, particularly fungi static agents, negatively effect laboratory-based diagnostic tests.

Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and qPCR detection – rats

Take-home messages

- Optimised and standardised qPCR reactions are statistically superior to galactamannan for the early detection of IA.
- Antifungal treatments, particularly fungi static agents, negatively effect laboratory-based diagnostic tests.
- When patients are receiving antifungal drugs the results of diagnostic tests should always be interpreted with this in mind.

Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and qPCR detection – rats

Take-home messages

- Optimised and standardised qPCR reactions are statistically superior to galactamannan for the early detection of IA.
- Antifungal treatments, particularly fungi static agents, negatively effect laboratory-based diagnostic tests.
- When patients are receiving antifungal drugs the results of diagnostic tests should always be interpreted with this in mind.
- Regardless of how well optimised a diagnostic test the appropriateness of the clinical samples taken and the stage of infection is key to meaningful diagnostic results.

Mc Culloch et al 2012 J Clin Pathol 65:83-6

Antifungals and in-vivo release of GM, BG and DNA

Antifungals and in-vivo release of GM, BG and DNA

Patient population

GM detection in serum – meta-analysis

Diagnosis of Invasive Aspergillosis Using a Galactomannan Assay: A Meta-Analysis

Christopher D. Pfeiffer,[1] Jason P. Fine,[2] and Nasia Safdar[1]

Departments of [1]Medicine and [2]Biostatistics, University of Wisconsin Medical School, Madison, Wisconsin

Pfeiffer et al Clin Infect Dis 2006; 42: 1417–27.

GM detection in serum – meta-analysis

Diagnosis of Invasive Aspergillosis Using a Galactomannan Assay: A Meta-Analysis

Christopher D. Pfeiffer,[1] Jason P. Fine,[2] and Nasia Safdar[1]

Departments of [1]Medicine and [2]Biostatistics, University of Wisconsin Medical School, Madison, Wisconsin

A major cause of variable test performance may be prior antifungal therapy, which may be expected to result in lower sensitivity and specificity of the galactomannan assay by decreasing fungal bioburden

Pfeiffer et al Clin Infect Dis 2006; 42: 1417–27.

GM detection in serum – meta-analysis

Diagnosis of Invasive Aspergillosis Using a Galactomannan Assay: A Meta-Analysis

Christopher D. Pfeiffer,[1] Jason P. Fine,[2] and Nasia Safdar[1]

Departments of [1]Medicine and [2]Biostatistics, University of Wisconsin Medical School, Madison, Wisconsin

A major cause of variable test performance may be prior antifungal therapy, which may be expected to result in lower sensitivity and specificity of the galactomannan assay by decreasing fungal bioburden

However, too few studies included in our analysis reported whether patients were receiving or had received antifungal therapy at the time that blood samples were obtained for galactomannan testing, and we were unable to perform a subgroup analysis to explore this finding further.

Pfeiffer et al Clin Infect Dis 2006; 42: 1417–27.

UMC St Radboud

Another meta-analysis of GM tests in serum

Galactomannan detection for invasive aspergillosis in immunocompromized patients (Review)

Leeflang MM, Debets-Ossenkopp YJ, Visser CE, Scholten RJ, Hooft L, Bijlmer HA, Reitsma JB, Bossuyt PMM, Vandenbroucke-Grauls CM

THE COCHRANE COLLABORATION®

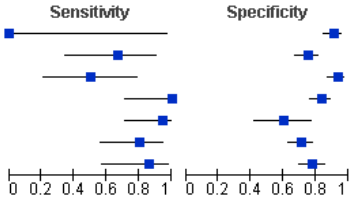
Another meta-analysis of GM tests in serum

0.5

N= 7

Platelia - cutoff 0.5

Study	TP	FP	FN	TN	Sensitivity	Specificity
Allan 2005	0	11	1	113	0.00 [0.00, 0.97]	0.91 [0.85, 0.95]
Florent 2006	8	39	4	116	0.67 [0.35, 0.90]	0.75 [0.67, 0.81]
Foy 2007	6	7	6	102	0.50 [0.21, 0.79]	0.94 [0.87, 0.97]
Kawazu 2004	11	23	0	115	1.00 [0.72, 1.00]	0.83 [0.76, 0.89]
Suankratay 2006	16	13	1	20	0.94 [0.71, 1.00]	0.61 [0.42, 0.77]
Weisser 2005	16	41	4	100	0.80 [0.56, 0.94]	0.71 [0.63, 0.78]
Yoo 2005	12	25	2	89	0.86 [0.57, 0.98]	0.78 [0.69, 0.85]

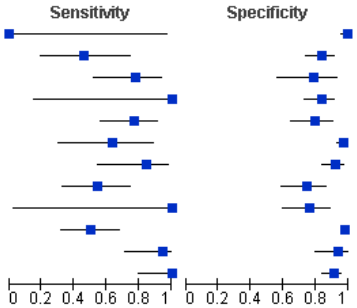


1.0

N= 12

Platelia - cutoff 1.0

Study	TP	FP	FN	TN	Sensitivity	Specificity
Allan 2005	0	1	1	123	0.00 [0.00, 0.97]	0.99 [0.96, 1.00]
Becker 2003	6	12	7	62	0.46 [0.19, 0.75]	0.84 [0.73, 0.91]
Bretagne 1998	14	5	4	18	0.78 [0.52, 0.94]	0.78 [0.56, 0.93]
Busca 2006	2	12	0	60	1.00 [0.16, 1.00]	0.83 [0.73, 0.91]
Challier 2004	20	9	6	35	0.77 [0.56, 0.91]	0.80 [0.65, 0.90]
Kawazu 2004	7	4	4	134	0.64 [0.31, 0.89]	0.97 [0.93, 0.99]
Maertens 2002	11	7	2	80	0.85 [0.55, 0.98]	0.92 [0.84, 0.97]
Marr 2004	13	11	11	32	0.54 [0.33, 0.74]	0.74 [0.59, 0.86]
Pereira 2005	1	9	0	29	1.00 [0.03, 1.00]	0.76 [0.60, 0.89]
Pinel 2003	17	17	17	756	0.50 [0.32, 0.68]	0.98 [0.97, 0.99]
Suankratay 2006	16	2	1	31	0.94 [0.71, 1.00]	0.94 [0.80, 0.99]
Ulusakarya 2000	16	11	0	108	1.00 [0.79, 1.00]	0.91 [0.84, 0.95]

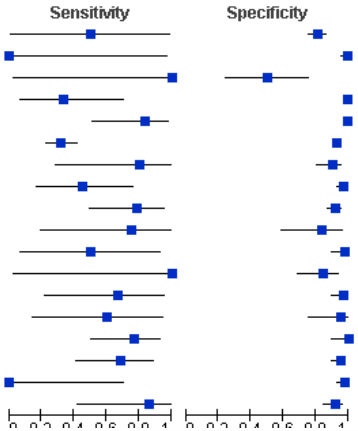


1.5

N= 18

Platelia - cutoff 1.5

Study	TP	FP	FN	TN	Sensitivity	Specificity
Adam 2004	1	41	1	175	0.50 [0.01, 0.99]	0.81 [0.75, 0.86]
Allan 2005	0	1	1	123	0.00 [0.00, 0.97]	0.99 [0.96, 1.00]
Bialek 2002	1	8	0	8	1.00 [0.03, 1.00]	0.50 [0.25, 0.75]
Buchheidt 2004	3	1	6	167	0.33 [0.07, 0.70]	0.99 [0.97, 1.00]
Doermann 2002	10	4	2	407	0.83 [0.52, 0.98]	0.99 [0.98, 1.00]
Herbrecht 2002	31	49	67	650	0.32 [0.23, 0.42]	0.93 [0.91, 0.95]
Kallel 2003	4	7	1	62	0.80 [0.28, 0.99]	0.90 [0.80, 0.96]
Kawazu 2004	5	4	6	134	0.45 [0.17, 0.77]	0.97 [0.93, 0.99]
Lai 2007	11	14	3	161	0.79 [0.49, 0.95]	0.92 [0.87, 0.96]
Machetti 1998	3	3	1	15	0.75 [0.19, 0.99]	0.83 [0.59, 0.96]
Moragues 2003	2	1	2	49	0.50 [0.07, 0.93]	0.98 [0.89, 1.00]
Pereira 2005	1	6	0	32	1.00 [0.03, 1.00]	0.84 [0.69, 0.94]
Rovira 2004	4	2	2	66	0.67 [0.22, 0.96]	0.97 [0.90, 1.00]
Scotter 2005	3	1	2	19	0.60 [0.15, 0.95]	0.95 [0.75, 1.00]
Suankratay 2006	13	0	4	33	0.76 [0.50, 0.93]	1.00 [0.89, 1.00]
Ulusakarya 2000	11	6	5	113	0.69 [0.41, 0.89]	0.95 [0.89, 0.98]
White 2005	0	2	3	100	0.00 [0.00, 0.71]	0.98 [0.93, 1.00]
Williamson 2000	6	8	1	89	0.86 [0.42, 1.00]	0.92 [0.84, 0.96]



Leeflang et al The Cochrane library Issue 4 2008

Antifungal prophylaxis and GM test performance

Cutoff	Antifungal prophylaxis	Sensitivity	95% CI	Specificity	95% CI
0.5	Yes	0.82	0.69–0.96	0.88	0.80–0.96
	No	0.71	0.51–0.92	0.77	0.65–0.89

Leeflang et al 2004 Cochrane Library 2009 issue 1.

Antifungal prophylaxis and GM test performance

Cutoff	Antifungal prophylaxis	Sensitivity	95% CI	Specificity	95% CI
0.5	Yes	0.82	0.69–0.96	0.88	0.80–0.96
	No	0.71	0.51–0.92	0.77	0.65–0.89
1.0	Yes	0.77	0.64–0.89	0.93	0.90–0.97
	No	0.64	0.47–0.80	0.86	0.80–0.92

Leeflang et al 2004 Cochrane Library 2009 issue 1.

Antifungal prophylaxis and GM test performance

Cutoff	Antifungal prophylaxis	Sensitivity	95% CI	Specificity	95% CI
0.5	Yes	0.82	0.69–0.96	0.88	0.80–0.96
	No	0.71	0.51–0.92	0.77	0.65–0.89
1.0	Yes	0.77	0.64–0.89	0.93	0.90–0.97
	No	0.64	0.47–0.80	0.86	0.80–0.92
1.5	Yes	0.55	0.34–0.77	0.96	0.94–0.99
	No	0.70	0.51–0.89	0.92	0.87–0.97

Leeflang et al 2004 Cochrane Library 2009 issue 1.

Antifungals and GM detection in BAL fluid

Mould active agents given	Galactomannan Positive	Galactomannan Negative	

Luong et al Diagn Microbiol Infect Dis 2010: 68; 132-9

Antifungals and GM detection in BAL fluid

Mould active agents given	Galactomannan Positive	Galactomannan Negative	
Yes	24	41	**65**

Luong et al Diagn Microbiol Infect Dis 2010: 68; 132-9

Antifungals and GM detection in BAL fluid

Mould active agents given	Galactomannan Positive	Galactomannan Negative	
Yes	24	41	**65**
No	14	43	**57**

Luong et al Diagn Microbiol Infect Dis 2010: 68; 132-9

Antifungals and GM detection in BAL fluid

Mould active agents given	Galactomannan Positive	Galactomannan Negative	
Yes	24	41	**65**
No	14	43	**57**
	38	**84**	**122**

Fisher's Exact Test = 2-sided P value = 0.1719
Relative risk = 1.503 (95% CI: 0.8629 to 2.619

Luong et al Diagn Microbiol Infect Dis 2010: 68; 132-9

Antifungals and performance of PCR test on BAL

Regimen	Proven+ probable IA	Possible + no IA	Prevalence	Sensitivity	Specificity
Amphotericin B formulations	6	30	0.17	0.67	0.83

Reinwald et al 2011 Poster 45

Antifungals and performance of PCR test on BAL

Regimen	Proven+ probable IA	Possible + no IA	Prevalence	Sensitivity	Specificity
Amphotericin B formulations	6	30	0.17	0.67	0.83
Caspofungin	3	9	0.25	0.67	0.90

Reinwald et al 2011 Poster 45

Antifungals and performance of PCR test on BAL

Regimen	Proven+ probable IA	Possible + no IA	Prevalence	Sensitivity	Specificity
Amphotericin B formulations	6	30	0.17	0.67	0.83
Caspofungin	3	9	0.25	0.67	0.90
Posaconazole	2	7	0.28	0.50	1.00

5th ADVANCES AGAINST ASPERGILLOSIS
Istanbul, Turkey
26-28 January 2012
Lutfi Kirdar Convention & Exhibition Centre

Reinwald et al 2011 Poster 45

Antifungals and performance of PCR test on BAL

Regimen	Proven+ probable IA	Possible + no IA	Prevalence	Sensitivity	Specificity
Amphotericin B formulations	6	30	0.17	0.67	0.83
Caspofungin	3	9	0.25	0.67	0.90
Posaconazole	2	7	0.28	0.50	1.00
Voriconazole	12	26	0.31	0.83	0.85

5th ADVANCES AGAINST ASPERGILLOSIS
Istanbul, Turkey
26-28 January 2012
Lutfi Kirdar Convention & Exhibition Centre

Reinwald et al 2011 Poster 45

Antifungals and test performance in patients

UMC St Radboud

Test performance parameters

		Proven + probable IA		
		Present	*Absent*	
Test outcome	*Positive*	**True Positive**	**False Positive**	**Positive predictive value = True Positive/ (True Positive + False Positive)**
	Negative	**False Negative**	**True Negative**	**Negative predictive value = True Negative (True Negative + False Negative)**
		Sensitivity = True positive/ (True positive + False negative)	**Specificity = (True negative/ (True negative + False positive)**	

UMC St Radboud

Test performance parameters - **screening**

		Proven + probable IA		
		Present	*Absent*	
Test outcome	*Positive*	**True Positive**	**False Positive**	**Positive predictive value = True Positive/ (True Positive + False Positive)**
	Negative	**False Negative**	**True Negative**	**Negative predictive value = True Negative (True Negative + False Negative)**
		Sensitivity = True positive/ (True positive + False negative)	**Specificity = (True negative/ (True negative + False positive)**	

UMC St Radboud

Test performance parameters - **screening**

		Proven + probable IA		
		Present	*Absent*	
Test outcome	*Positive*	True Positive	False Positive	Positive predictive value = True Positive/ (True Positive + False Positive)
		False Negative	True Negative	Negative predictive value = True Negative (True Negative + False Negative)
		Sensitivity = True positive/ (True positive + False negative)	Specificity = (True negative/ (True negative + False positive)	

As low as possible

UMC St Radboud

Test performance parameters - **diagnosis**

		Proven + probable IA		
		Present	*Absent*	
Test outcome	*Positive*	**True Positive**	**False Positive**	**Positive predictive value = True Positive/ (True Positive + False Positive)**
	Negative	**False Negative**	**True Negative**	**Negative predictive value = True Negative (True Negative + False Negative)**
		Sensitivity = True positive/ (True positive + False negative)	**Specificity = (True negative/ (True negative + False positive)**	

Test performance parameters - **diagnosis**

		Proven + probable IA		
		Present	*Absent*	
Test outcome	*Positive*	**As low as possible**	**False Positive**	**Positive predictive value = True Positive/ (True Positive + False Positive)**
	Negative	**False Negative**	**True Negative**	**Negative predictive value = True Negative (True Negative + False Negative)**
		Sensitivity = True positive/ (True positive + False negative)	**Specificity = (True negative/ (True negative + False positive)**	

Effect of prevalence on performance of GM test in serum

	Cases of proven or probable IA Sensitivity = 0.89; Specificity = 0.86			
Prevalence	Positive predictive value	(95% CI)	Negative predictive value	(95% CI)

*Any threshold: 0.5, 1.0, 1.5

Pfeiffer et al 2006 Clin Infect Dis 42:1417-27.

Effect of prevalence on performance of GM test in serum

Prevalence	Cases of proven or probable IA Sensitivity = 0.89; Specificity = 0.86 Positive predictive value	(95% CI)	Negative predictive value	(95% CI)
0.05	0.31	(0.28–0.35)	0.98	(0.97–0.99)

*Any threshold: 0.5, 1.0, 1.5

Pfeiffer et al 2006 Clin Infect Dis 42:1417-27.

UMC St Radboud

Effect of prevalence on performance of GM test in serum

Prevalence	Positive predictive value	(95% CI)	Negative predictive value	(95% CI)
	Cases of proven or probable IA Sensitivity = 0.89; Specificity = 0.86			
0.05	0.31	(0.28–0.35)	0.98	(0.97–0.99)
0.10	0.49	(0.45–0.53)	0.96	(0.95–0.97)

*Any threshold: 0.5, 1.0, 1.5

Pfeiffer et al 2006 Clin Infect Dis 42:1417-27.

Effect of prevalence on performance of GM test in serum

Prevalence	Cases of proven or probable IA Sensitivity = 0.89; Specificity = 0.86 Positive predictive value	(95% CI)	Negative predictive value	(95% CI)
0.05	0.31	(0.28–0.35)	0.98	(0.97–0.99)
0.10	0.49	(0.45–0.53)	0.96	(0.95–0.97)
0.15	0.61	(0.57–0.64)	0.93	(0.92–0.94)

*Any threshold: 0.5, 1.0, 1.5

Pfeiffer et al 2006 Clin Infect Dis 42:1417-27.

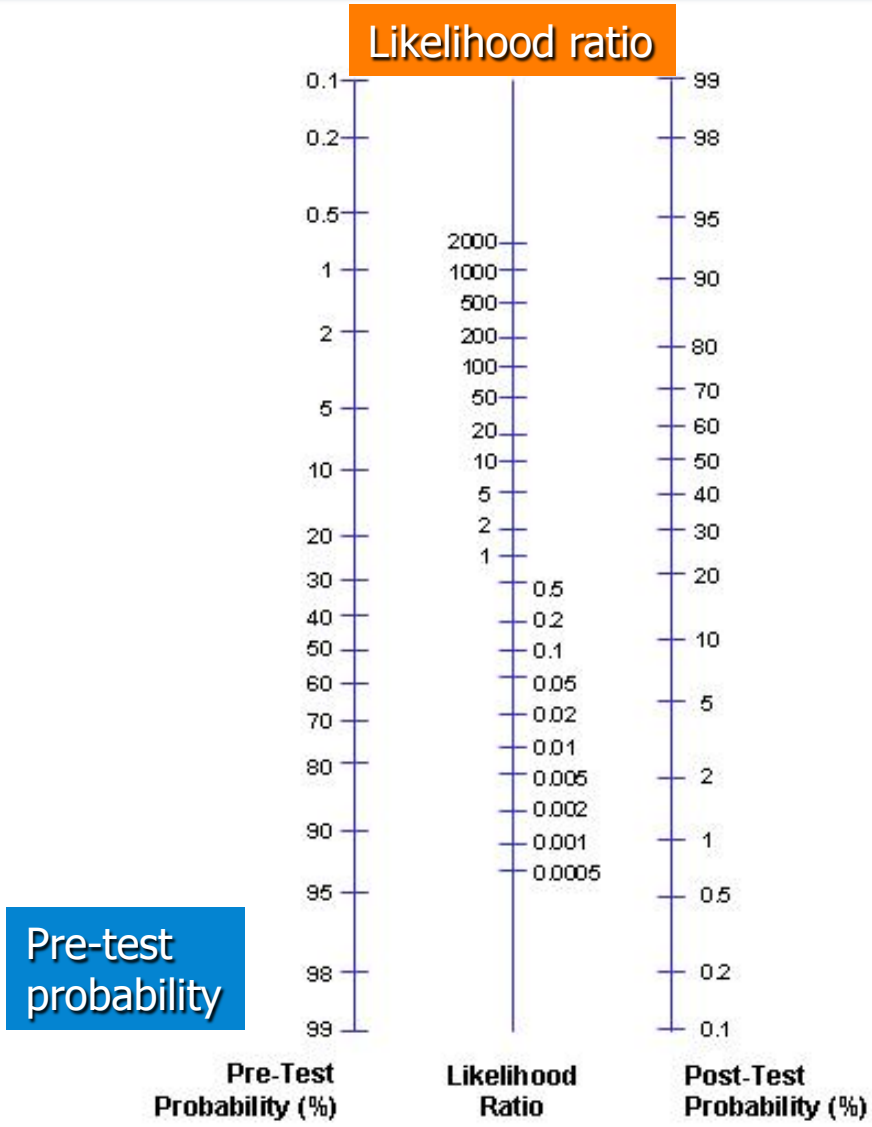
Effect of prevalence on performance of GM test in serum

Prevalence	Cases of proven or probable IA Sensitivity = 0.89; Specificity = 0.86 Positive predictive value	(95% CI)	Negative predictive value	(95% CI)
0.05	0.31	(0.28–0.35)	0.98	(0.97–0.99)
0.10	0.49	(0.45–0.53)	0.96	(0.95–0.97)
0.15	0.61	(0.57–0.64)	0.93	(0.92–0.94)
0.20	0.69	(0.65–0.72)	0.91	(0.89–0.92)

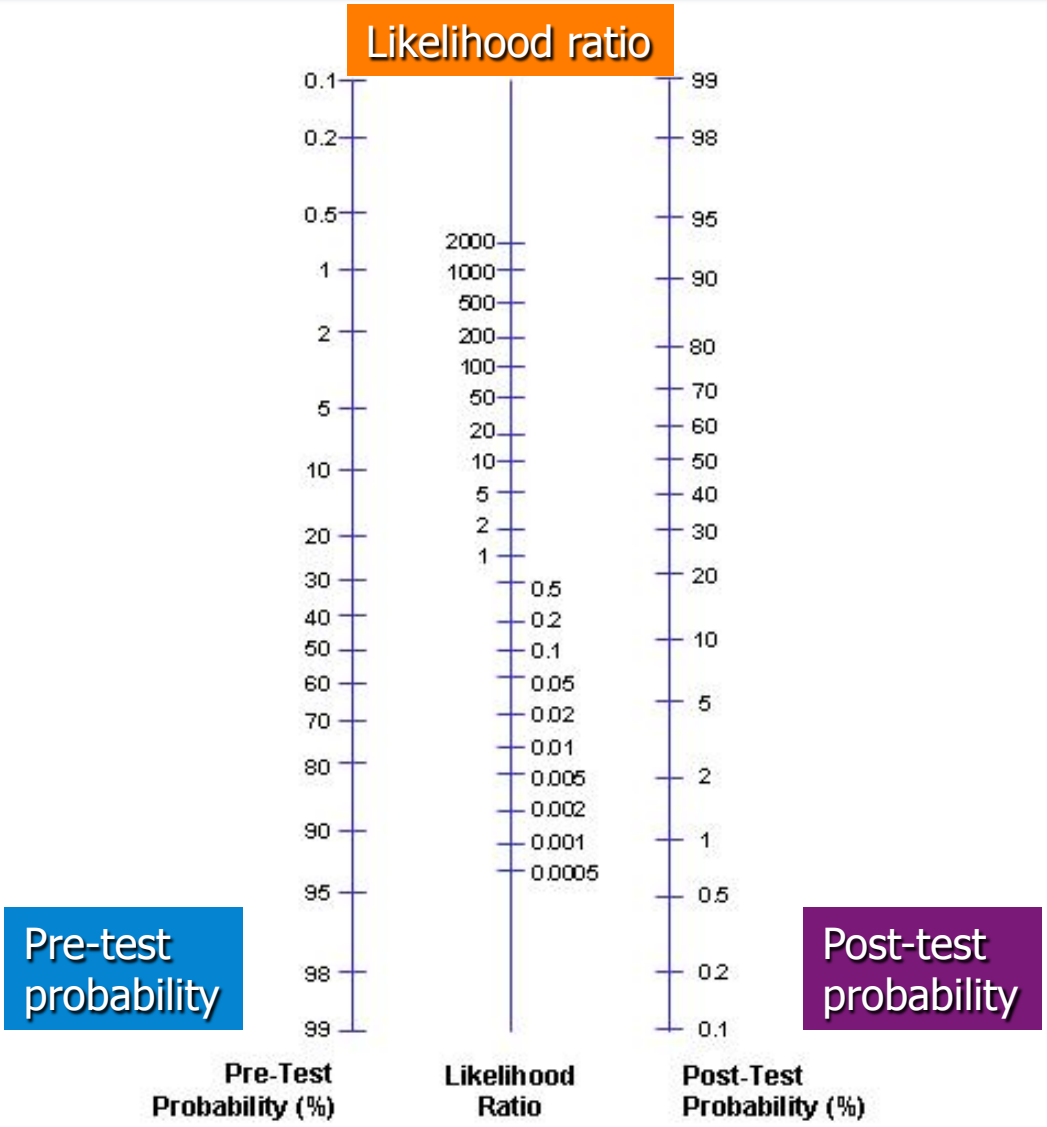
*Any threshold: 0.5, 1.0, 1.5

Pfeiffer et al 2006 Clin Infect Dis 42:1417-27.

Post-test probability

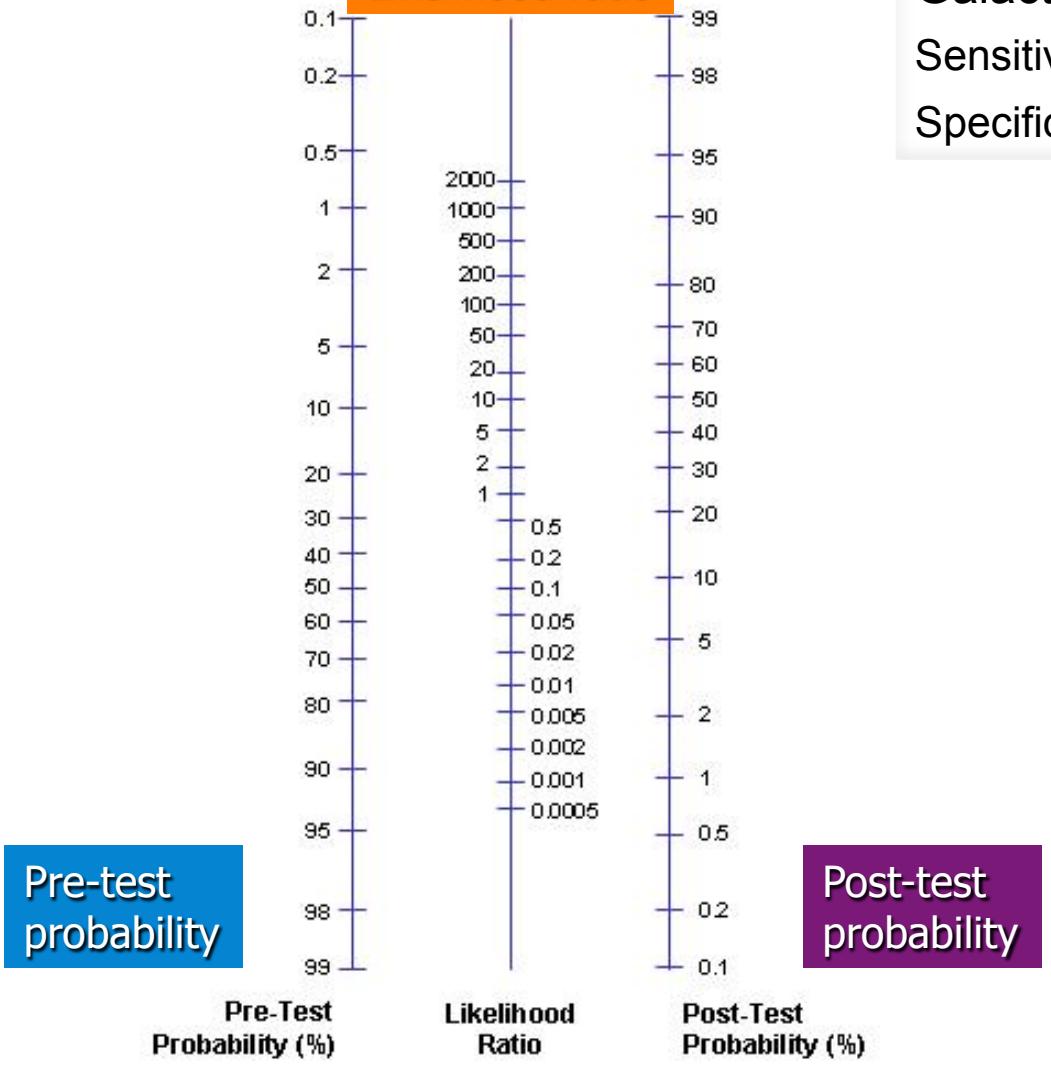


Post-test probability



Post-test probability

Likelihood ratio



Pre-test probability

Post-test probability

Galactomannan or PCR

Sensitivity = 0.83

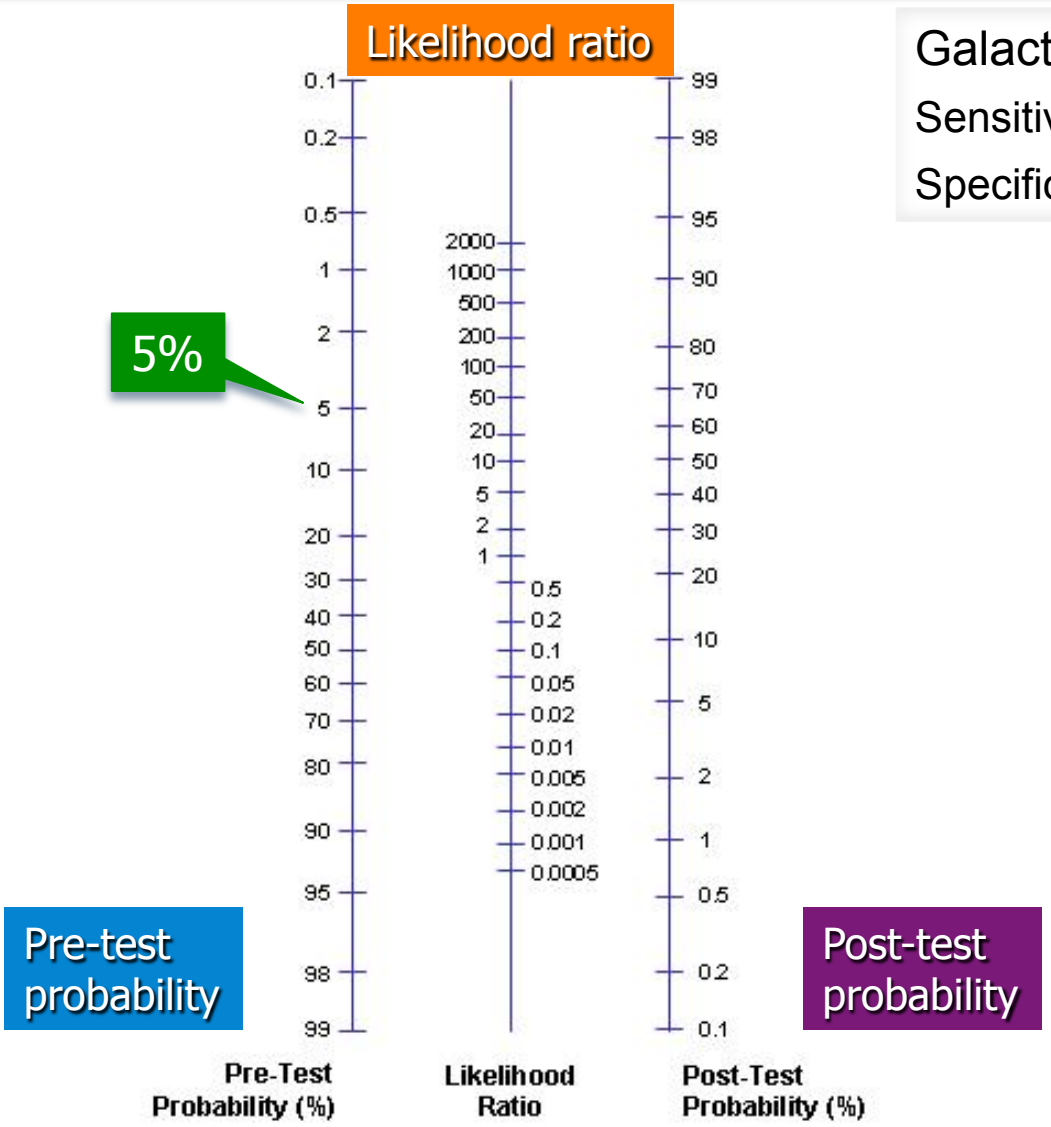
Specificity = 0.85

Post-test probability - screening

Galactomannan or PCR

Sensitivity = 0.83

Specificity = 0.85

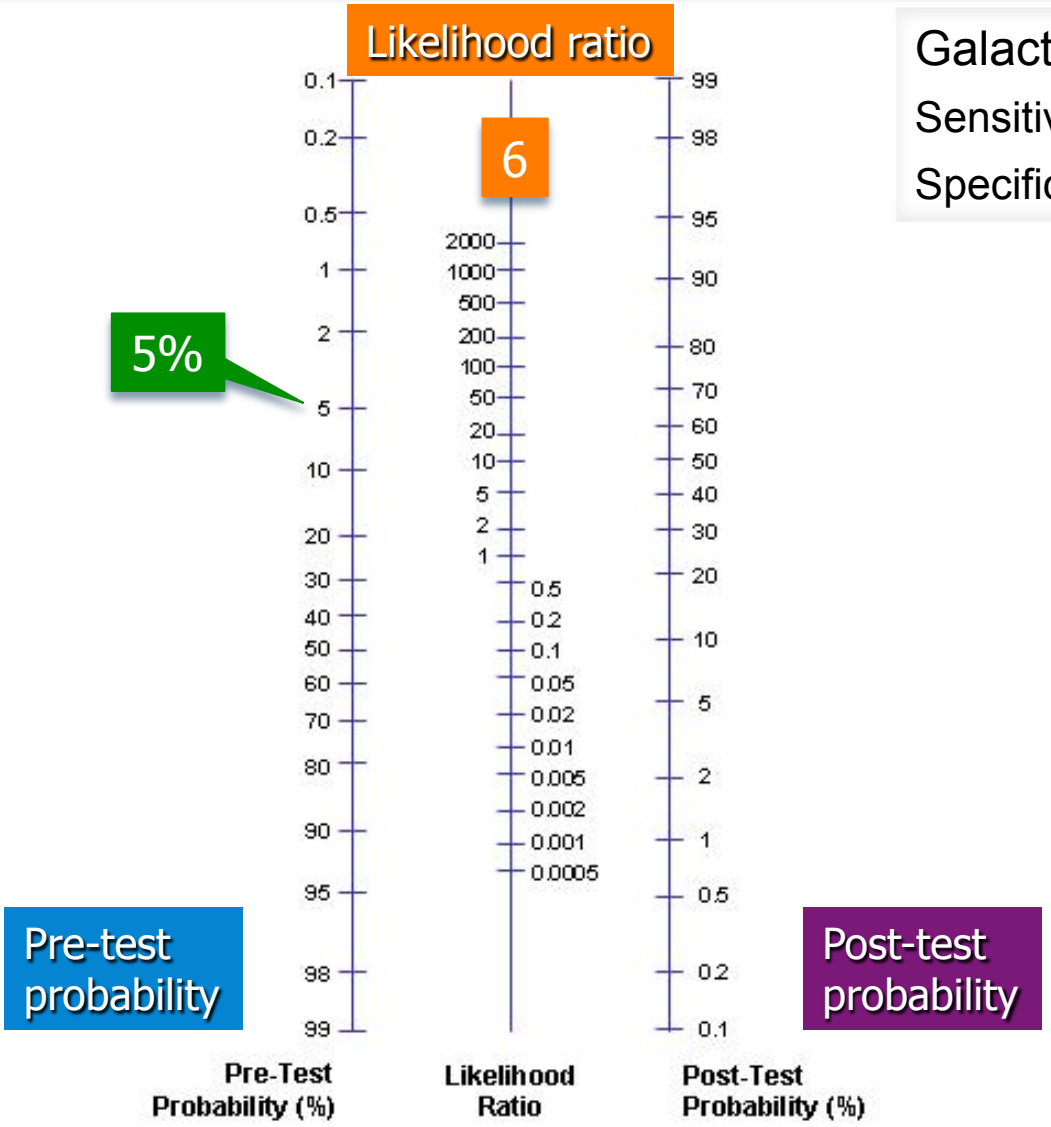


Post-test probability - screening

Galactomannan or PCR

Sensitivity = 0.83

Specificity = 0.85

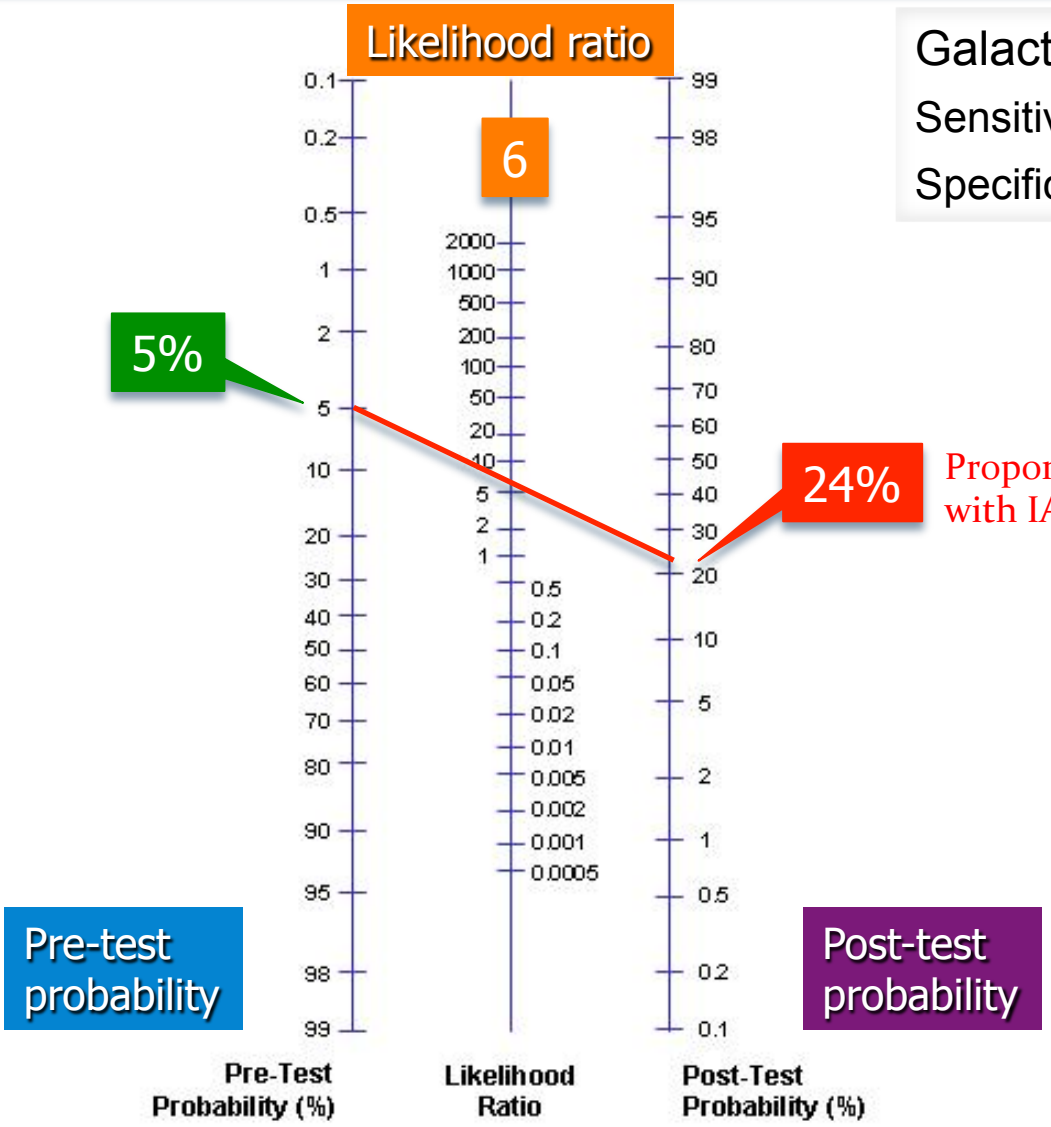


Post-test probability - screening

Galactomannan or PCR

Sensitivity = 0.83

Specificity = 0.85

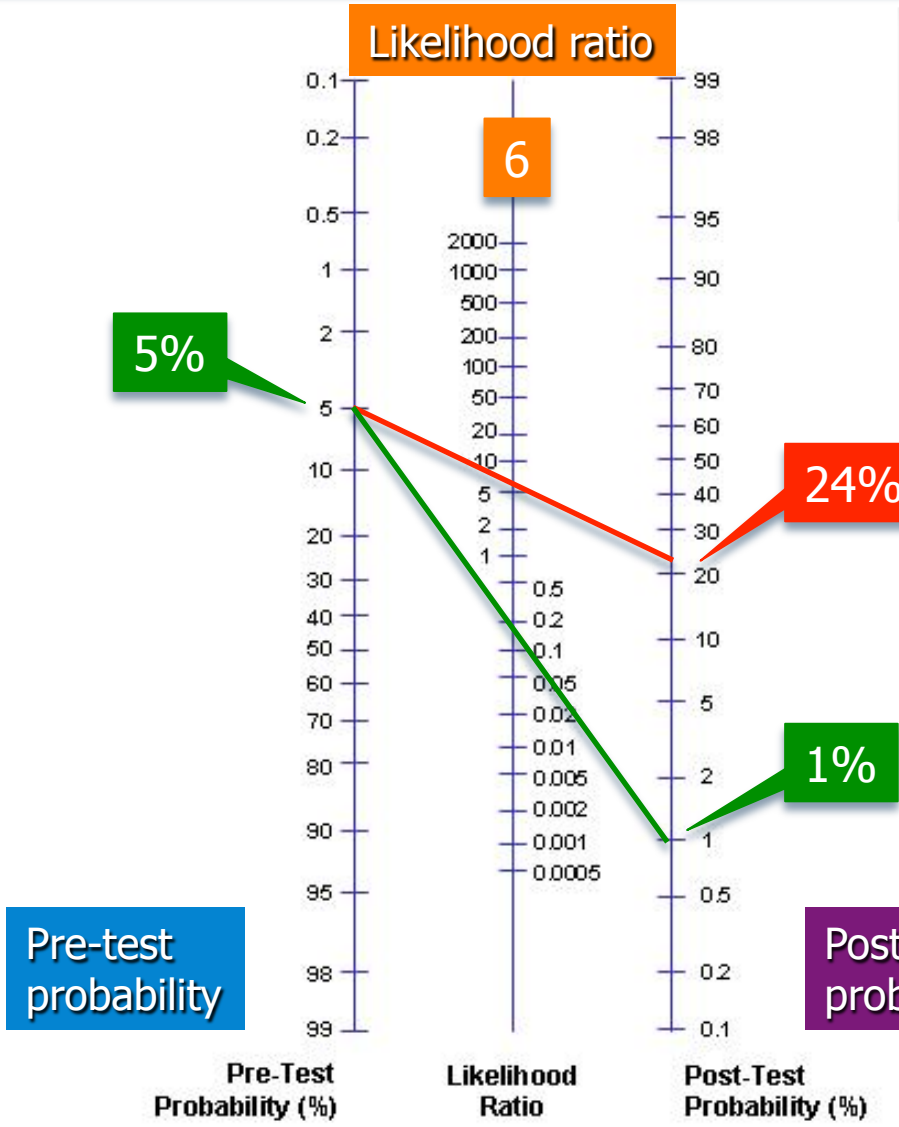


Post-test probability - screening

Galactomannan or PCR

Sensitivity = 0.83

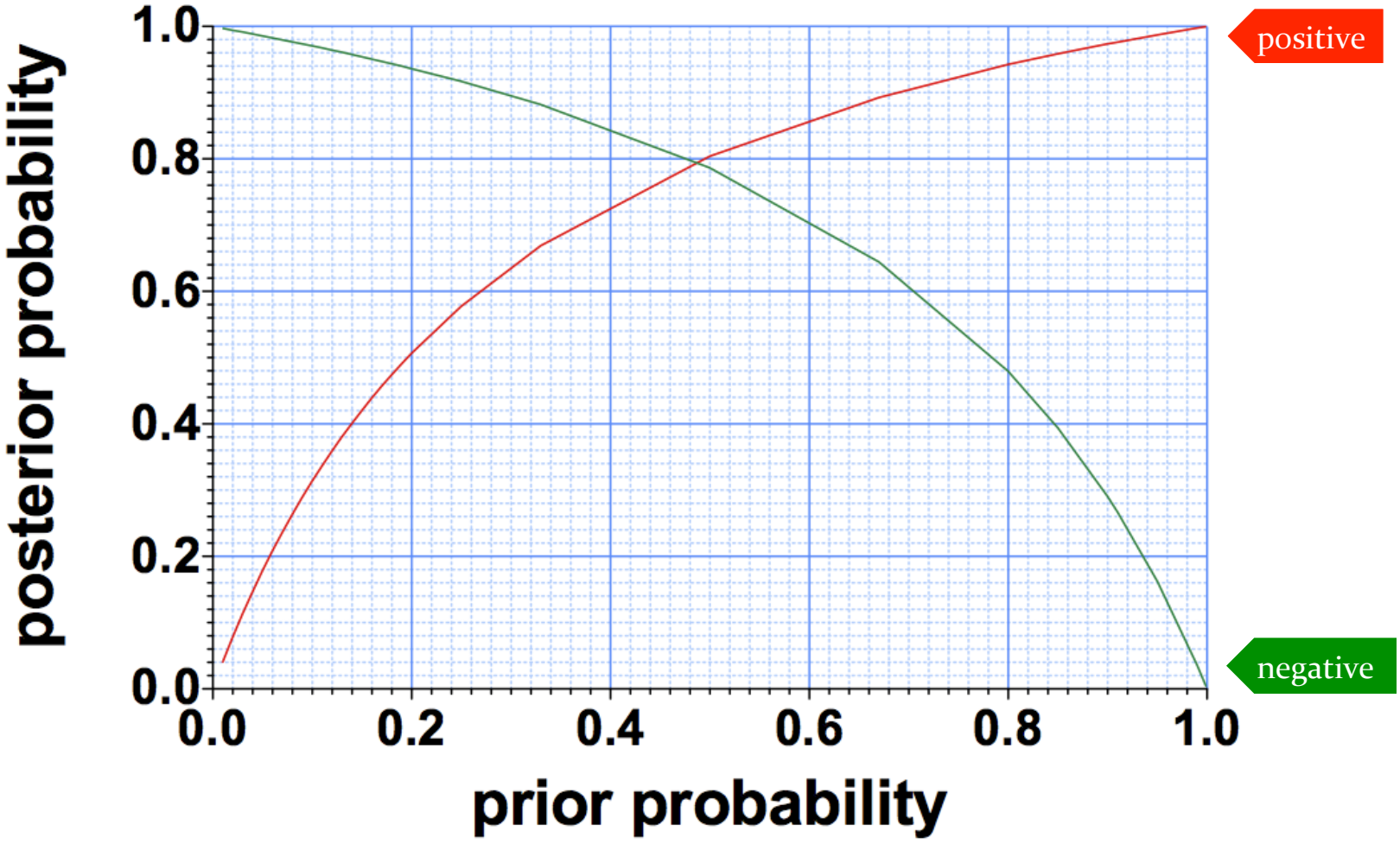
Specificity = 0.85



Proportion of patients with IA that test positive

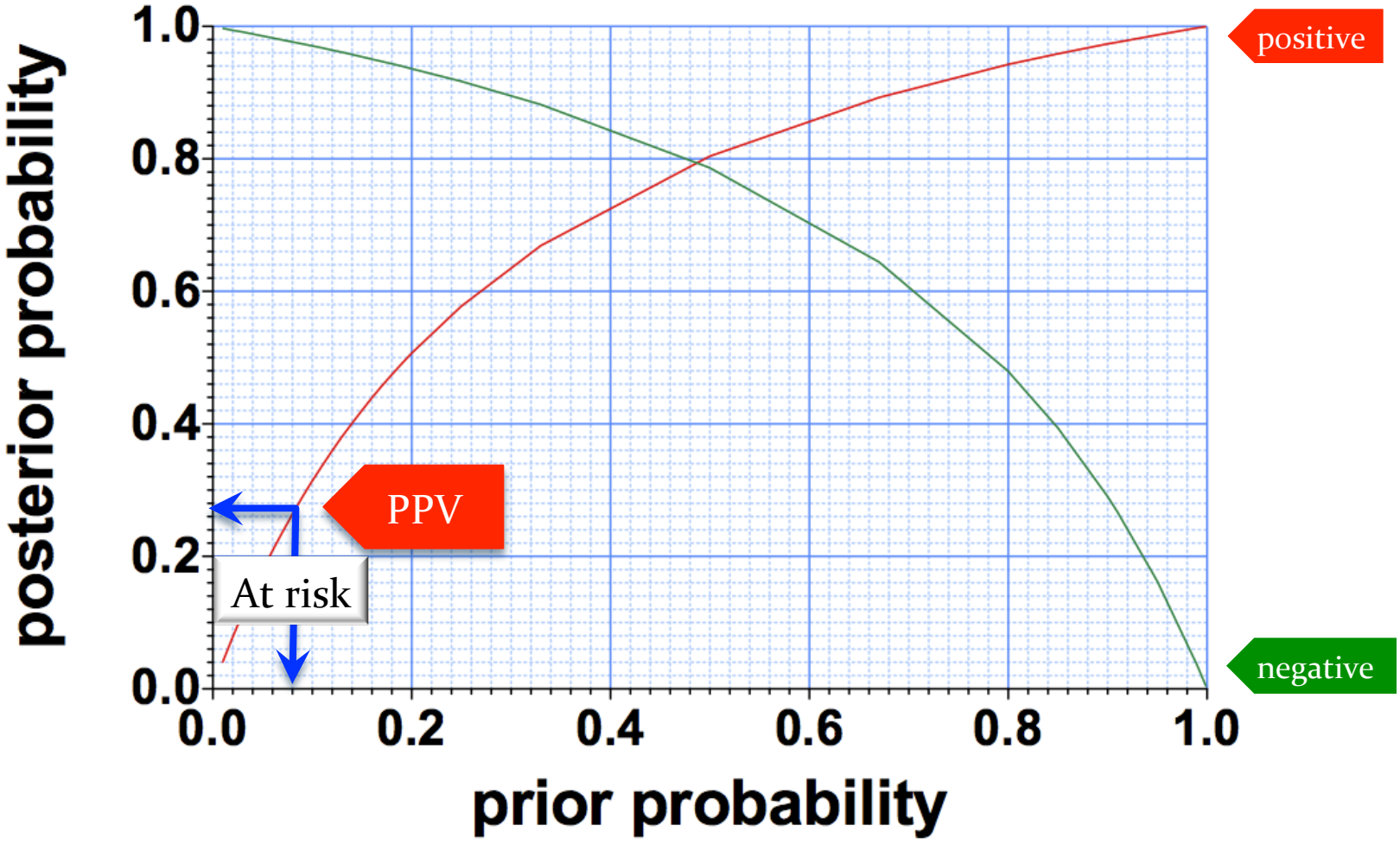
Proportion of patients without IA that test positive

Post-test probabilities – serum/plasma GM



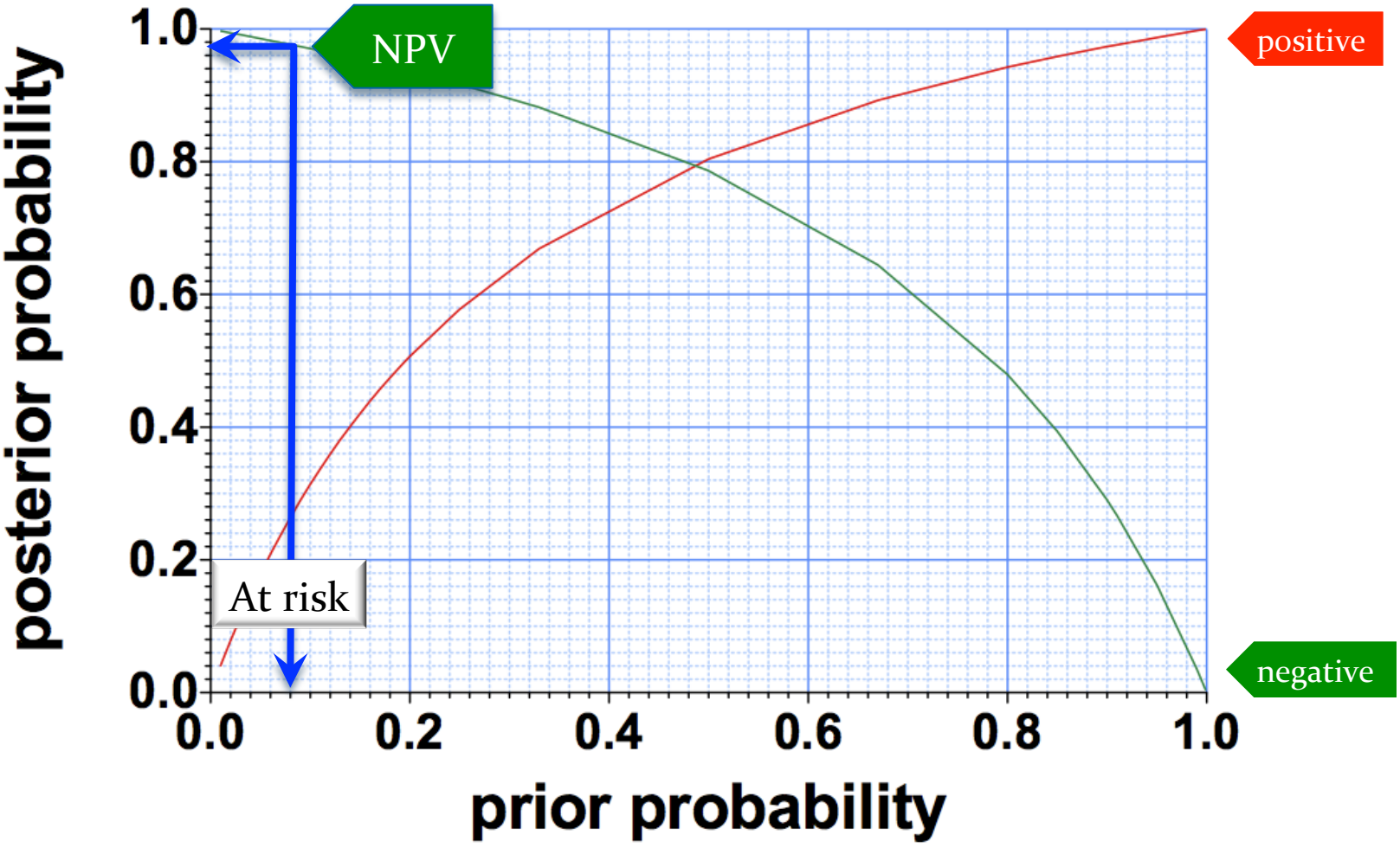
Sensitivity = 0.83 Specificity = 0.85

Post-test probabilities – serum/plasma GM



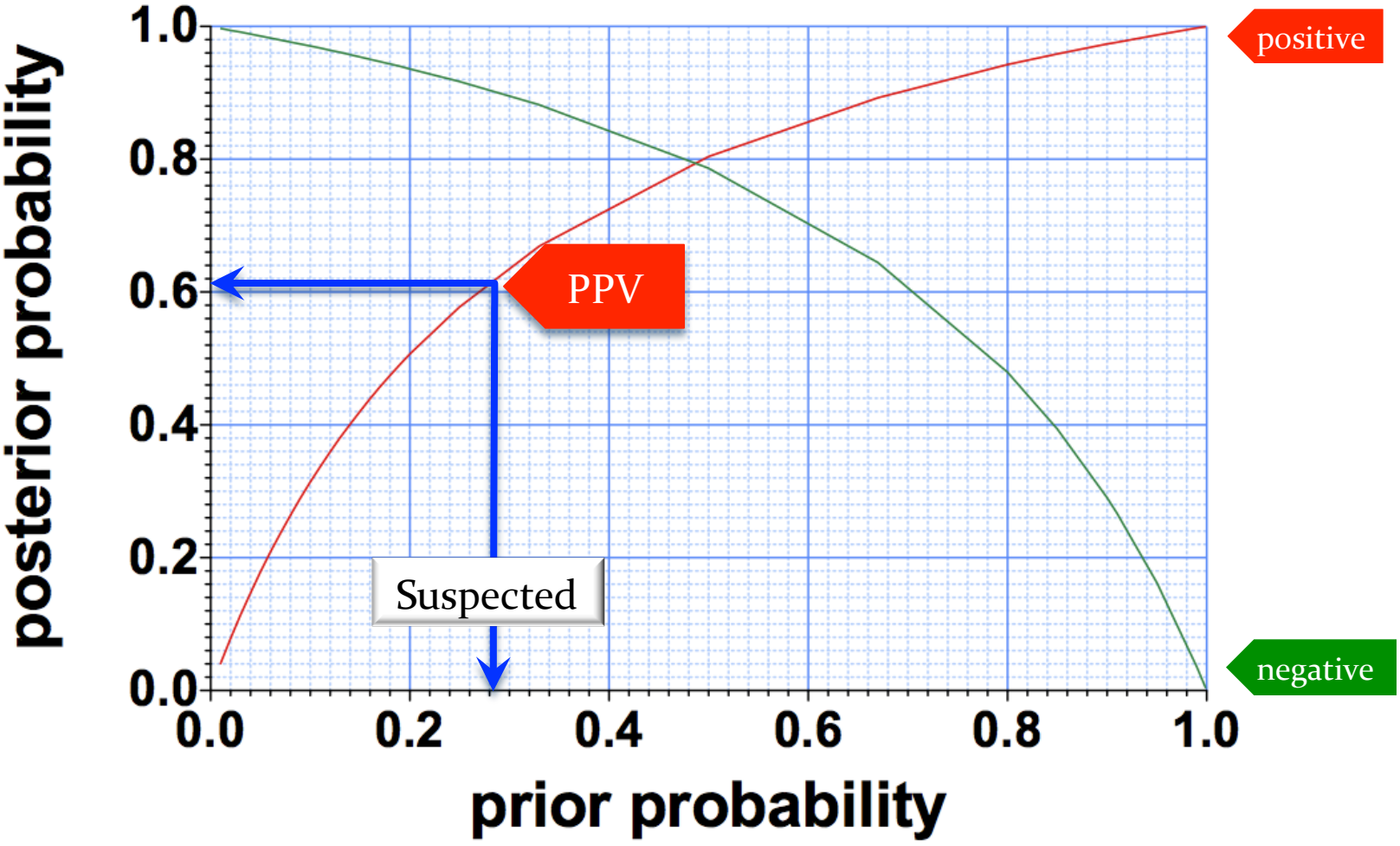
Sensitivity = 0.83 Specificity = 0.85

Post-test probabilities – serum/plasma GM



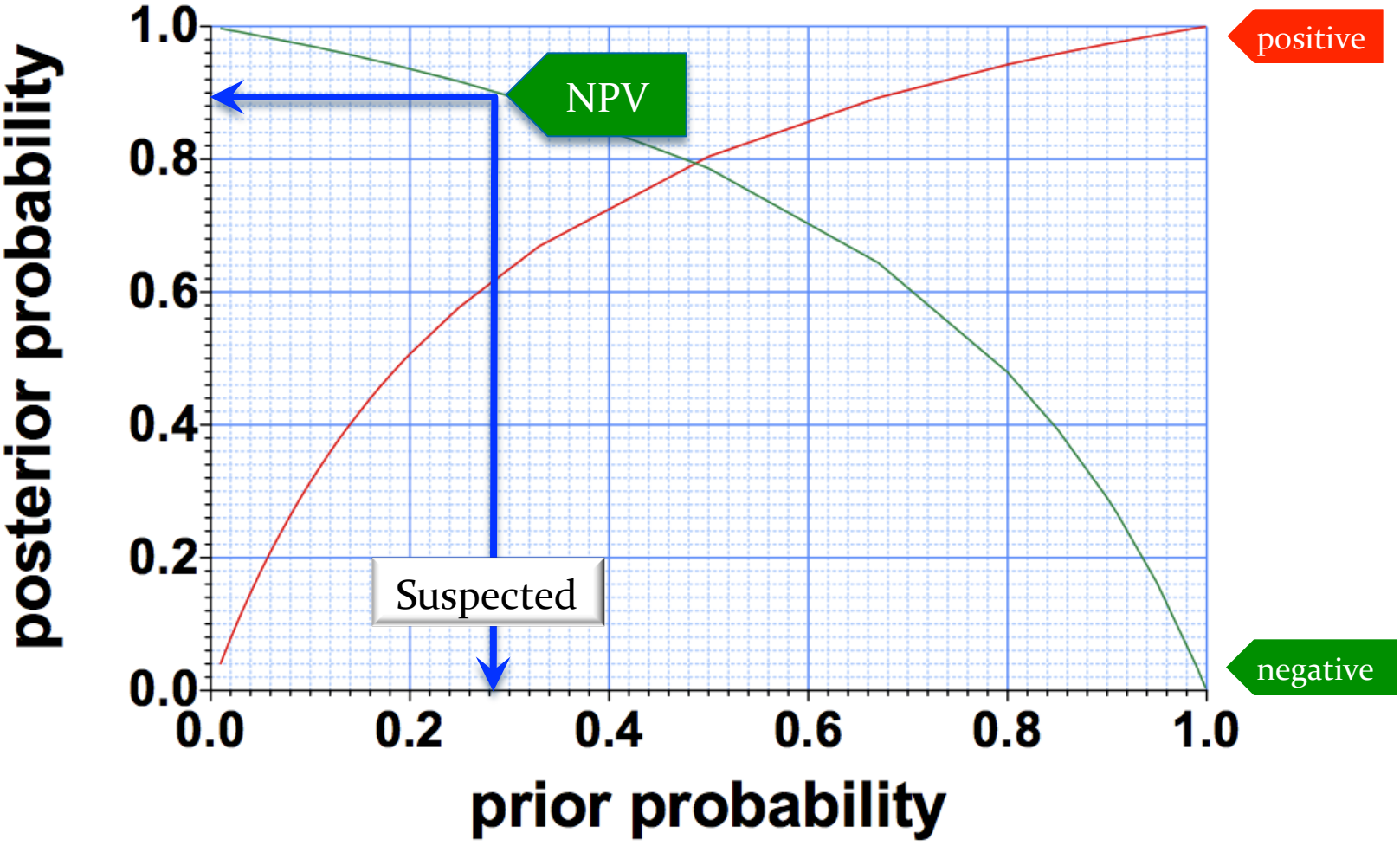
Sensitivity = 0.83 Specificity = 0.85

Post-test probabilities – serum/plasma GM



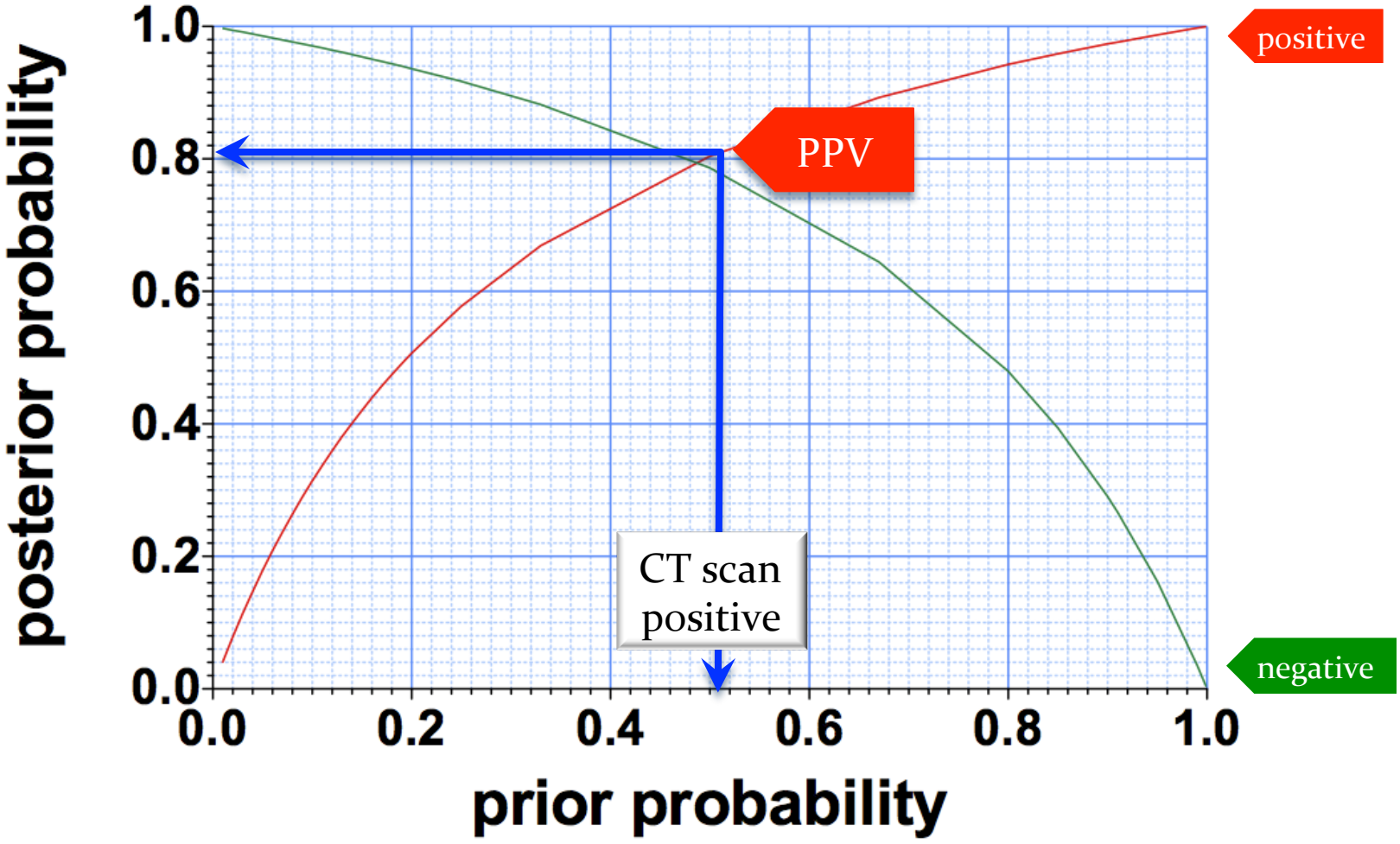
Sensitivity = 0.83 Specificity = 0.85

Post-test probabilities – serum/plasma GM



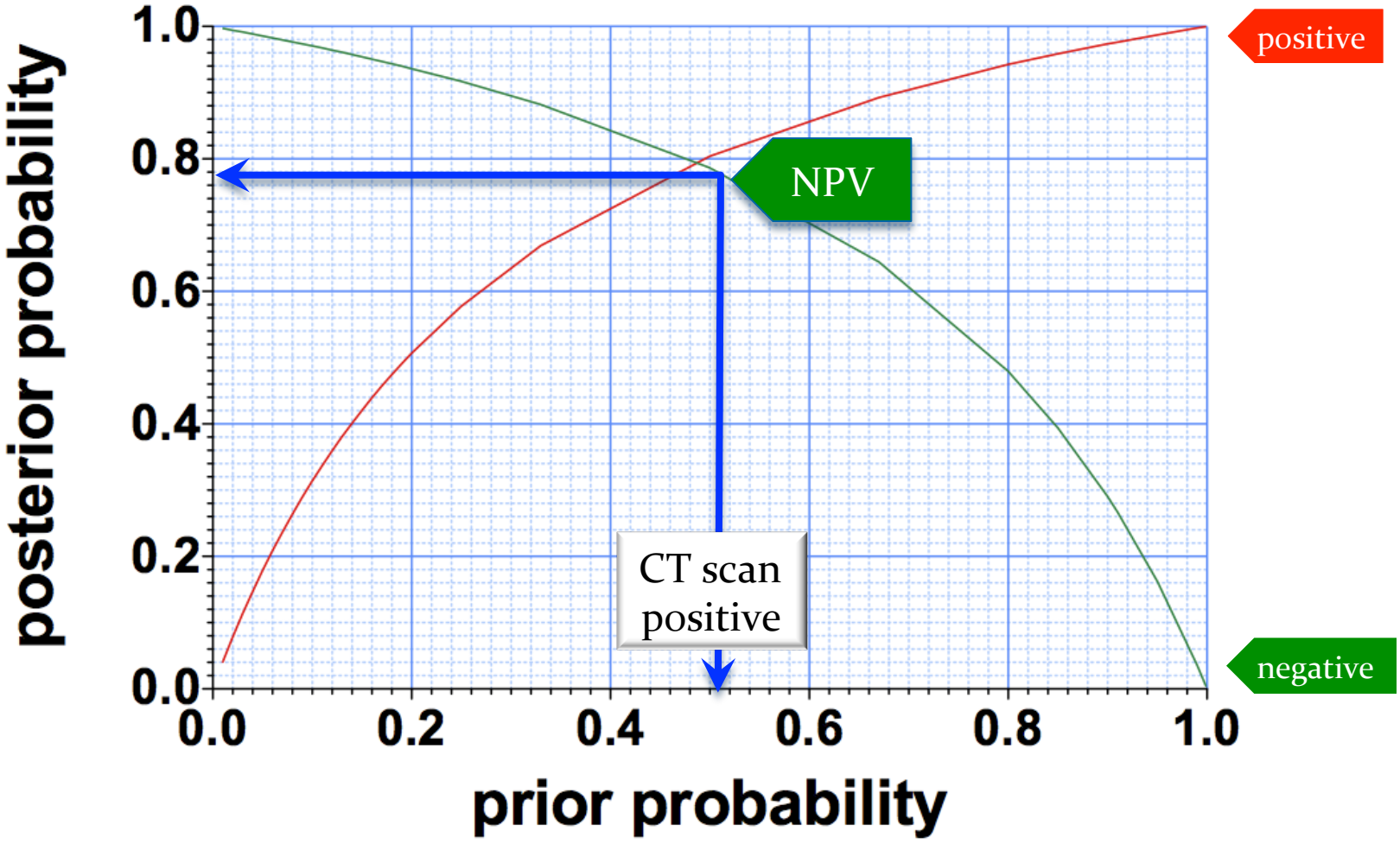
Sensitivity = 0.83 Specificity = 0.85

Post-test probabilities – serum/plasma GM



Sensitivity = 0.83 Specificity = 0.85

Post-test probabilities – serum/plasma GM



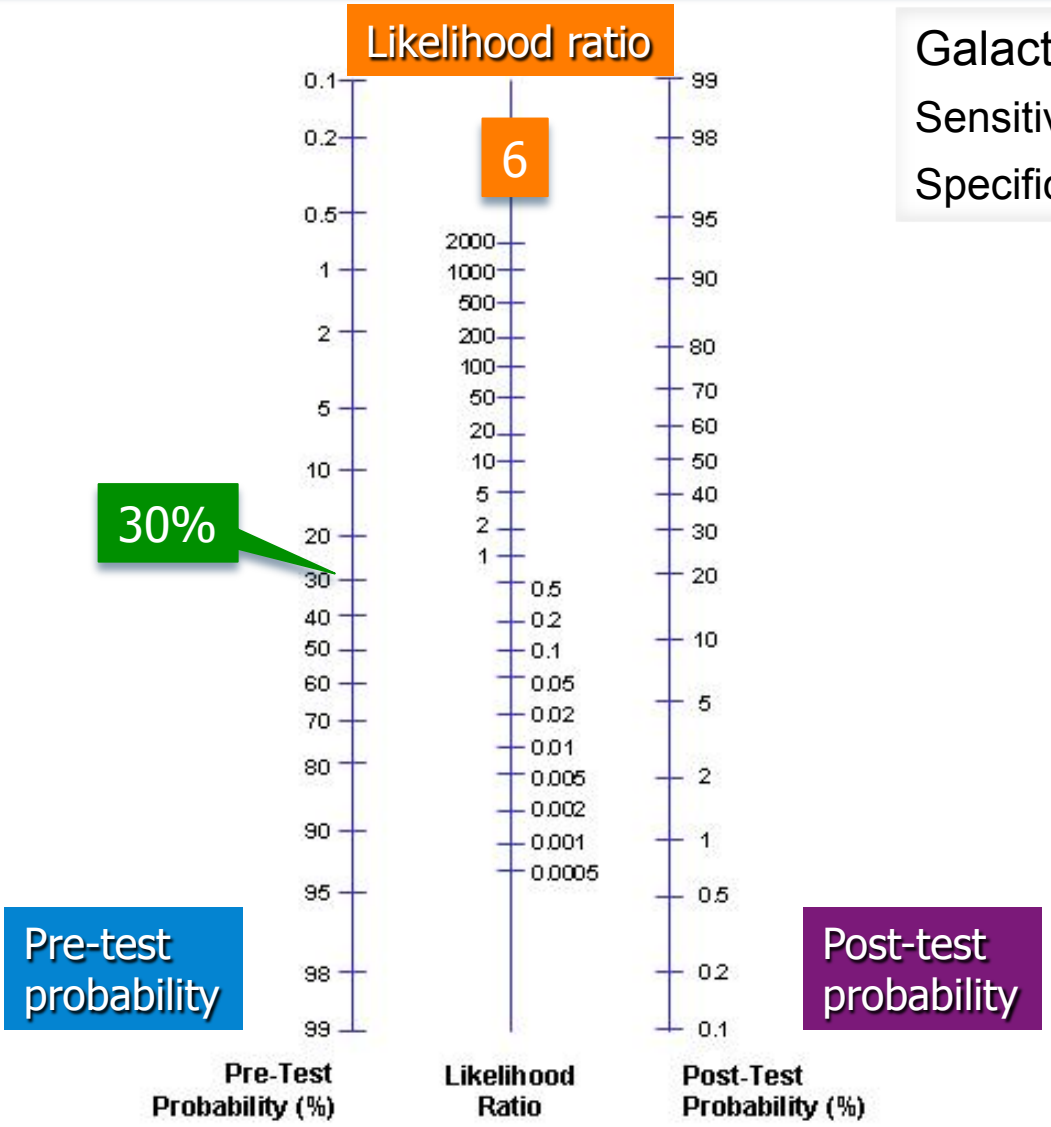
Sensitivity = 0.83 Specificity = 0.85

Post-test probability - diagnosis

Galactomannan or PCR

Sensitivity = 0.83

Specificity = 0.85



Post-test probability - diagnosis

Likelihood ratio

6

Galactomannan or PCR

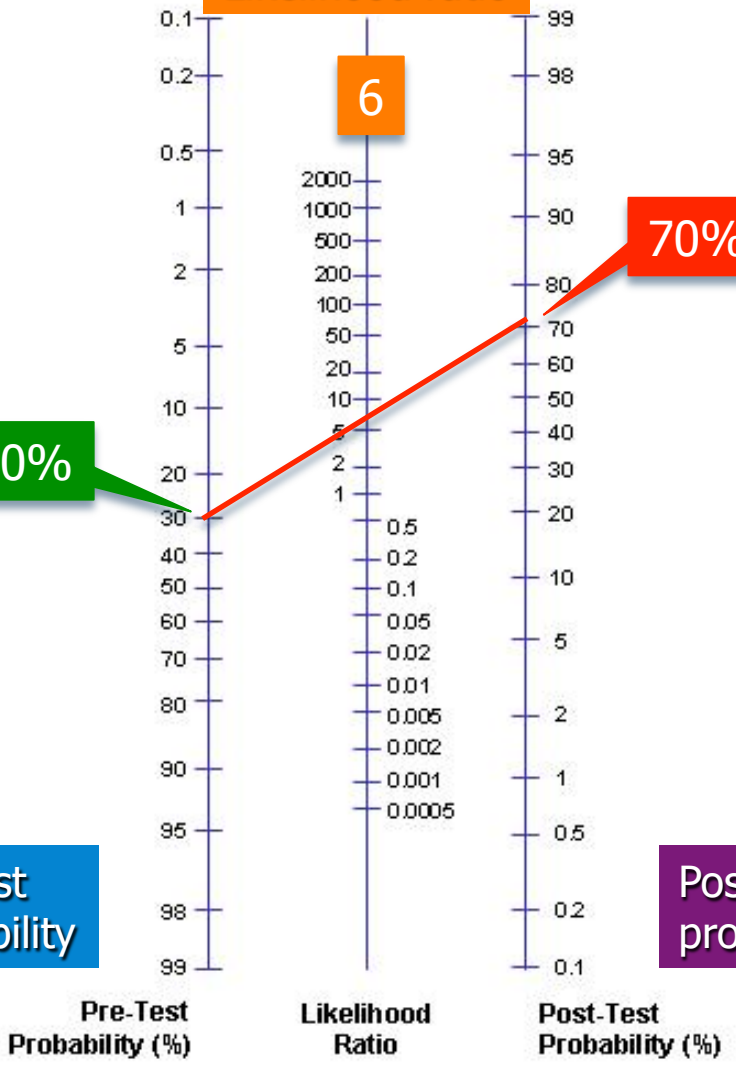
Sensitivity = 0.83

Specificity = 0.85

70%

Proportion of patients with IA that test positive

30%



Pre-test probability

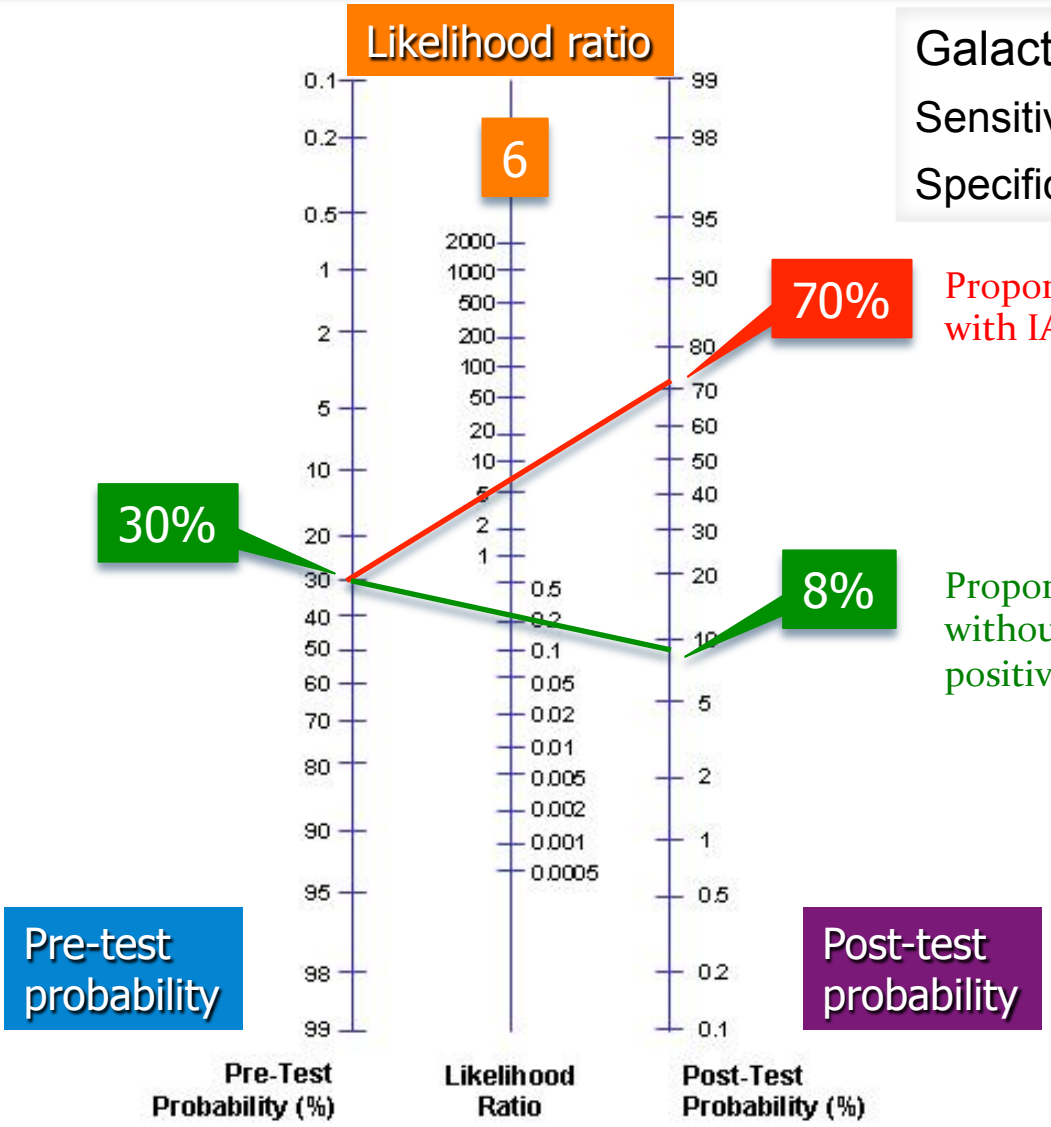
Post-test probability

Post-test probability - diagnosis

Galactomannan or PCR

Sensitivity = 0.83

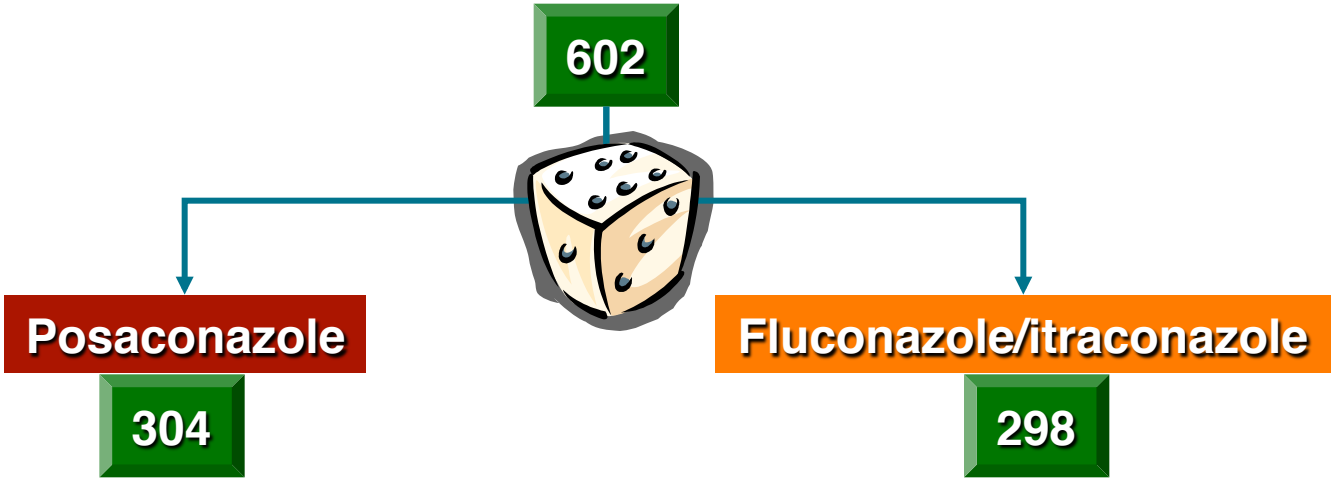
Specificity = 0.85



Proportion of patients with IA that test positive

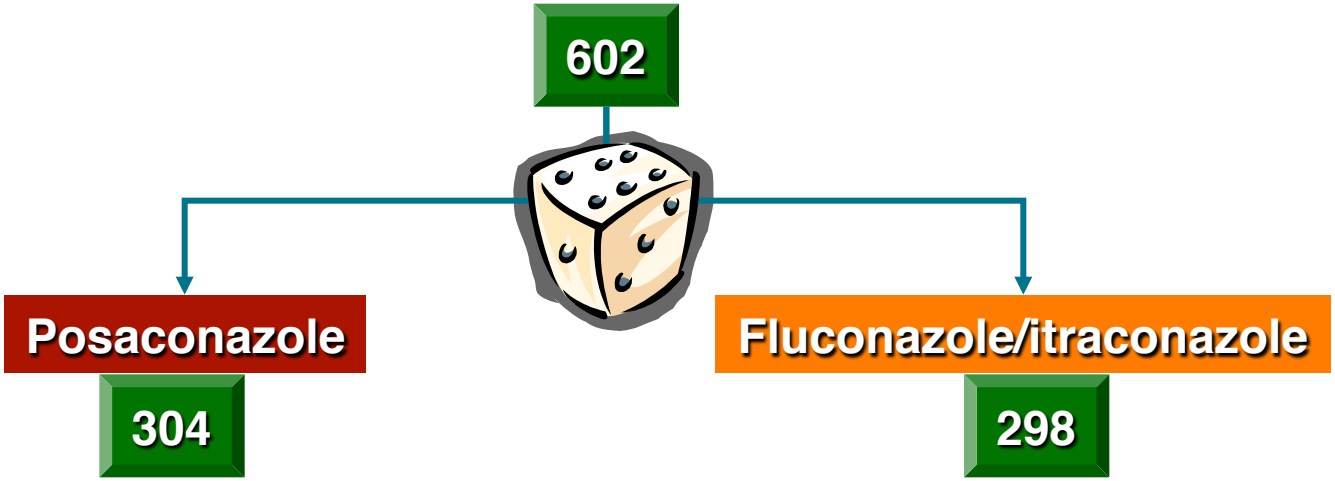
Proportion of patients without IA that test positive

Effect of antifungal prophylaxis



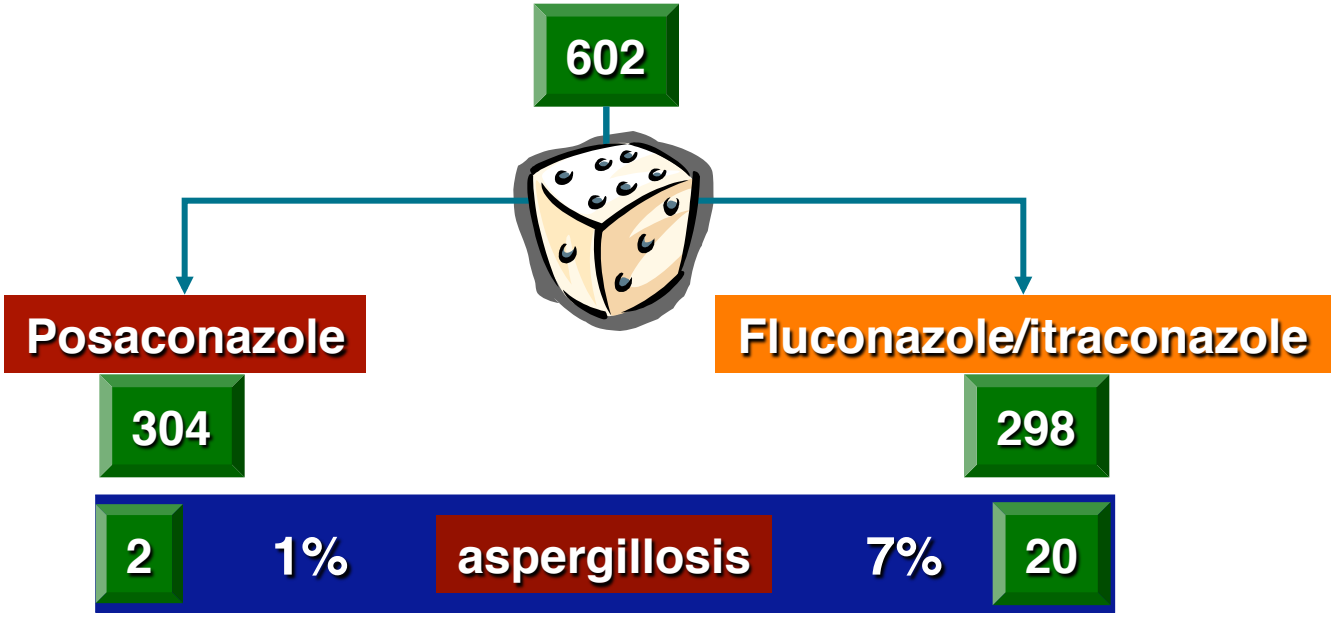
Cornely et al. N Eng J Med 2007 356:348

Effect of antifungal prophylaxis - posaconazole study



Cornely et al. N Eng J Med 2007 356:348

Effect of antifungal prophylaxis - posaconazole study



Cornely et al. N Eng J Med 2007 356:348

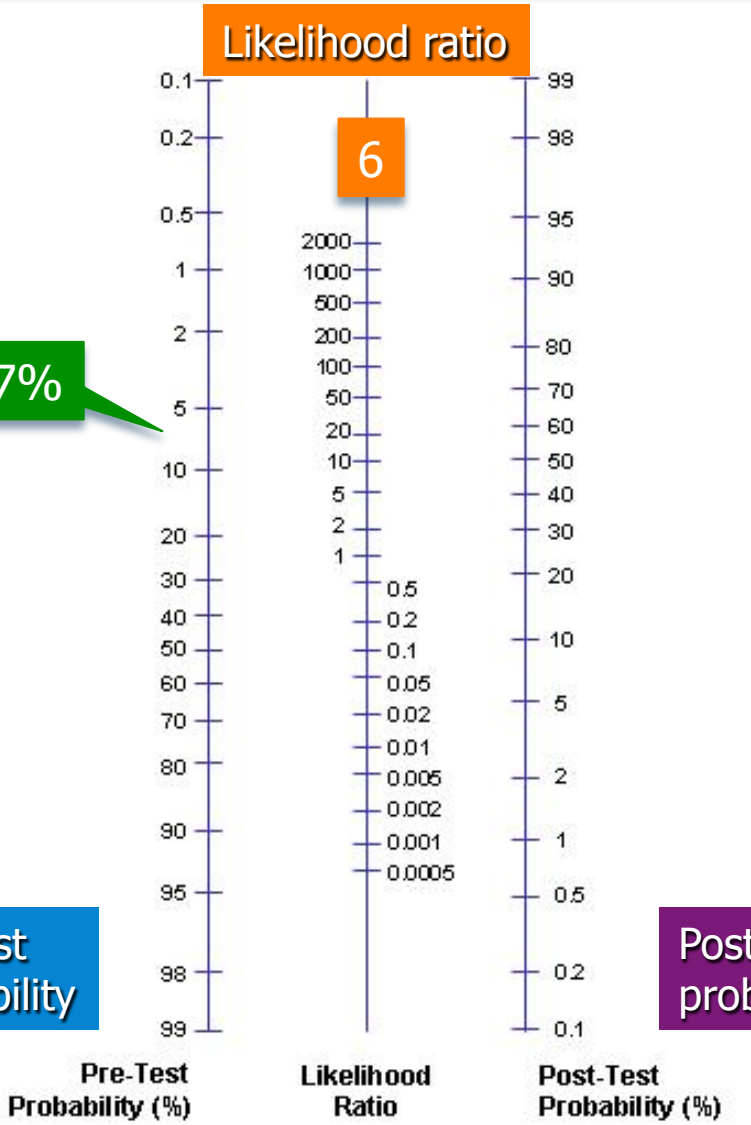
Post-test probability – fluconazole/itraconazole

Data from Cornely et al.
N Eng J Med 2007 356:348

Galactomannan or PCR
Sensitivity = 0.83
Specificity = 0.85

Fluconazole/ itraconazole

7%



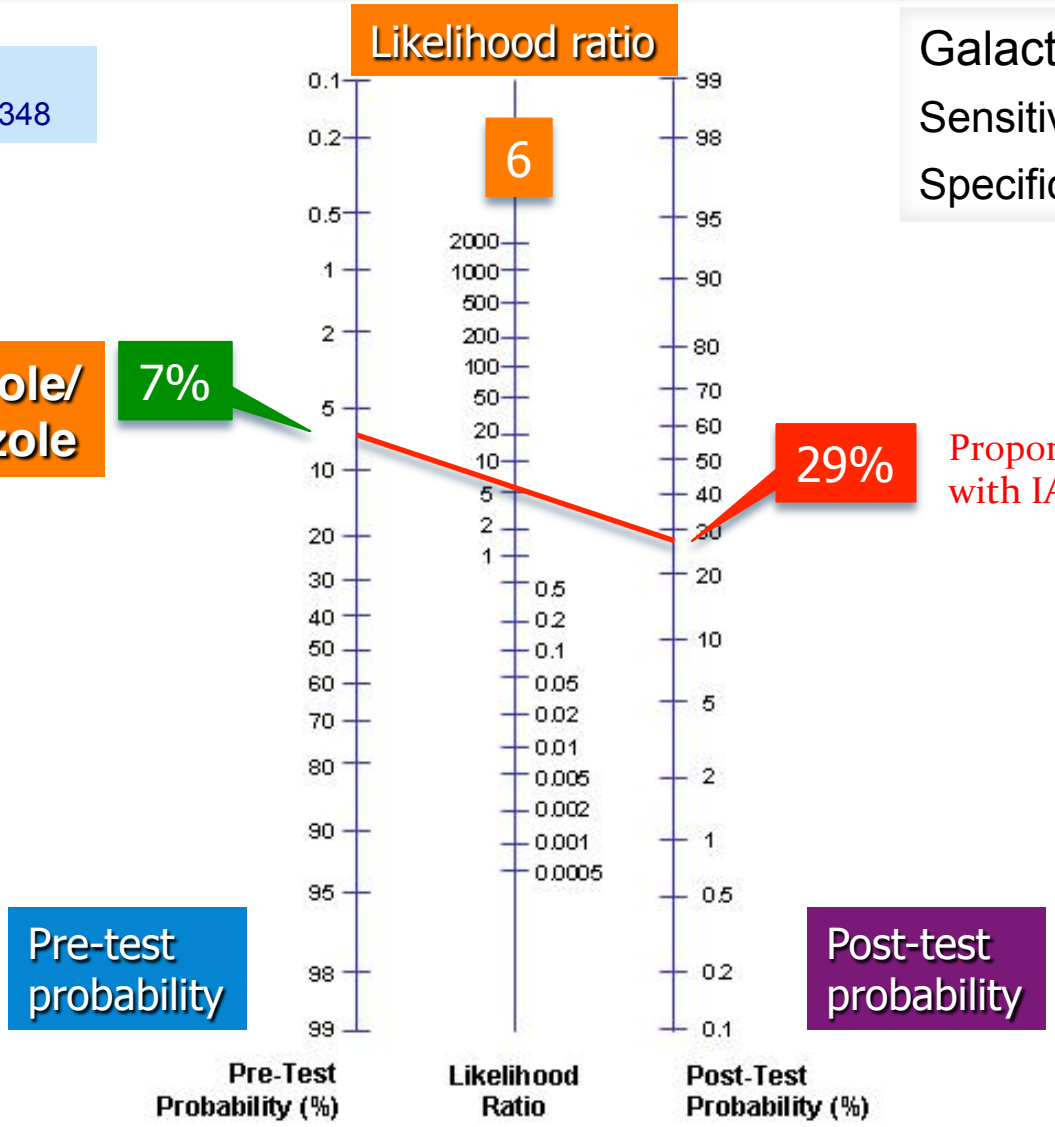
Pre-test probability

Post-test probability

Post-test probability – fluconazole/itraconazole

Data from Cornely et al.
N Eng J Med 2007 356:348

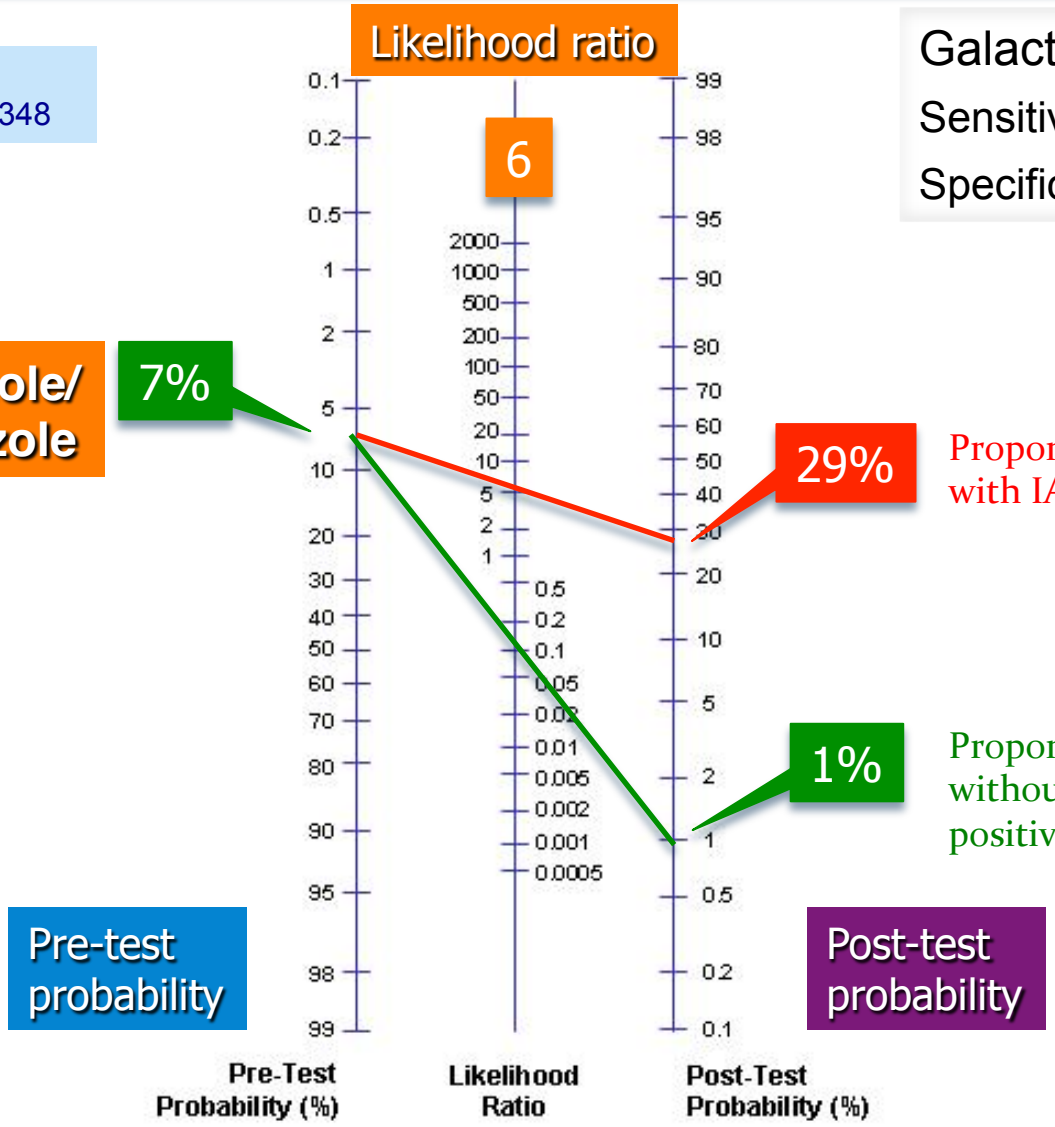
Galactomannan or PCR
Sensitivity = 0.83
Specificity = 0.85



Post-test probability – fluconazole/itraconazole

Data from Cornely et al.
N Eng J Med 2007 356:348

Galactomannan or PCR
Sensitivity = 0.83
Specificity = 0.85



Post-test probability – posaconazole

Data from Cornely et al.
N Eng J Med 2007 356:348

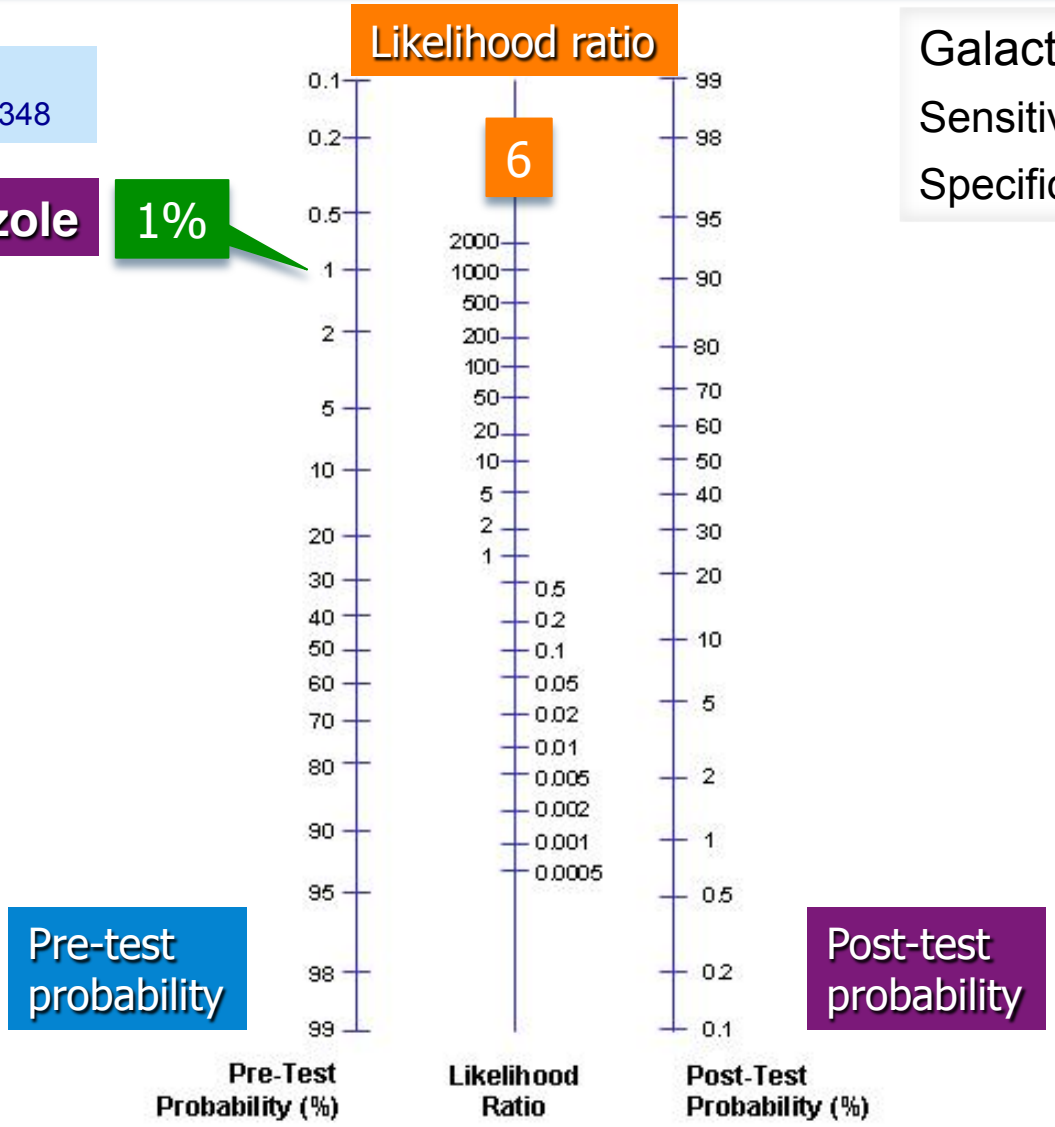
Posaconazole

1%

Galactomannan or PCR

Sensitivity = 0.83

Specificity = 0.85

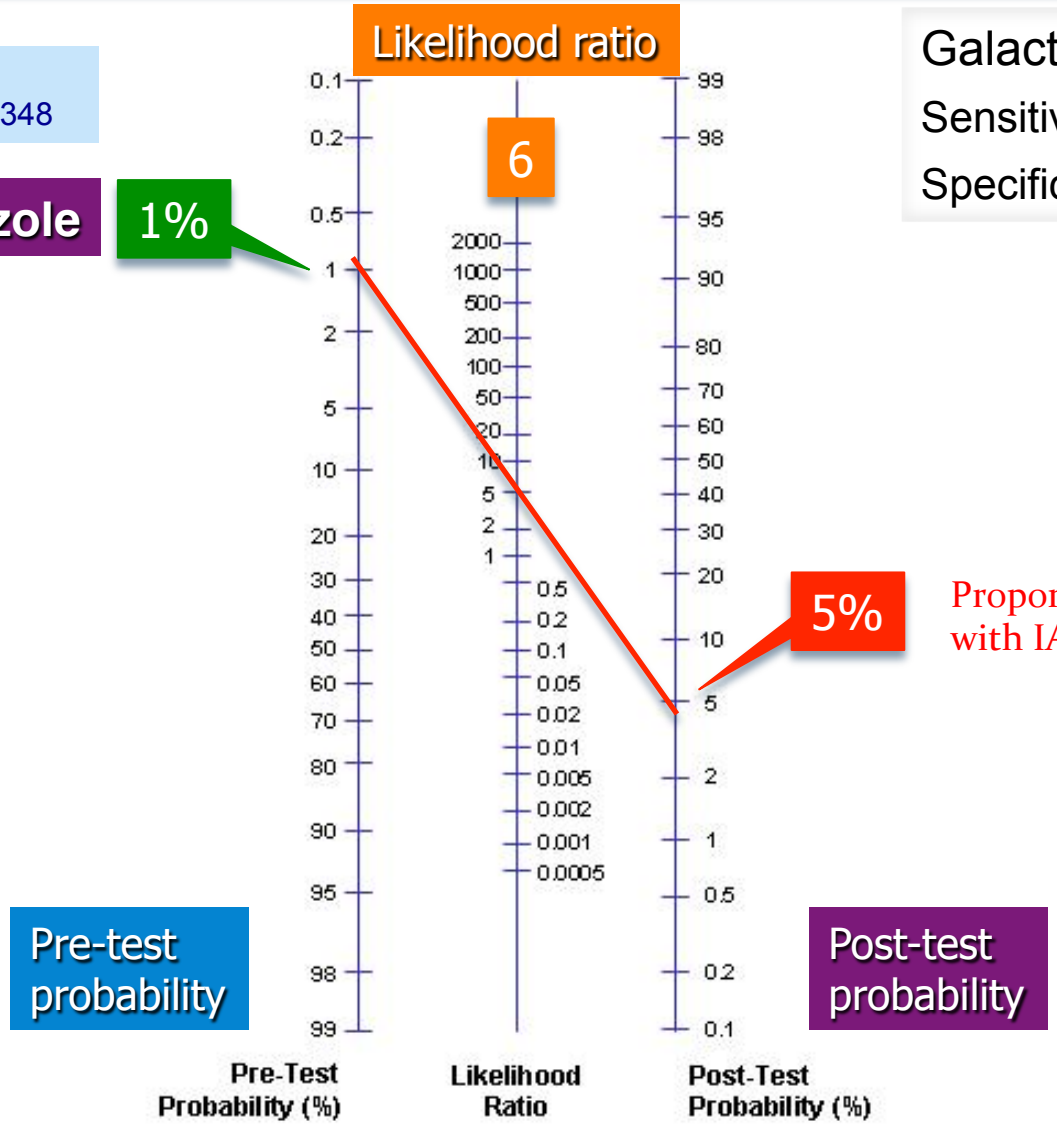


Post-test probability – posaconazole

Data from Cornely et al.
N Eng J Med 2007 356:348

Posaconazole

Galactomannan or PCR
Sensitivity = 0.83
Specificity = 0.85

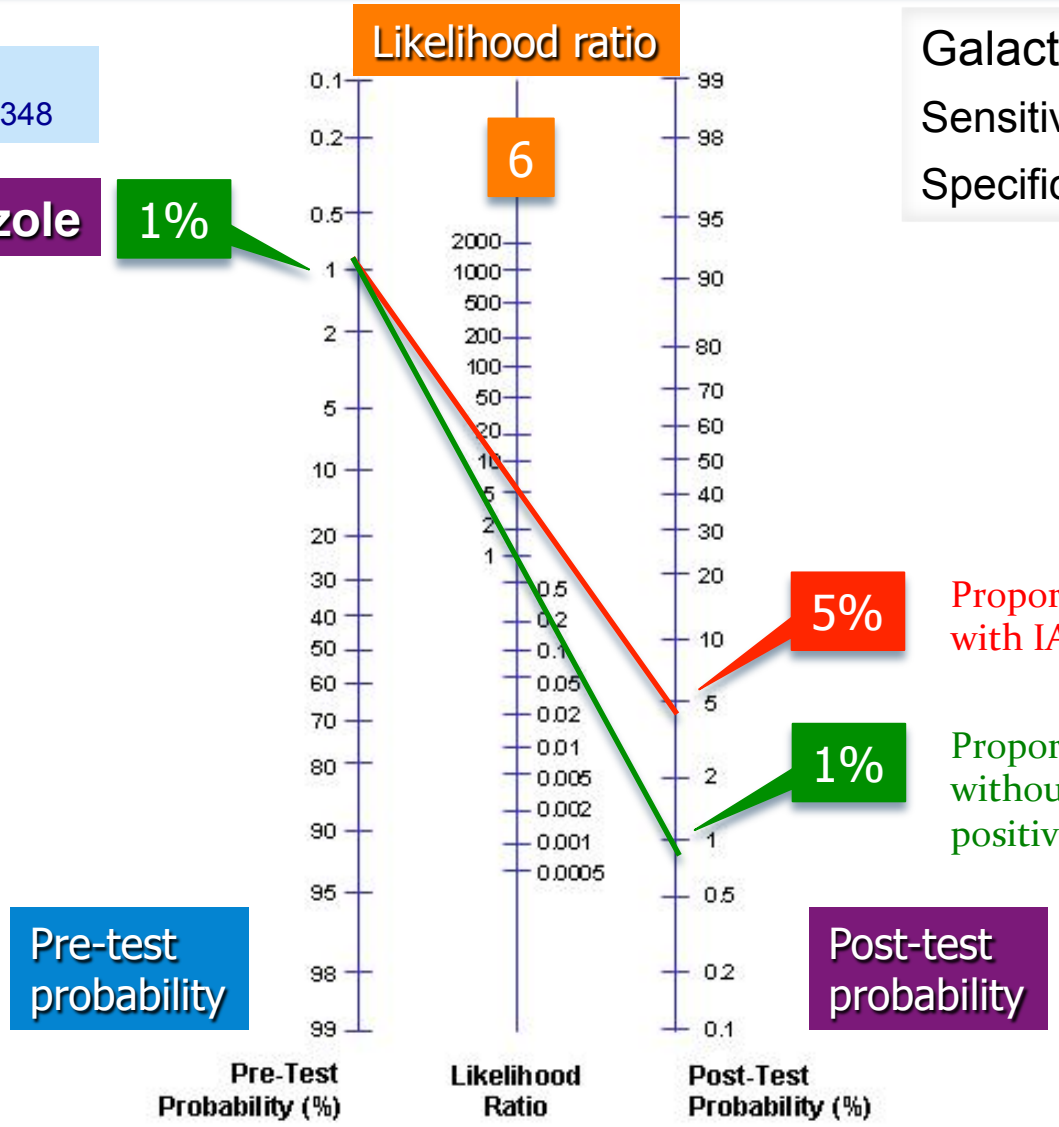


Proportion of patients with IA that test positive

Post-test probability – posaconazole

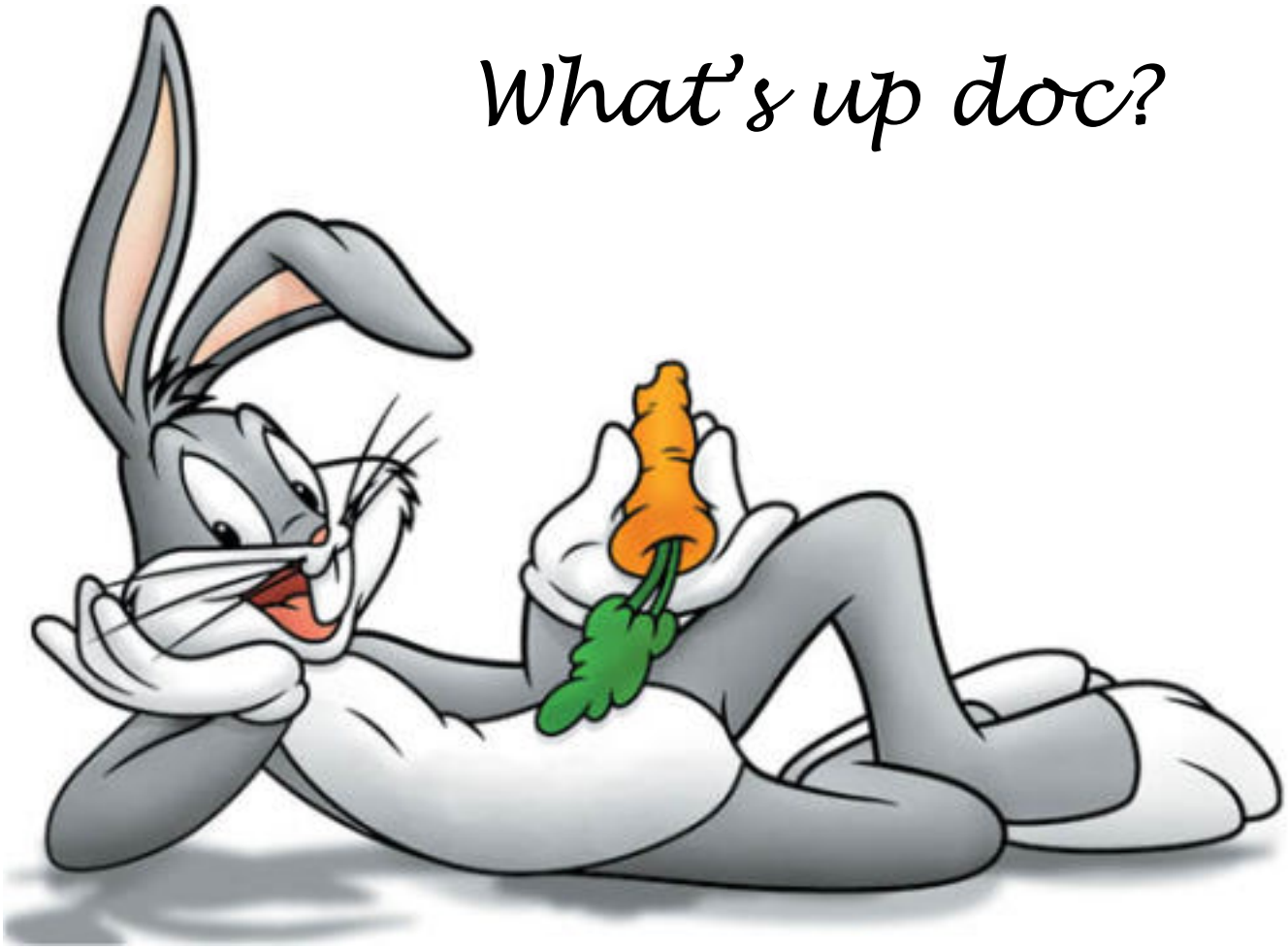
Data from Cornely et al.
N Eng J Med 2007 356:348

Galactomannan or PCR
Sensitivity = 0.83
Specificity = 0.85



Impact of prophylaxis on galactomannan, beta-D-glucan and PCR

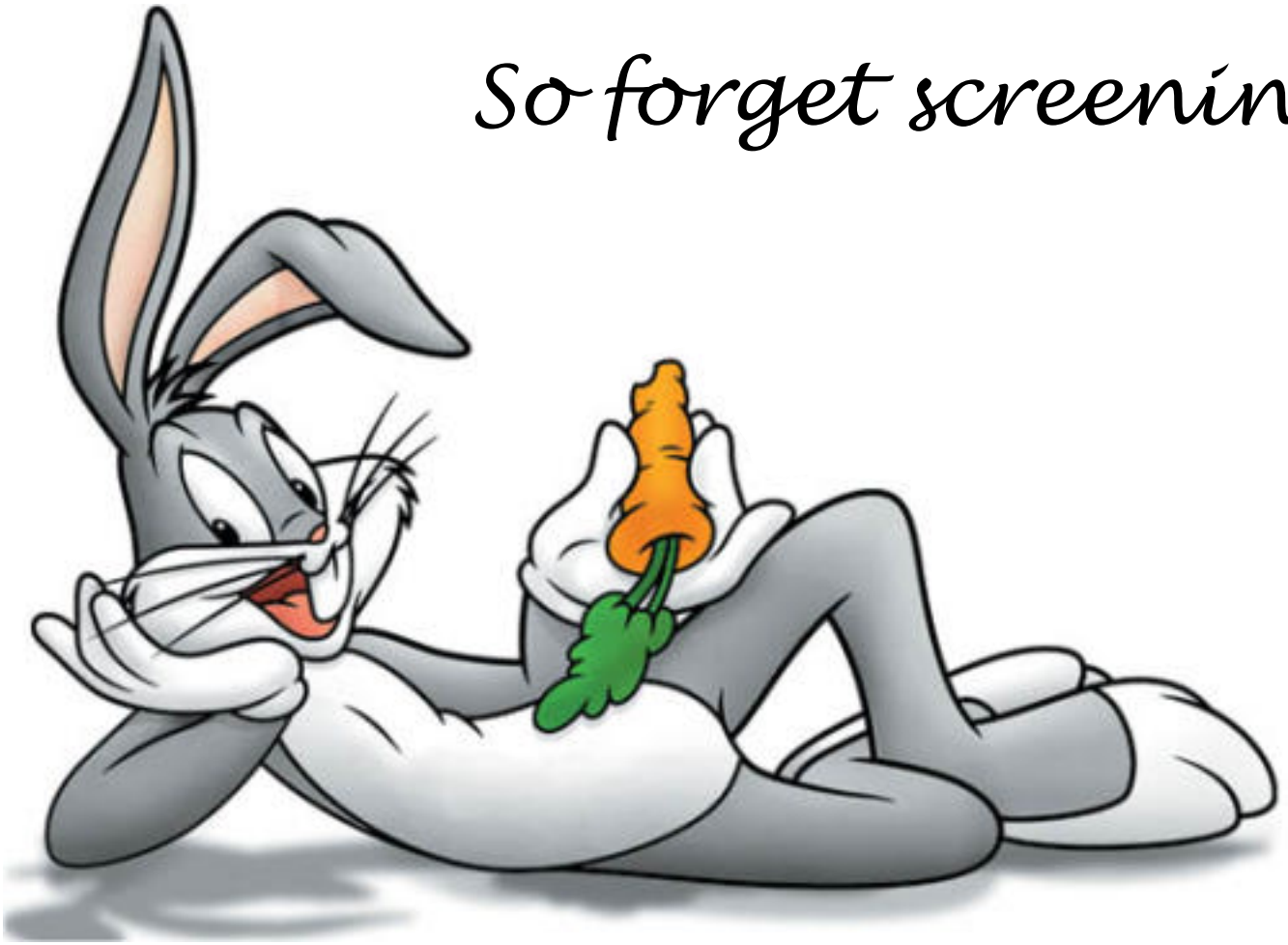
Impact of prophylaxis on galactomannan, beta-D-glucan and PCR



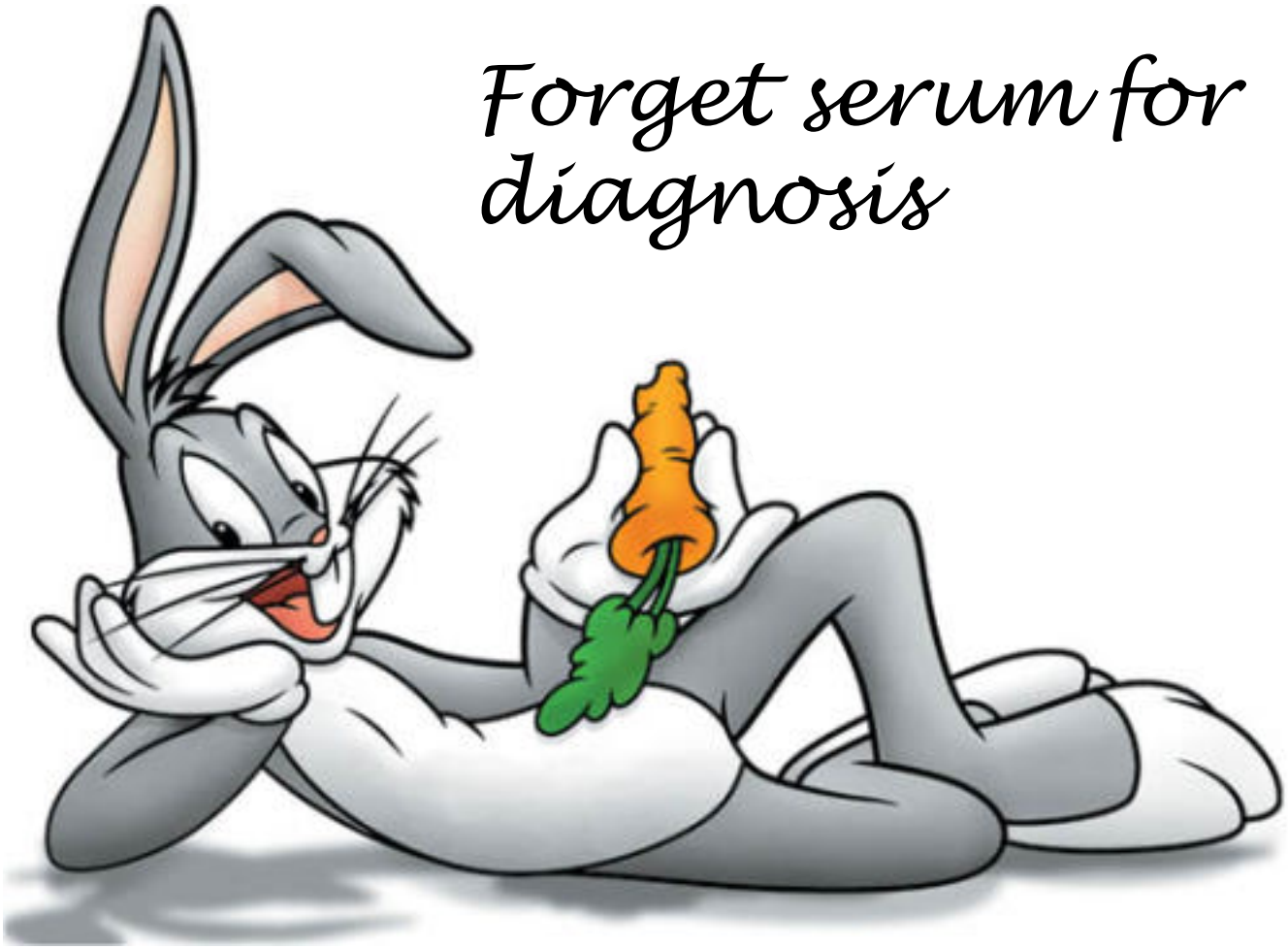
Impact of prophylaxis on galactomannan, beta-D-glucan and PCR

Impact of prophylaxis on galactomannan, beta-D-glucan and PCR

Impact of prophylaxis on galactomannan, beta-D-glucan and PCR

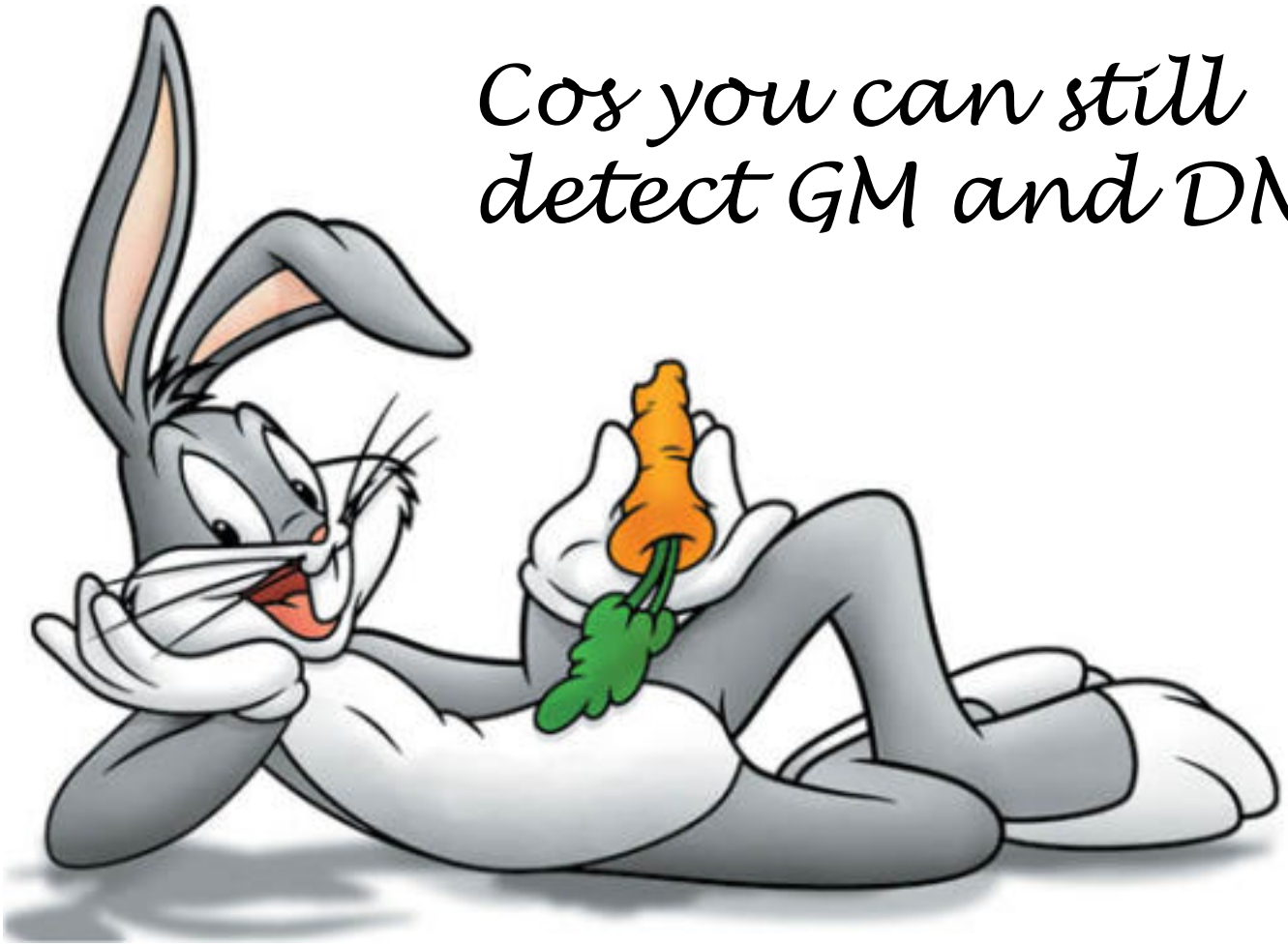


Impact of prophylaxis on galactomannan, beta-D-glucan and PCR



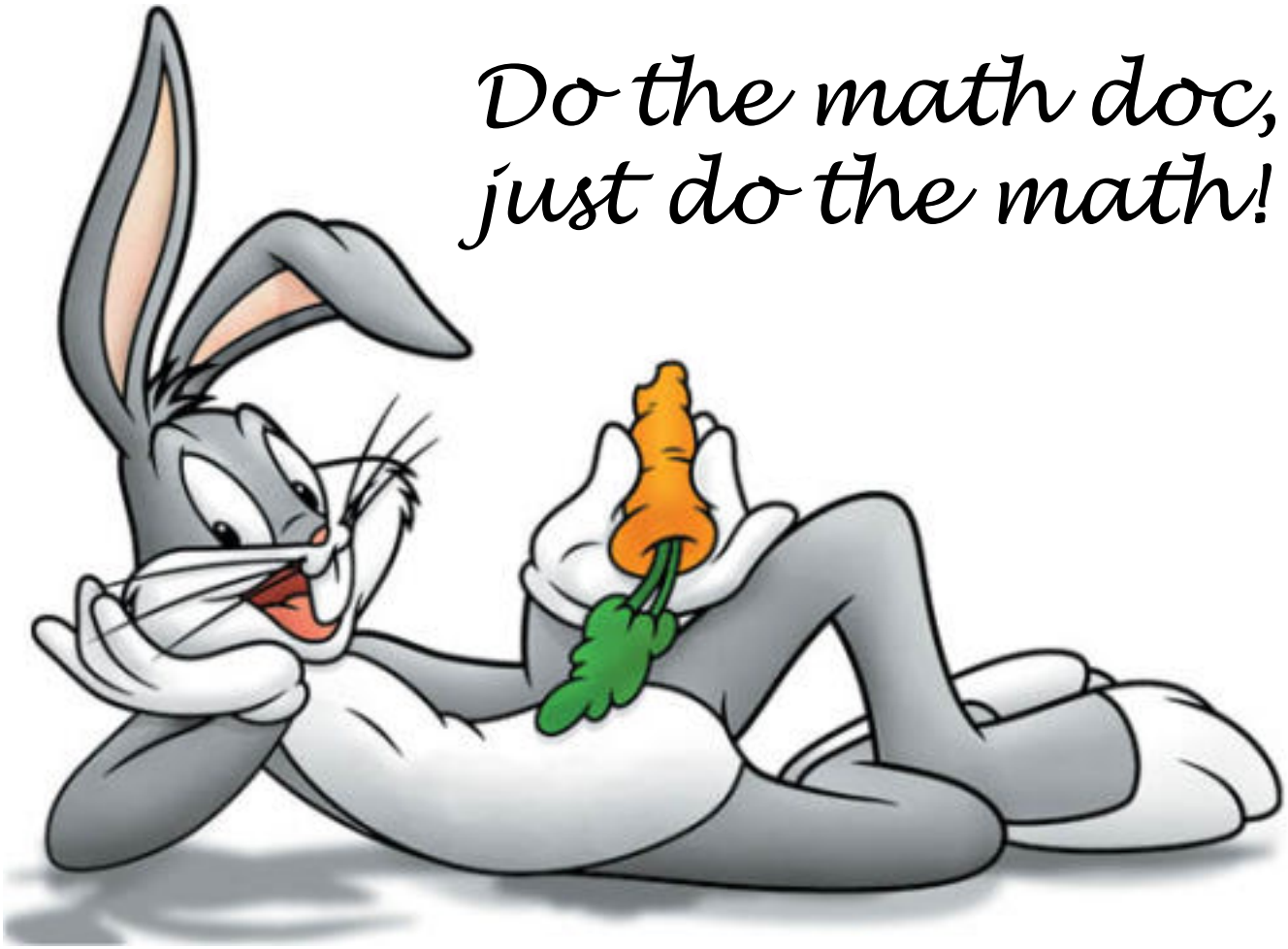
Impact of prophylaxis on galactomannan, beta-D-glucan and PCR

Impact of prophylaxis on galactomannan, beta-D-glucan and PCR



Impact of prophylaxis on galactomannan, beta-D-glucan and PCR

Impact of prophylaxis on galactomannan, beta-D-glucan and PCR



Question 1

Does antifungal prophylaxis have an adverse impact on tests for galactomannan, ß-D-glucan and DNA?

- Yes
- No
- Don’t know

Question 2

Does antifungal prophylaxis have an adverse impact only on tests for **galactomannan**?

- Yes
- No
- Don’t know

Question 3

Does antifungal prophylaxis have an adverse impact only on tests for **ß-D-glucan**?

- Yes
- No
- Don’t know

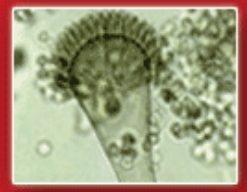
Question 4

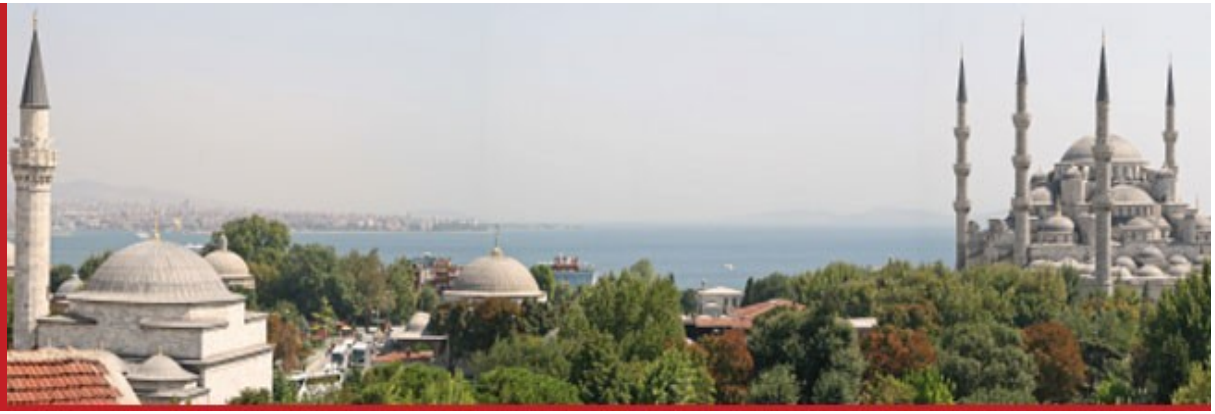
Does antifungal prophylaxis have an adverse impact only on PCR tests for **DNA**?

- Yes
- No
- Don’t know

5th ADVANCES AGAINST
ASPERGILLOSIS

Istanbul, Turkey
26-28 January 2012
Lutfi Kirdar Convention &
Exhibition Centre





Thank you