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Diagnostic strategies in suspected PE across different healthcare settings; what model to use in what patient

Geert-Jan Geersing, M.D. Ph.D., on behalf of IPD-MA Diagnosing Pulmonary Embolism working group

International collaboration

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

UNIVERSITÉ
DE GENÈVE
FACULTÉ DE MÉDECINE

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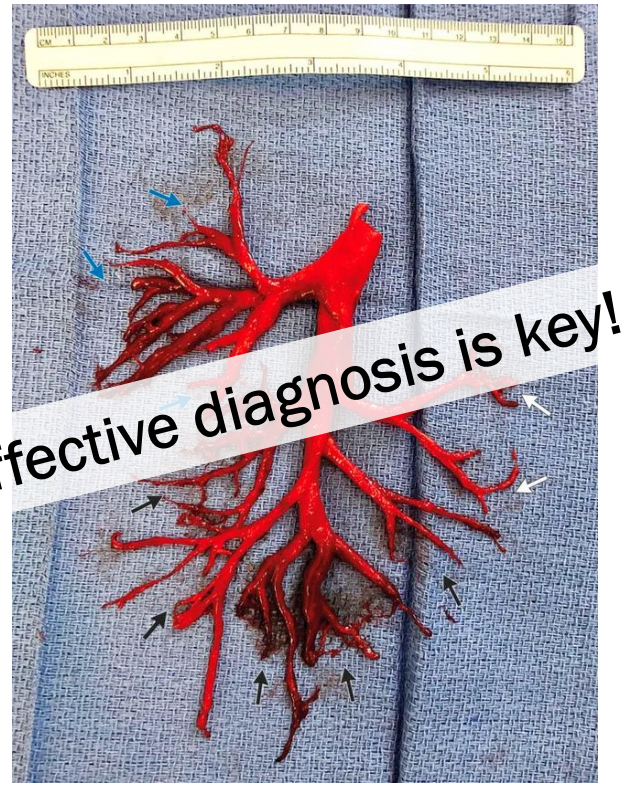
Background Pulmonary Embolism



Pulmonary Embolism is:

- *A common condition*
- *Excellent treatment options*
- *Still, many preventable deaths*
- *Missed or delayed diagnoses*

- *A common condition*
- *Uncertainty on treatment*
- *Notably sub-segmental PE*
- *Overdiagnosis / Overtreatment*

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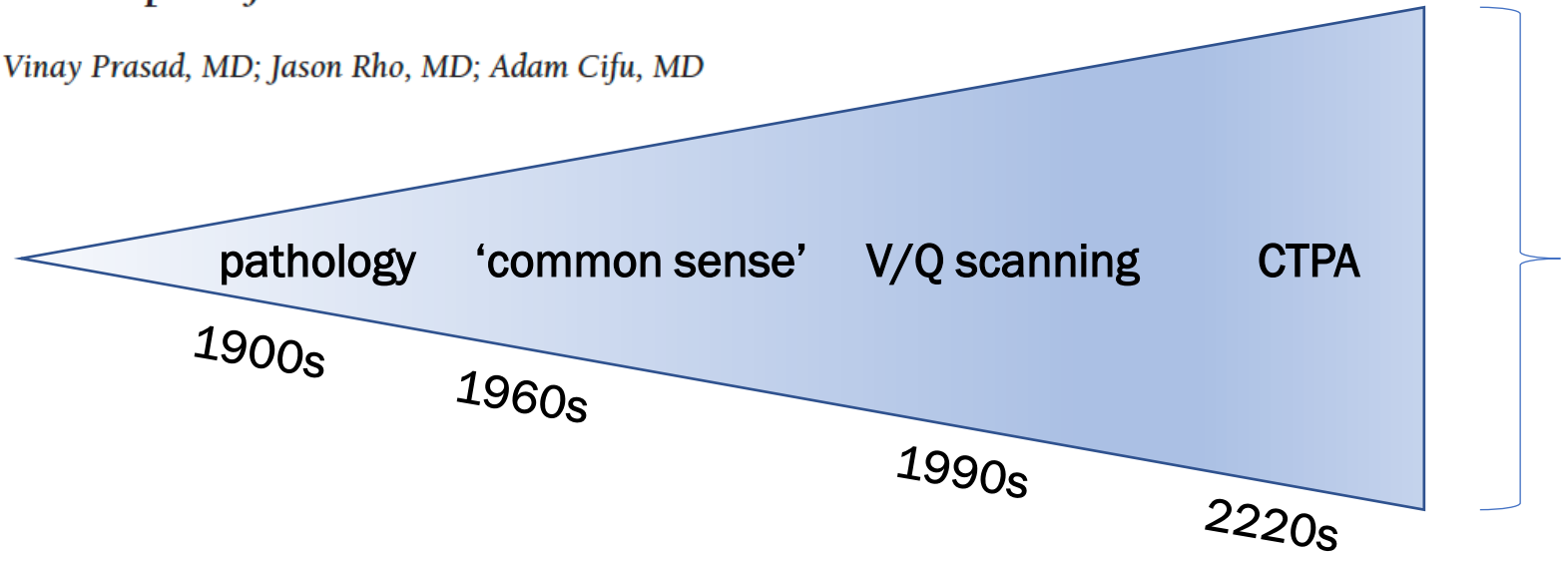
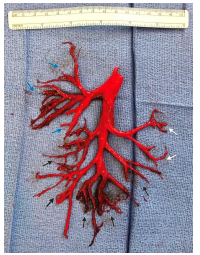
LESS IS MORE

The Diagnosis and Treatment of Pulmonary Embolism

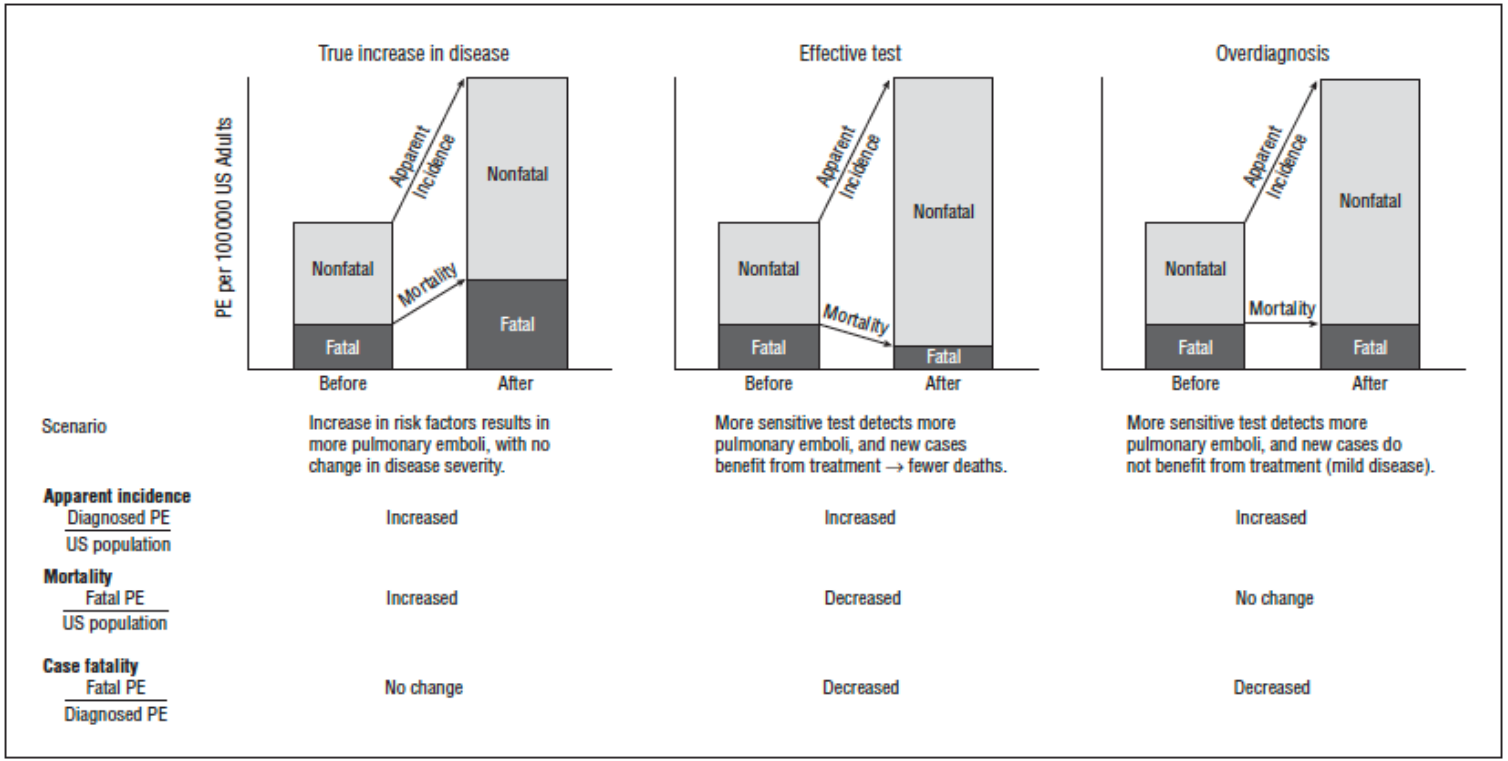
A Metaphor for Medicine in the Evidence-Based Medicine Era

Vinay Prasad, MD; Jason Rho, MD; Adam Cifu, MD





Evidence of overdiagnosis?



Scenario	Increase in risk factors results in more pulmonary emboli, with no change in disease severity.	More sensitive test detects more pulmonary emboli, and new cases benefit from treatment → fewer deaths.	More sensitive test detects more pulmonary emboli, and new cases do not benefit from treatment (mild disease).
Apparent incidence Diagnosed PE / US population	Increased	Increased	Increased
Mortality Fatal PE / US population	Increased	Decreased	No change
Case fatality Fatal PE / Diagnosed PE	No change	Decreased	Decreased

Figure 1. Expected change in mortality and case fatality in various scenarios of rising apparent incidence. PE indicates pulmonary embolism.

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Evidence of overdiagnosis?

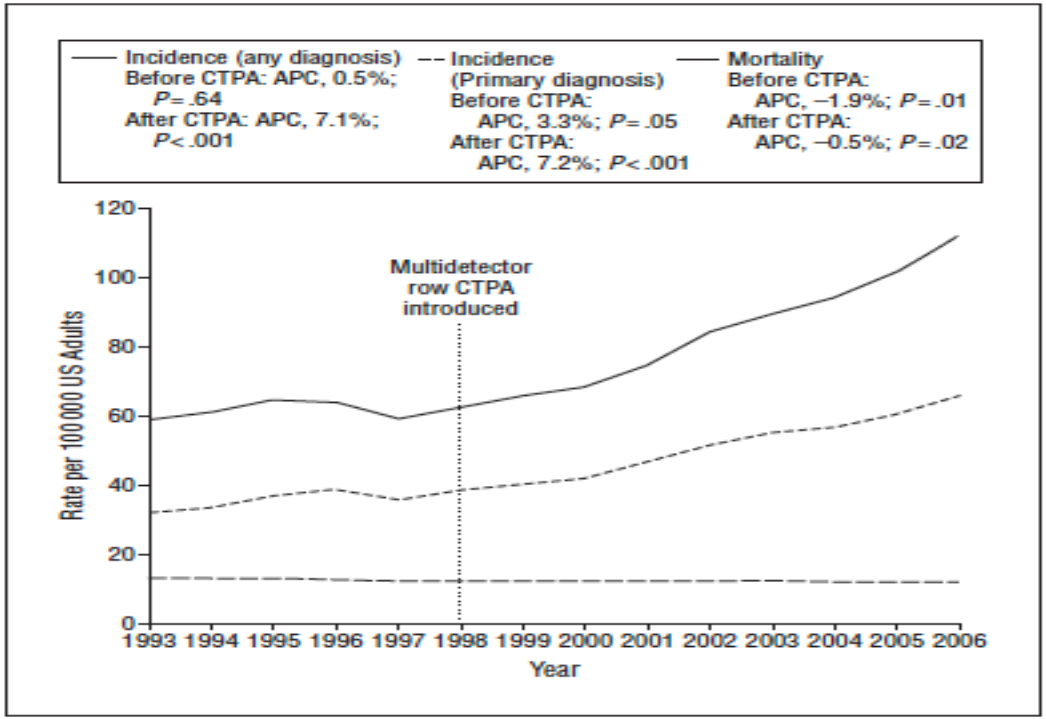

Figure 2. Incidence and mortality of pulmonary embolism in the United States, 1993-2006. APC indicates annual percentage change; and CTPA, computed tomographic pulmonary angiography.

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Suspected PE in different healthcare settings

Increasing PE prevalence
Differences in case-mix
Differences in physician experience
Difference in overdiagnosis?

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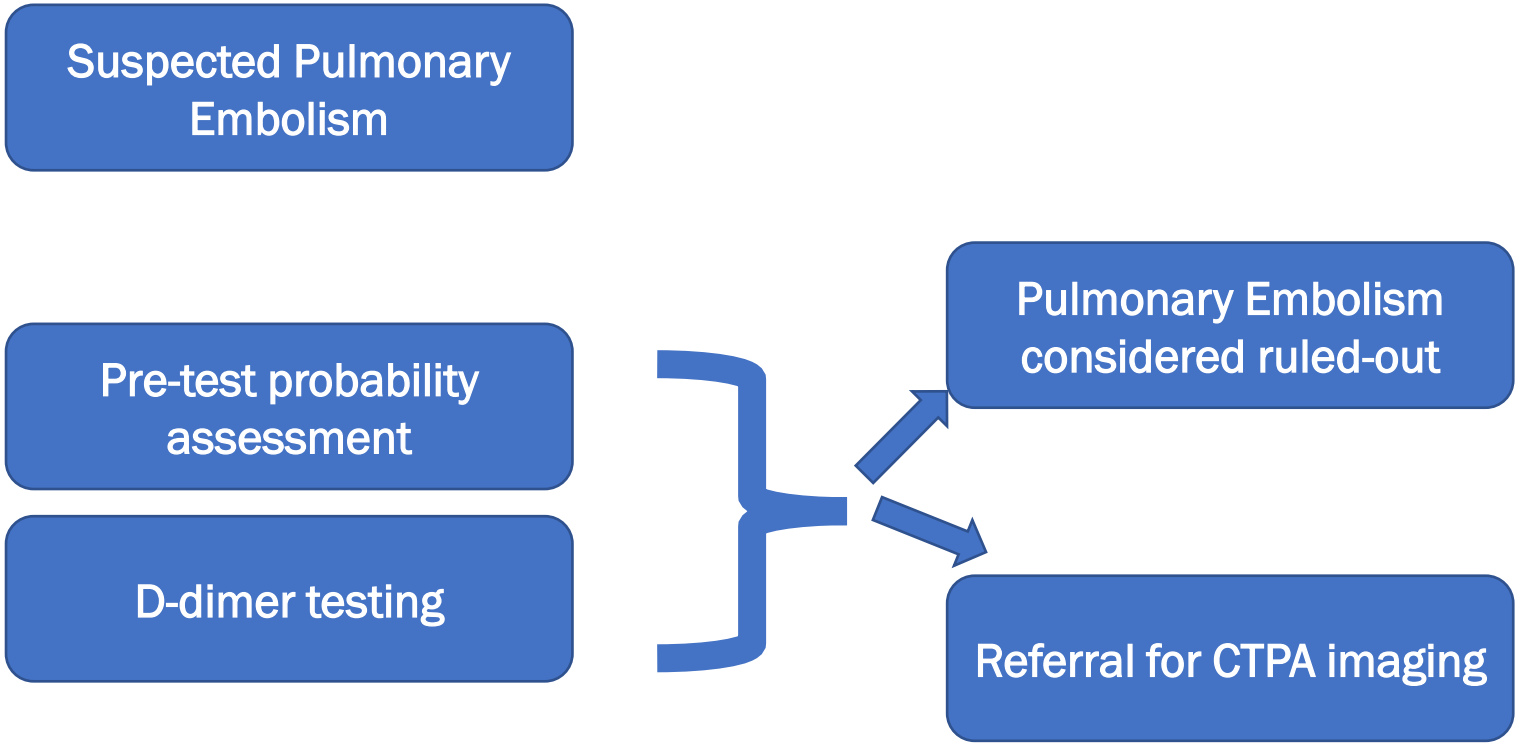
Diagnostic pathway in suspected PE



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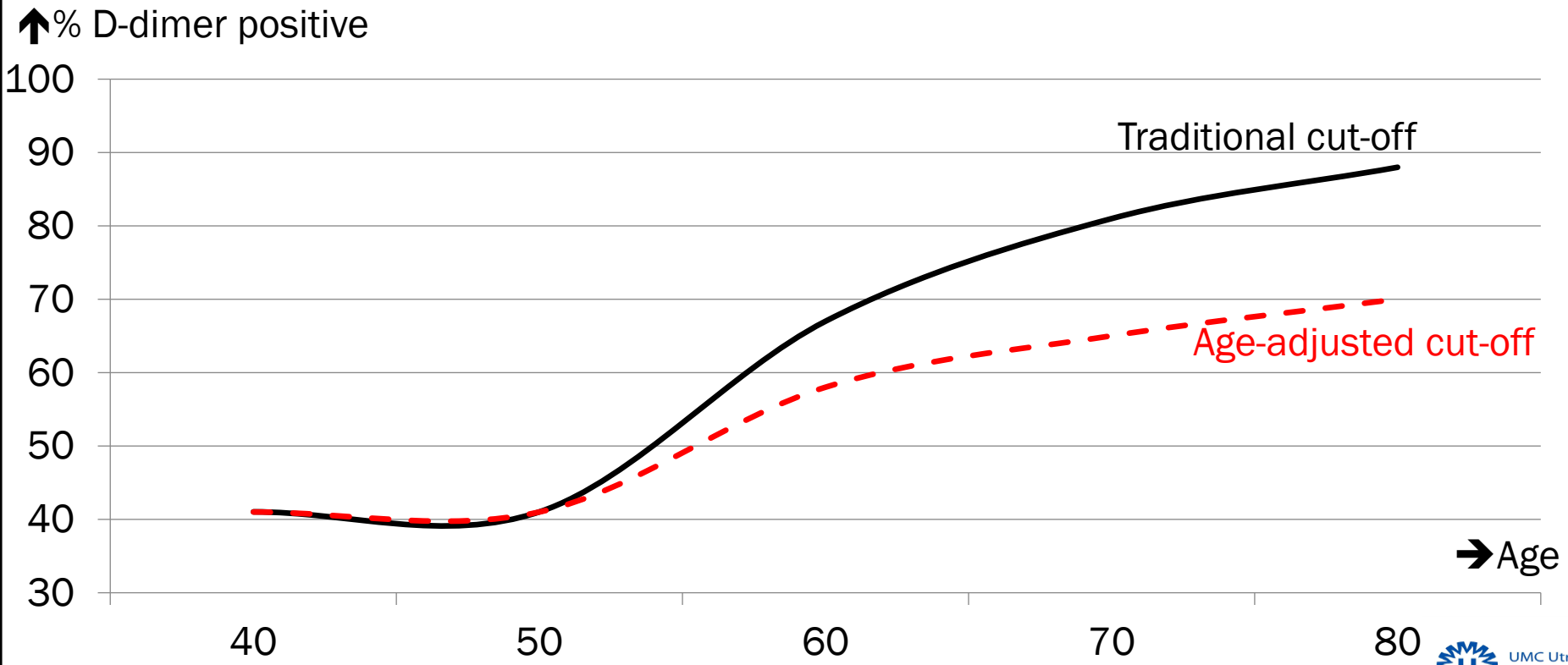
Pre-test probability assessment and D-dimer

- PERC rule
- Wells rule
- Revised Geneva score
- YEARS algorithm

- No D-dimer
- D-dimer with fixed threshold
- D-dimer age-adjusted
- D-dimer pre-test probability adjusted

Problem of D-dimer



H. Schouten, et.al. BMJ; 2013:346; f2492 R. Douma, et.al. BMJ; 2010:340; c1475

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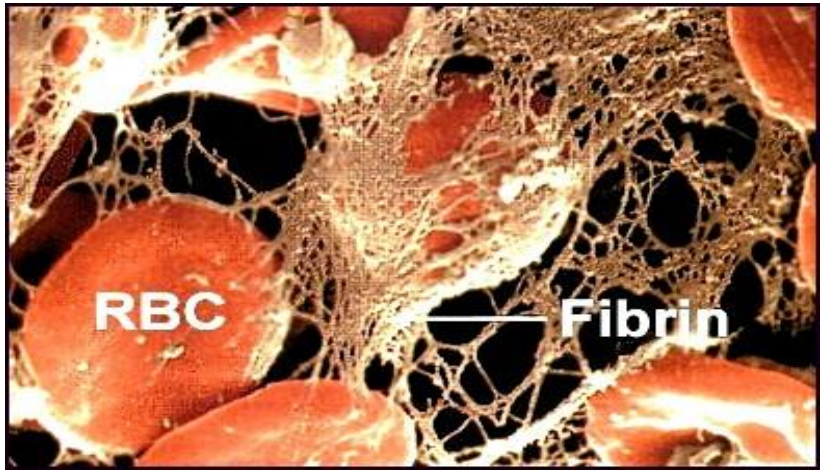
Diagnosis of Pulmonary Embolism with D-Dimer Adjusted to Clinical Probability

Clive Kearon, M.B., Ph.D., Kerstin de Wit, M.B., Sameer Parpia, Ph.D., Sam Schulman, M.D., Ph.D., Marc Afilalo, M.D., Andrew Hirsch, M.D., Frederick A. Spencer, M.D., Sangita Sharma, M.D., Frédérick D'Aragon, M.D., Jean-François Deshaies, M.D., Gregoire Le Gal, M.D., Ph.D., Alejandro Lazo-Langner, M.D., Cynthia Wu, M.D., Lisa Rudd-Scott, R.N., Shannon M. Bates, M.D., and Jim A. Julian, M.Math., for the PEGeD Study Investigators*

Age-adjusted or clinical pre-test probability adjusted D-dimer



Fewer false-positives D-dimer

Still: ≈70% positive if age > 80 years

Not incorporated: gender, comorbidity, cancer, previous VTE, etc.

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Solution: IPD meta-analysis

Geersing *et al. Diagnostic and Prognostic Research* (2018) 2:10
https://doi.org/10.1186/s41512-018-0032-7

Diagnostic and
Prognostic Research

PROTOCOL Open Access

Ruling out pulmonary embolism across different subgroups of patients and healthcare settings: protocol for a systematic review and individual patient data meta-analysis (IPDMA)

G.-J. Geersing[1*†], N. Kraaijpoel[2†], H. R. Büller[2], S. van Doorn[1], N. van Es[2], G. Le Gal[3], M. V. Huisman[4], C. Kearon[5], J. A. Kline[6], K. G. M. Moons[1], M. Miniati[7], M. Righini[8], P.-M. Roy[9], S. J. van der Wall[4], P. S. Wells[3] and F. A. Klok[4]

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Research question for this presentation

*What is the **most optimal diagnostic strategy** in terms of pre-test probability assessment and D-dimer interpretation of patients with suspected pulmonary embolism **across different healthcare settings** where such patients are encountered?*

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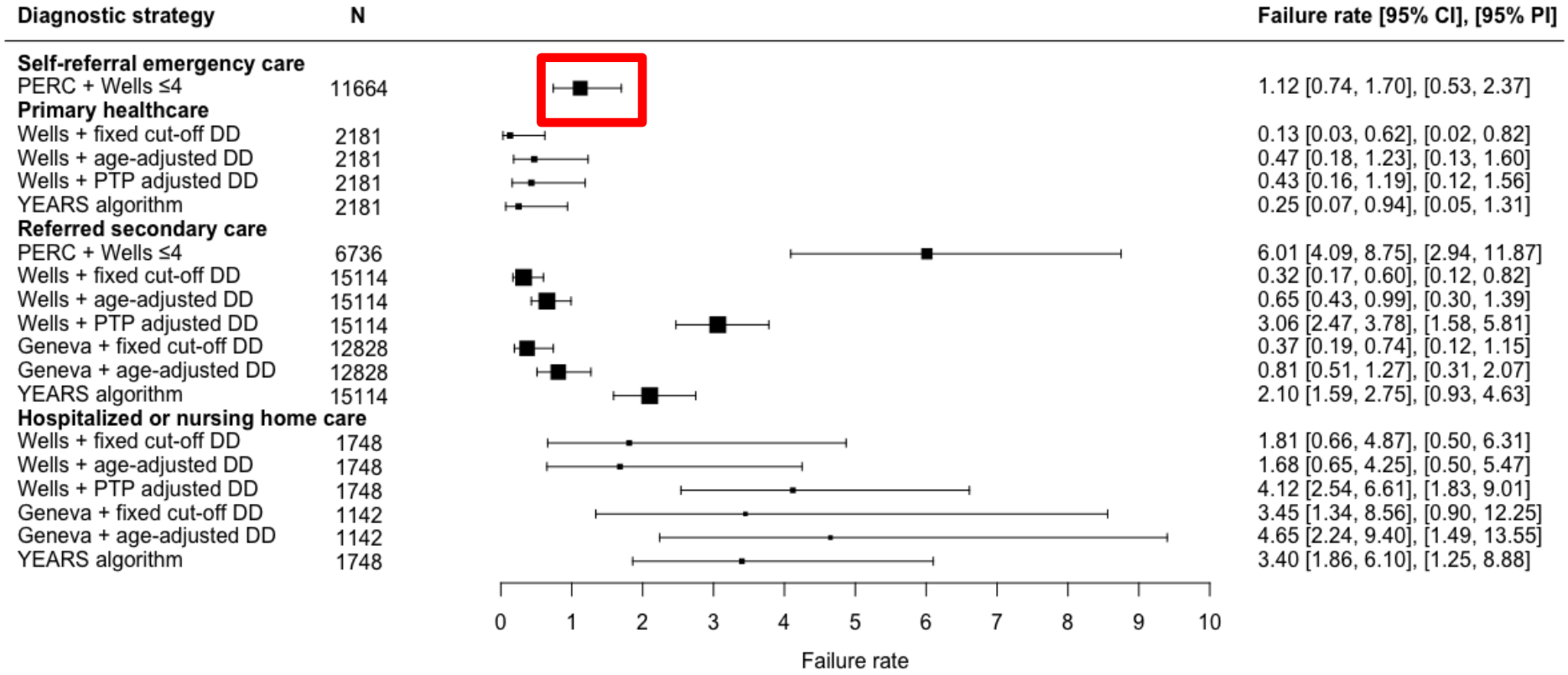
Methods

- **Systematic literature review** followed by RoB assessment
- **23 studies, > 35,000 patients suspected of PE**

- **Multilevel logistic regression** to provide:
- Estimates on the (marginal) probability of having PE in those in whom the strategy considers PE excluded = failure rate (or safety)
- Estimates on the proportion of patients in whom PE can be excluded without imaging (efficiency)



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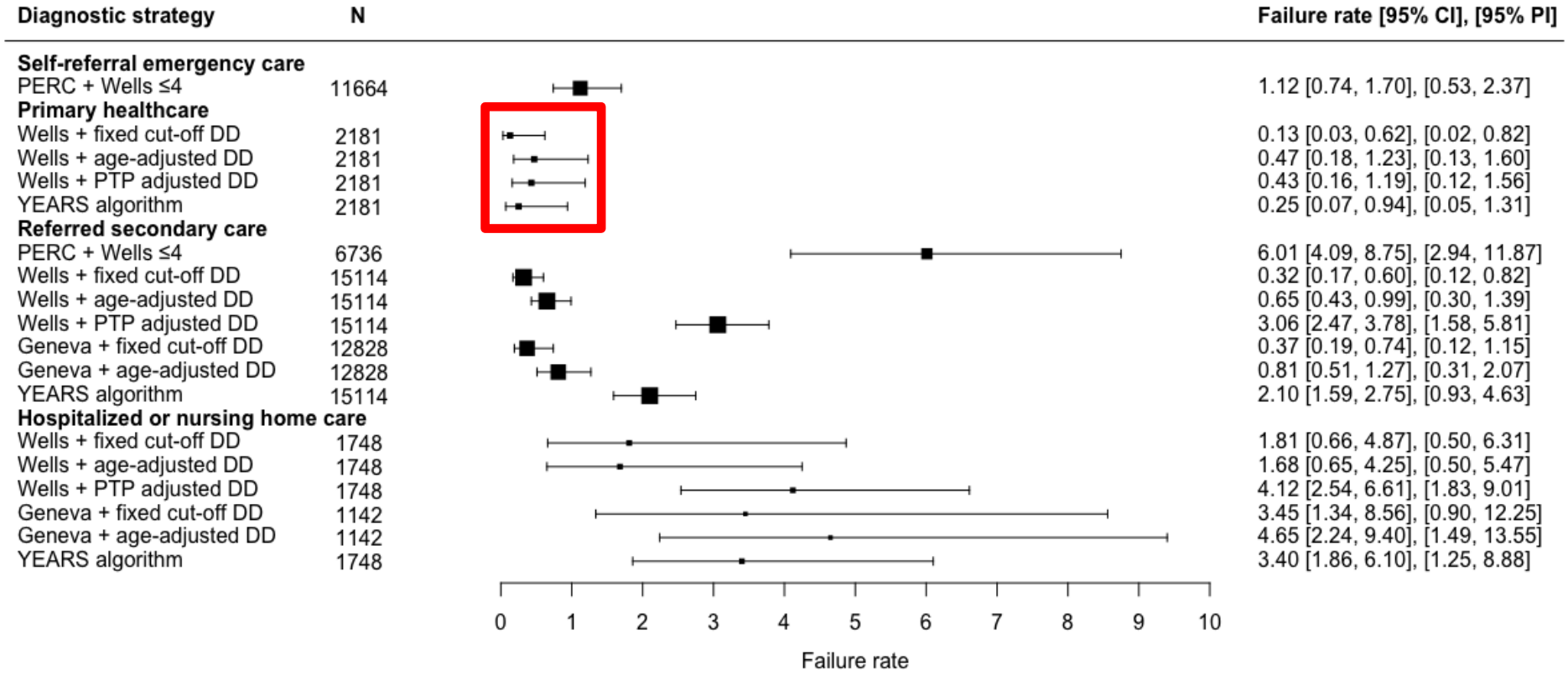

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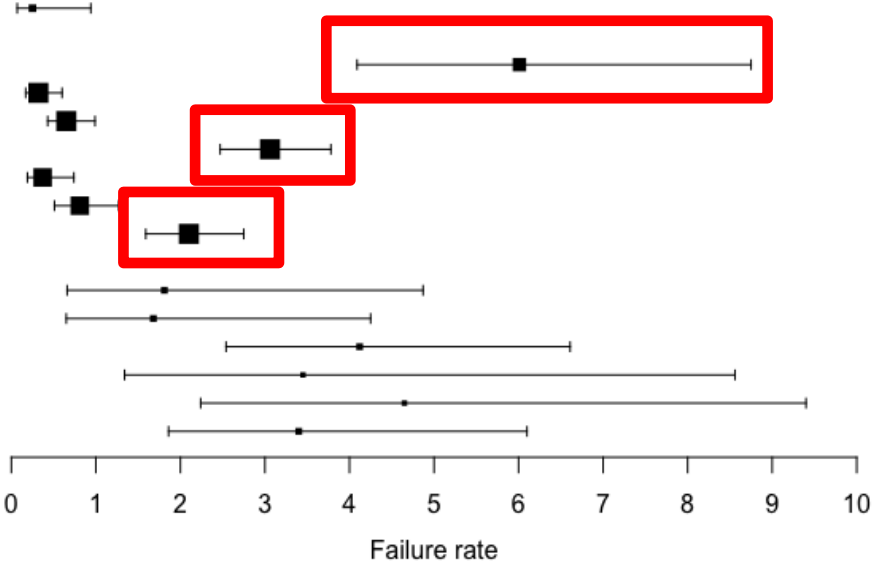
Diagnostic strategy	N	Failure rate [95% CI], [95% PI]
Self-referral emergency care		
PERC + Wells ≤4	11664	1.12 [0.74, 1.70], [0.53, 2.37]
Primary healthcare		
Wells + fixed cut-off DD	2181	0.13 [0.03, 0.62], [0.02, 0.82]
Wells + age-adjusted DD	2181	0.47 [0.18, 1.23], [0.13, 1.60]
Wells + PTP adjusted DD	2181	0.43 [0.16, 1.19], [0.12, 1.56]
YEARS algorithm	2181	0.25 [0.07, 0.94], [0.05, 1.31]
Referred secondary care		
PERC + Wells ≤4	6736	6.01 [4.09, 8.75], [2.94, 11.87]
Wells + fixed cut-off DD	15114	0.32 [0.17, 0.60], [0.12, 0.82]
Wells + age-adjusted DD	15114	0.65 [0.43, 0.99], [0.30, 1.39]
Wells + PTP adjusted DD	15114	3.06 [2.47, 3.78], [1.58, 5.81]
Geneva + fixed cut-off DD	12828	0.37 [0.19, 0.74], [0.12, 1.15]
Geneva + age-adjusted DD	12828	0.81 [0.51, 1.27], [0.31, 2.07]
YEARS algorithm	15114	2.10 [1.59, 2.75], [0.93, 4.63]
Hospitalized or nursing home care		
Wells + fixed cut-off DD	1748	1.81 [0.66, 4.87], [0.50, 6.31]
Wells + age-adjusted DD	1748	1.68 [0.65, 4.25], [0.50, 5.47]
Wells + PTP adjusted DD	1748	4.12 [2.54, 6.61], [1.83, 9.01]
Geneva + fixed cut-off DD	1142	3.45 [1.34, 8.56], [0.90, 12.25]
Geneva + age-adjusted DD	1142	4.65 [2.24, 9.40], [1.49, 13.55]
YEARS algorithm	1748	3.40 [1.86, 6.10], [1.25, 8.88]



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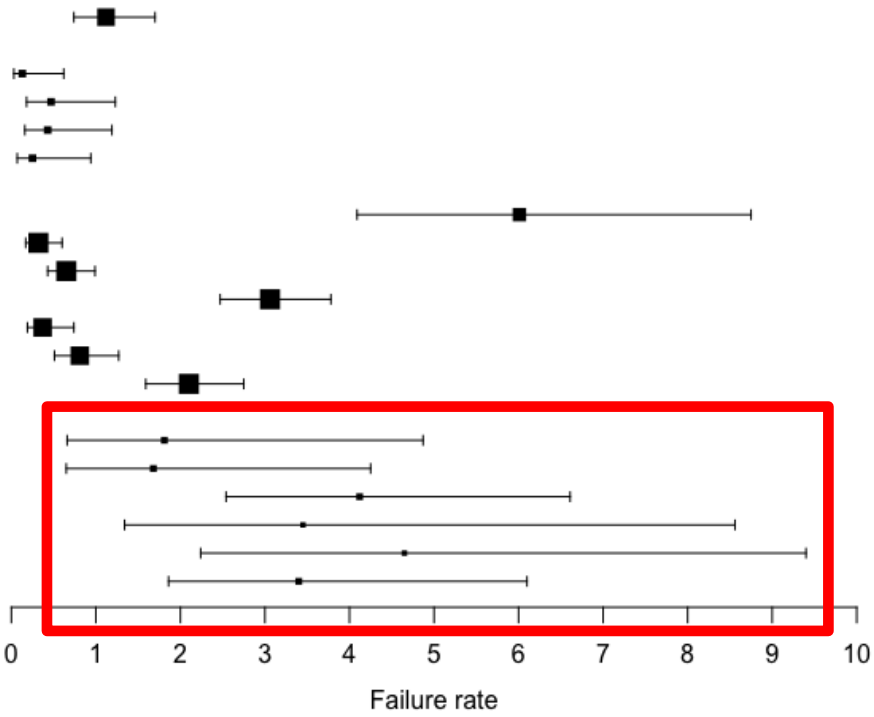

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Diagnostic strategy	N	Efficiency [95% CI], [95% PI]
Self-referral emergency care		
PERC + Wells ≤4	11664	21.09 [15.35, 28.20], [8.44, 43.31]
Primary healthcare		
Wells + fixed cut-off DD	2181	37.53 [24.83, 52.13], [15.85, 65.46]
Wells + age-adjusted DD	2181	43.52 [29.14, 59.03], [19.96, 70.31]
Wells + PTP adjusted DD	2181	61.75 [48.33, 73.62], [37.95, 81.07]
YEARS algorithm	2181	54.76 [42.63, 66.37], [33.75, 74.24]
Referred secondary care		
PERC + Wells ≤4	6736	9.85 [6.88, 13.89], [3.60, 24.02]
Wells + fixed cut-off DD	15114	27.77 [23.05, 33.03], [12.46, 50.62]
Wells + age-adjusted DD	15114	32.91 [27.85, 38.39], [16.25, 55.16]
Wells + PTP adjusted DD	15114	48.78 [43.64, 53.94], [30.12, 67.77]
Geneva + fixed cut-off DD	12828	28.77 [26.20, 31.48], [20.37, 38.92]
Geneva + age-adjusted DD	12828	35.25 [32.76, 37.82], [27.20, 44.23]
YEARS algorithm	15114	43.38 [38.86, 48.01], [27.43, 60.80]
Hospitalized or nursing home care		
Wells + fixed cut-off DD	1748	14.88 [11.66, 18.79], [5.95, 32.21]
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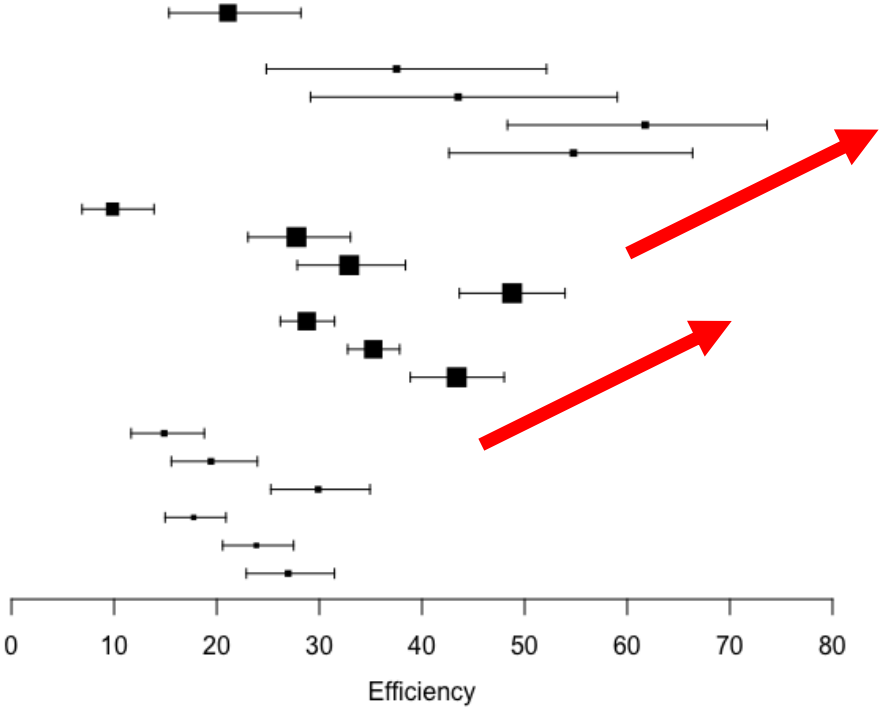

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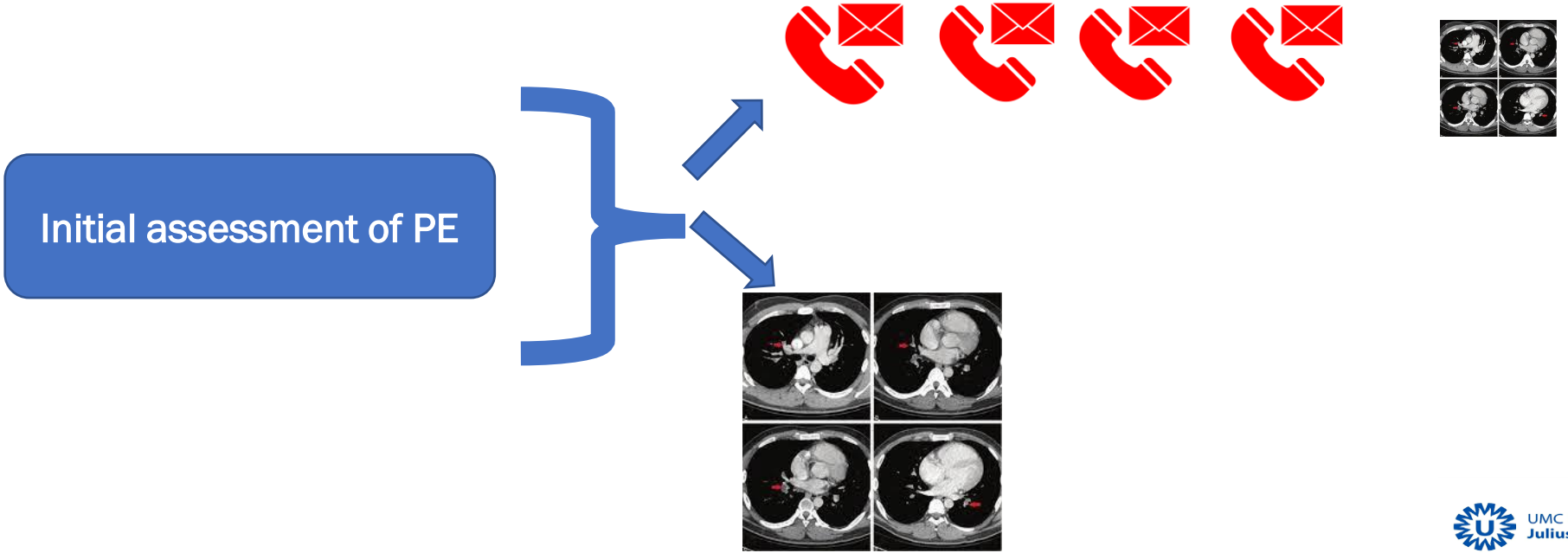
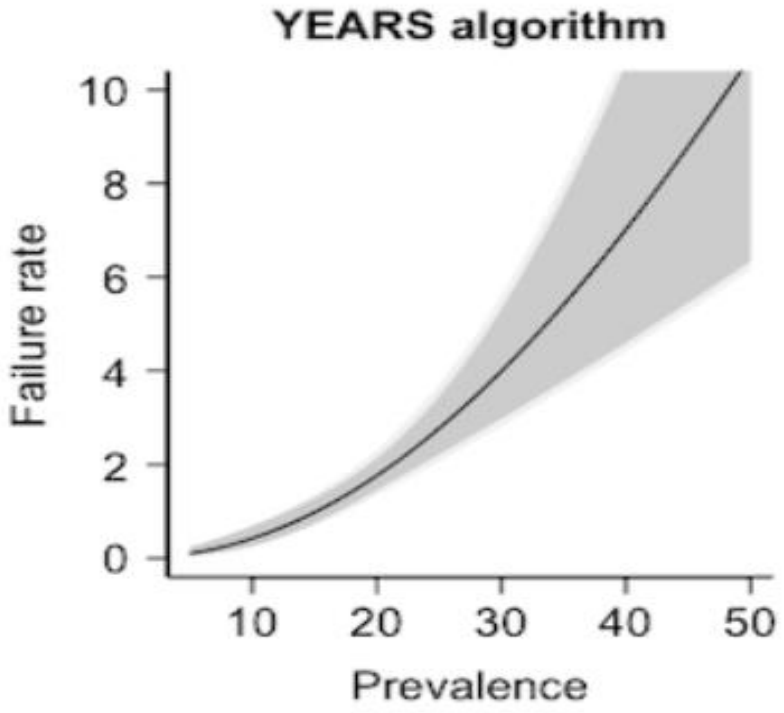
Strengths and Limitations; lessons learned

Bayes theorem: post-test probability = pre-test probability x test-result (+/-)

So, obviously, with a higher prevalence (pre-test probability), failure rate increases as well



Example: prevalence and failure rate YEARS



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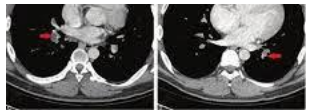
Strengths and Limitations; lessons learned

Strategies
more ong
follow-up

Failure rate in PE diagnostics is a function of
- Prevalence (Bayes theorem)
- Efficiency

And this function is distorted by detection of ssPE as well …

Only answer/solution: diagnostic randomized clinical trial



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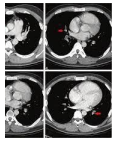

more
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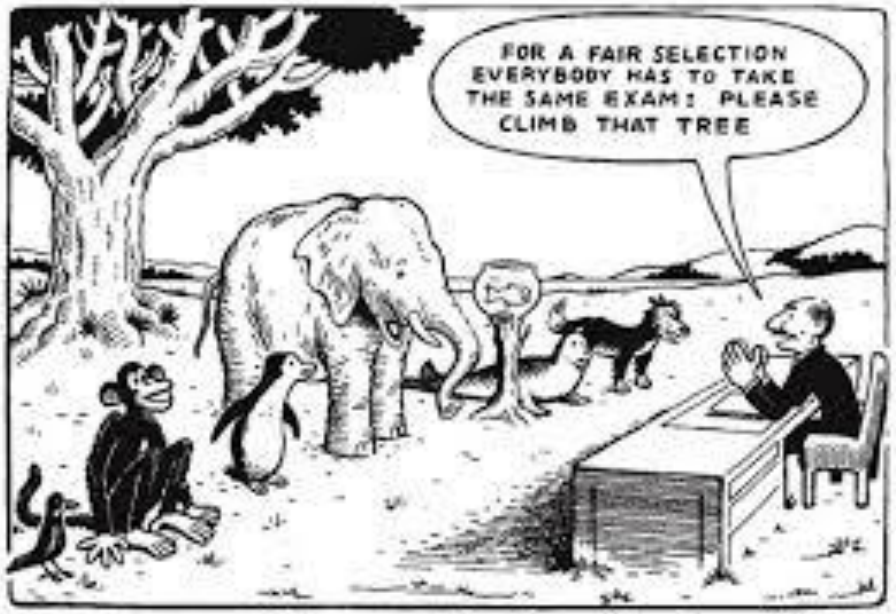
Conclusions

- In patients with a **low clinical impression of having PE**, as seen in **ER care**, the PERC is a safe and efficient instrument to exclude PE without D-dimer testing and imaging
- In **ambulatory outpatients** (community healthcare), strategies with D-dimer adjusting to CPTP are most attractive in terms of safety and efficiency
- In patients **referred to a hospital clinic** with a clear suspicion of having PE:
  - PERC appears to be no longer safe;
  - Strategies with an adjusted D-dimer threshold are most efficient;
  - An age-adjusted D-dimer approach is associated with a lower failure rate compared to a CPTP-adjusted D-dimer strategy, but the latter is also most efficient
- In **nursing homes or hospitalized patients**, diagnostic strategies with CPTP plus D-dimer are far less efficient while at the same time the failure rate ranges between 3-5%

'one size does not fit all' (also not in suspected PE)



Thanks for your attention

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Thanks to all my fellow IPD-MA investigators!

Toshihiko Takada, Frederikus A Klok, Harry R Büller, D Mark Courtney, Yonathan Freund, Javier Galipienzo, Gregoire Le Gal, Waleed Ghanima, Jeffery A Kline, Menno V Huisman, Karel G M Moons, Arnaud Perrier, Sameer Parpia, Helia Robert-Ebadi, Marc Righini, Pierre-Marie Roy, Maarten van Smeden, Milou A M Stals, Phil S Wells, Kerstin de Wit, Noémie Kraaijpoel, Nick van Es