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Overdiagnosis or real clinical benefit

How to evaluate new diagnostics that challenge existing disease definitions

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In this talk I would like to…

- Give a methodological overview of how continuously improving diagnostic technologies (tests, biomarkers, imaging modalities) may lead to overdiagnosis and overtreatment.
- Discuss why classic diagnostic accuracy measures can not be used to evaluate whether a new test that challenges the existing reference standard leads to clinical benefit or overdiagnosis and overtreatment.
- Stress the urgency of using different approaches of diagnostic test evaluation to get more insight in whether new diagnostic tests that challenge the existing disease definition have real clinical value and whether or not existing disease definitions should be modified.

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Rapid development of new ever-improving diagnostic technologies leads to increased need for physicians to carefully assess the meaning of diagnostic test results.

"The next generation of radiologists will face increasing volumes of data: there will always be more views, more slices, and more pixels to look at." – Dr. Gilbert Welch

"Their task will increasingly become sorting the wheat from the chaff, minimizing the cascades of diagnostic testing and the side effects of excessive intervention." – Dr. Gilbert Welch

"Using the subsegmental Pulmonary Embolisms example, we need to stand up and say that we are overtreating subsegmental PE, because we are overdiagnosing it." - Dr. Saurabh Jha

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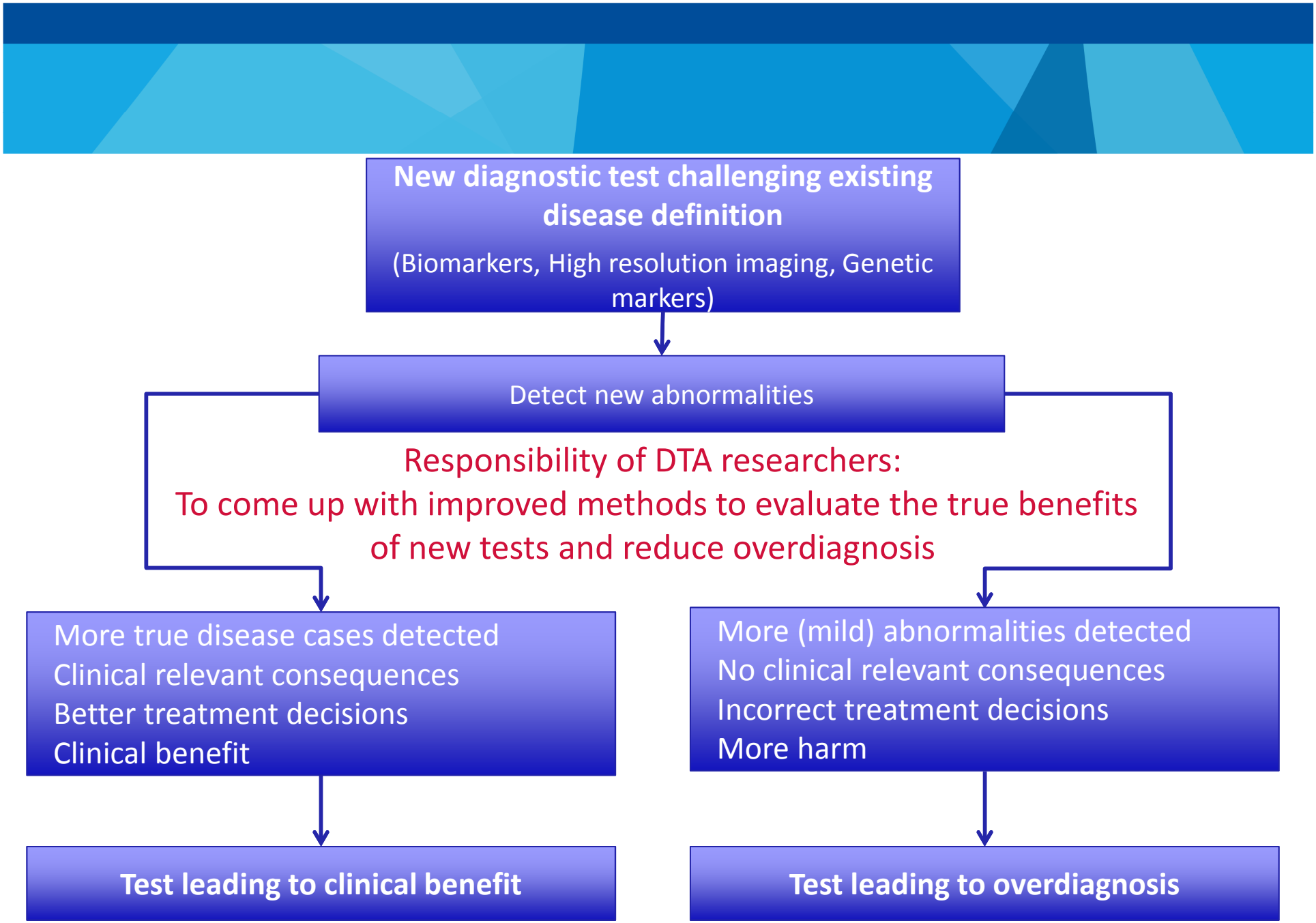
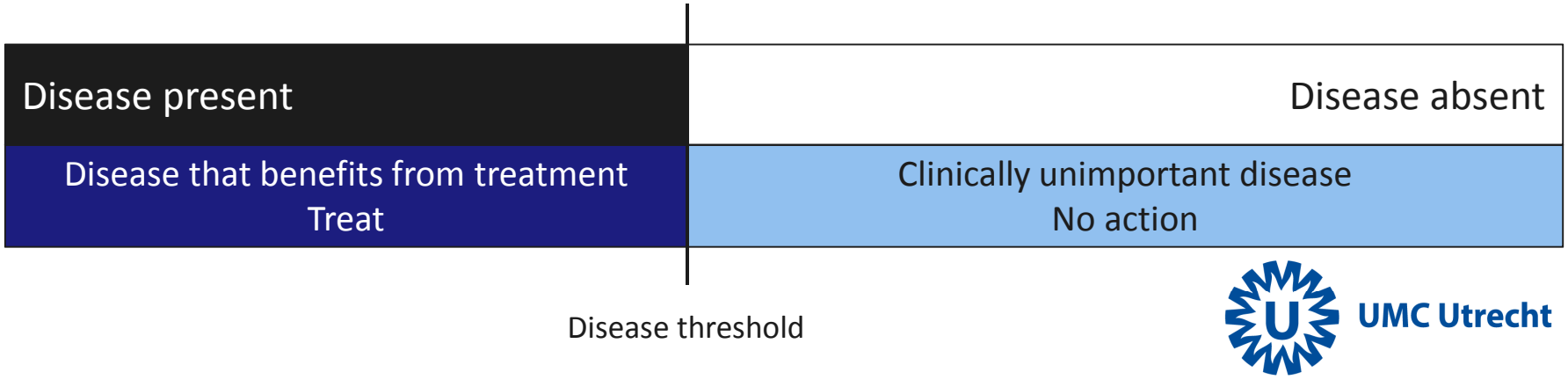

New diagnostic test challenging existing disease definition
(Biomarkers, High resolution imaging, Genetic markers)
Detect new abnormalities
Responsibility of DTA researchers:
To come up with improved methods to evaluate the true benefits of new tests and reduce overdiagnosis
More true disease cases detected
Clinical relevant consequences
Better treatment decisions
Clinical benefit
More (mild) abnormalities detected
No clinical relevant consequences
Incorrect treatment decisions
More harm
Test leading to clinical benefit
Test leading to overdiagnosis

Classic diagnostic accuracy studies

There is one (gold) reference standard test that discriminates between disease present or absent.

The results of a new diagnostic test or technology are verified by this reference standard and accuracy measures (such as sensitivity, specificity and predictive values) are calculated.

The (underlying) assumption is that patients that have the disease benefit from treatment and patients without the target disease do not.



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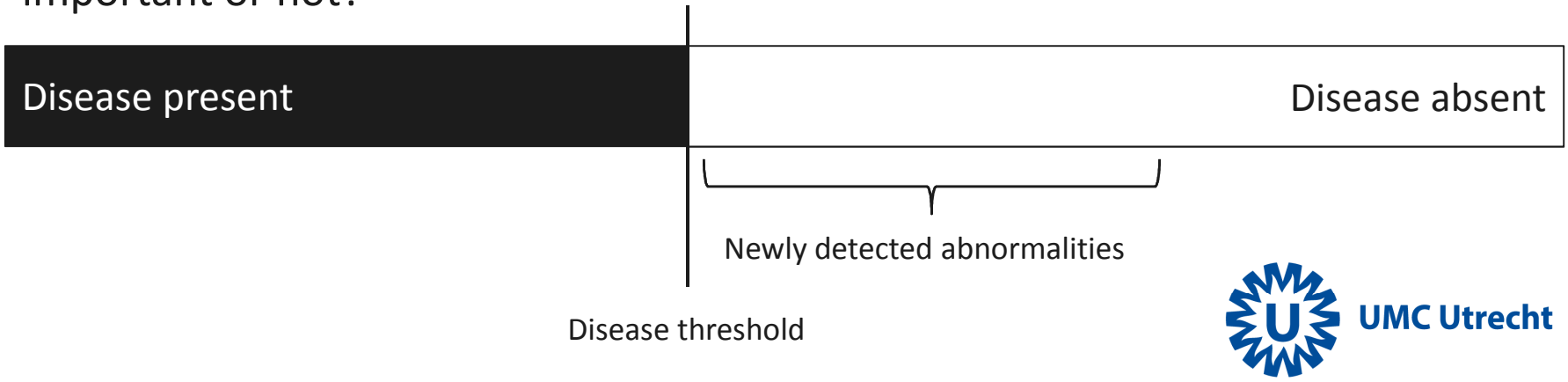
Classic diagnostic accuracy studies

But what if we try to evaluate the performance of a new test or technology that challenges the current reference standard or disease definition?

The improved technology might enable us to reveal more of the underlying disease continuum. It might pick up earlier, milder or different forms of the target disease.

If the results of the new technology and the prevailing reference standard disagree, the key question is: are these newly detected abnormalities clinically important or not?



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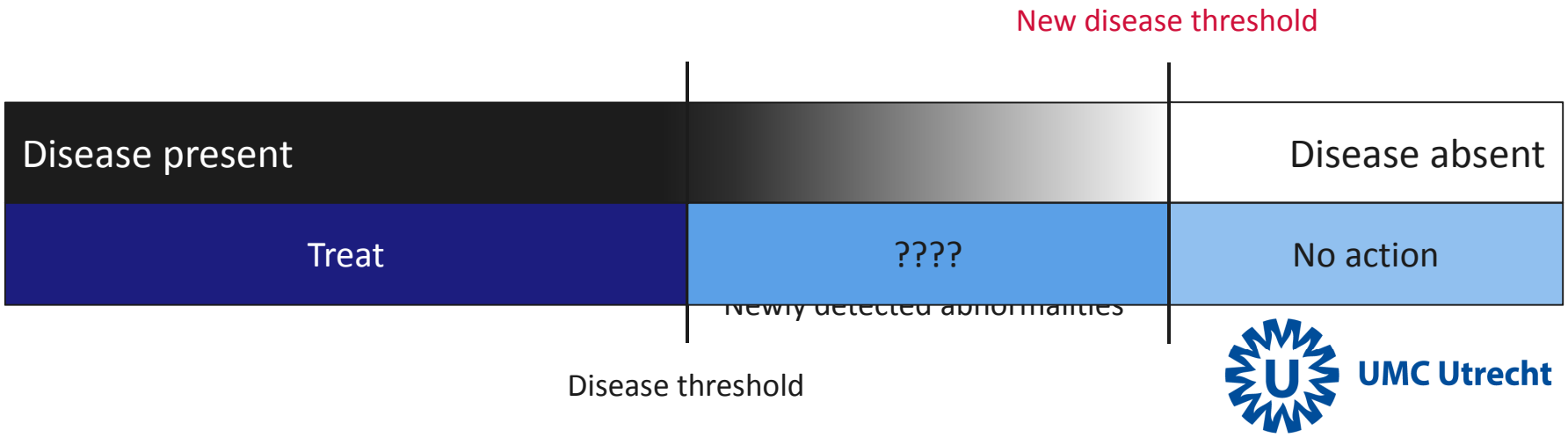
The key questions become:

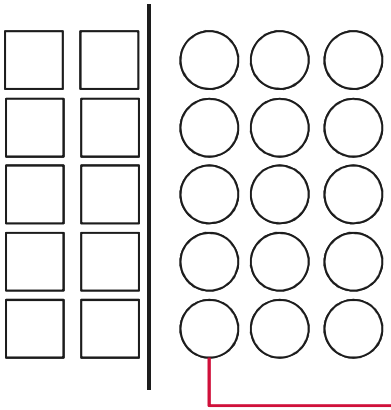
Should we change the disease threshold to include the newly detected abnormalities?

And what does this mean for treatment decisions?

Should we treat patients with the newly found abnormalities similarly as those that are defined as disease present by the prevailing reference standard? Should we monitor them more closely? Or even refrain from action?



Disease threshold



Key questions to answer:

Are these indeed false positive results or do they represent earlier/mild presentations of the target disease, picked up by the new technology?

Should we change the existing disease threshold?

	Current Reference Standard	
	Disease present	Disease absent
New test positive	True Positive	False Positive
New test negative	False Negative	True Negative

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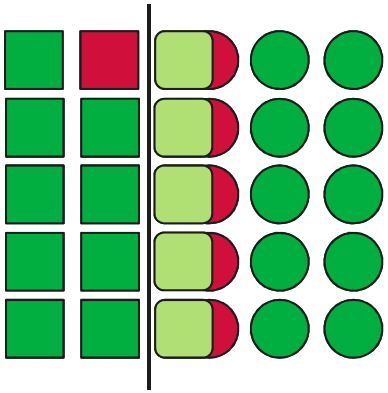
Disease threshold



Should we change the existing disease threshold?

If we change the disease threshold to include the newly found abnormalities…

…the false positive results are regarded as true positive results.

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If we change the disease threshold to include the newly found abnormalities…

…the false positive results are regarded as true positive results.

Only if the newly found abnormalities benefit from identification, changing the disease threshold to include the newly found abnormalities leads to clinical benefit.

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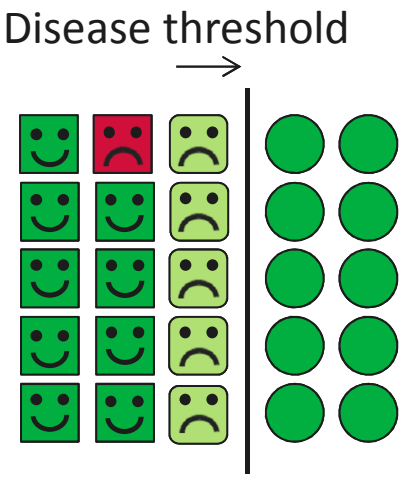

Should we change the existing disease threshold?

If we change the disease threshold to include the newly found abnormalities…

…the false positive results are regarded as true positive results.

Only if the newly found abnormalities also benefit from identification, changing the disease threshold to include the newly found abnormalities leads to clinical benefit.

If not, changing the disease threshold to include the newly found abnormalities possibly leads to overdiagnosis and overtreatment.

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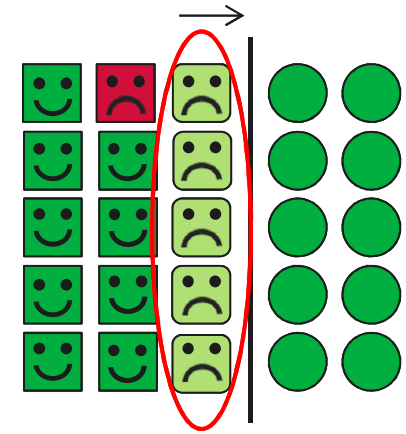

If a new technology challenges the existing reference standard, calculated accuracy measures become uninformative, because the new test can never outperform the reference test.

We should change the focus from classic accuracy analyses to critical assessment of patients in whom the results of the new test and the existing reference standard disagree:

Patients with discordant results

	Current Reference Standard	
	Disease present	Disease absent
New test positive	True Positive	False Positive
New test negative	False Negative	True Negative

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What type of patients?

Closely examine and report patient characteristics

Patients with discordant results

Readily available follow-up information?

Hospital registries Existing trial results

Observational study methods to assess the clinical value of new test

Test-Treatment trial needed?

(e.g. in discordant patients only)

Cross-sectional design not enough. Need for prospective study

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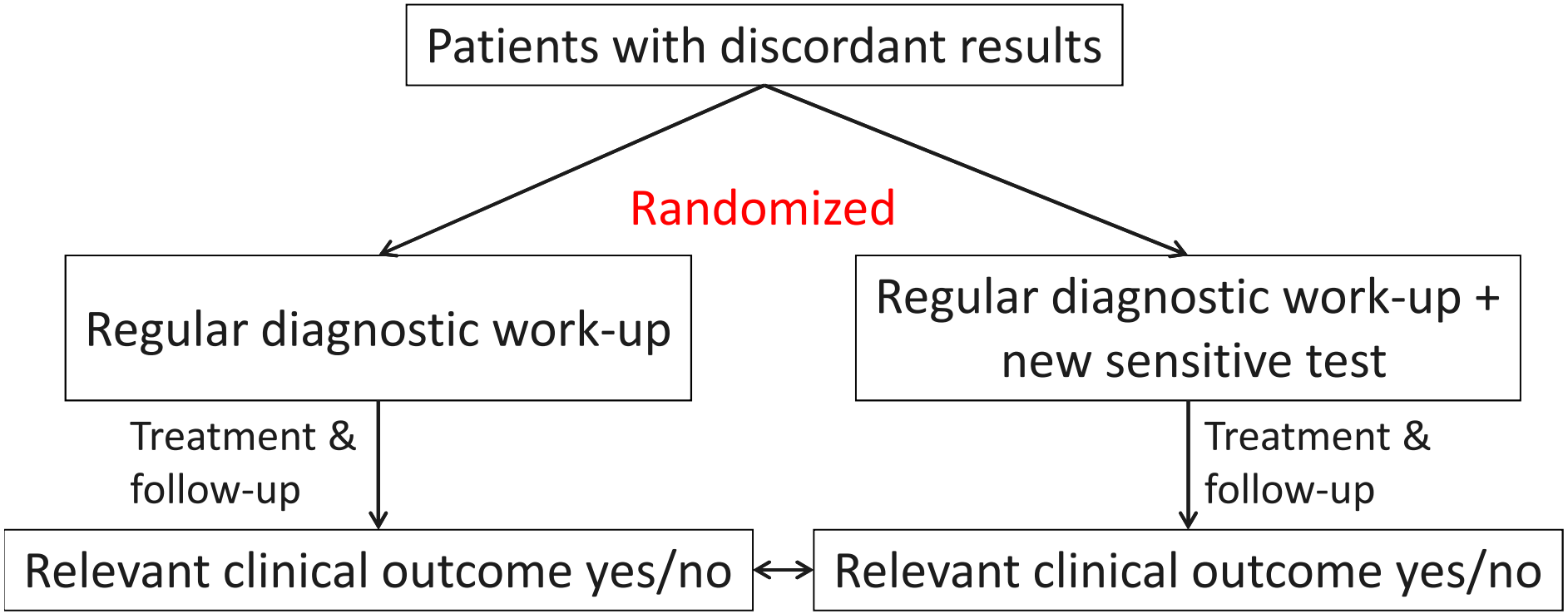
Efficient test treatment trial



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Conclusions

On-going technological and clinical advancements in modern society will only further increase the development of ever improving diagnostic tests that challenge existing disease definitions.

Not only clinical practitioners should be aware of the dangers of overdiagnosis and overtreatment. Researchers evaluating new diagnostic technologies should also acknowledge these topics **explicitly** in their evaluations.

To do this a shift in analysis of such studies is needed, changing the focus from classic accuracy analyses to critical assessment of patients in whom the results of the new sensitive test and the existing reference standard disagree.

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Conclusions

Readily available registry and trial data might provide additional (circumstantial) evidence on the prognosis and treatment effects of these specific patients with discordant test results.

Ultimately, efficient test-treatment trials might be needed to get insight in whether newly found abnormalities benefit from treatment or lead to overdiagnosis/overtreatment.

This additional evidence on the true clinical value of a new diagnostic technology should be used to assess whether changing the existing disease definition based on that new technology is justified or not.

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