Efficient design and analysis of clinical value for paired medical tests at single and serial time points

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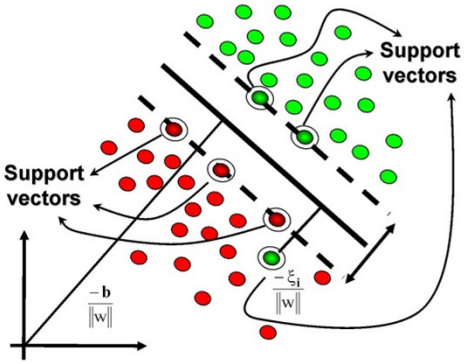
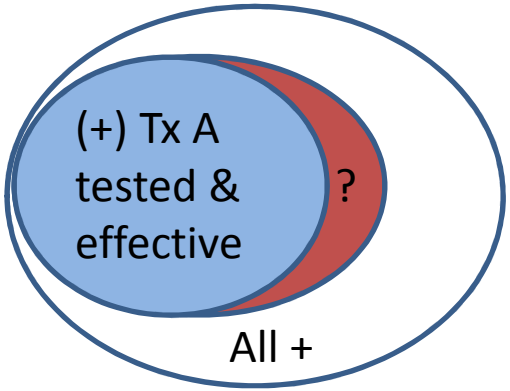
Medical testing for screening and diagnostics

- Biomarkers
- Genetics
- Imaging
- Computational modeling



Why are these not used more in practice?

Why do we need a RCT if a new medical test has higher accuracy?

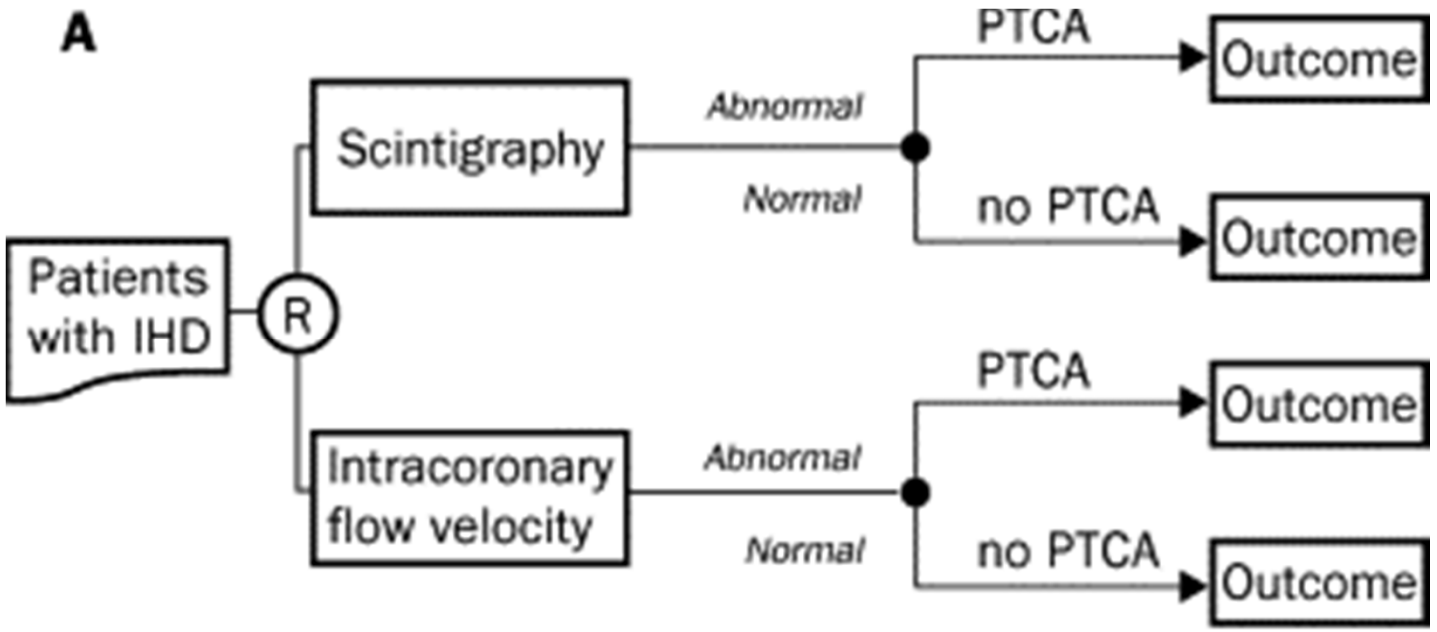


Do we have efficacious treatment for these new correctly diagnosed patients?

Lord, Ann Int Med. Jun 2006

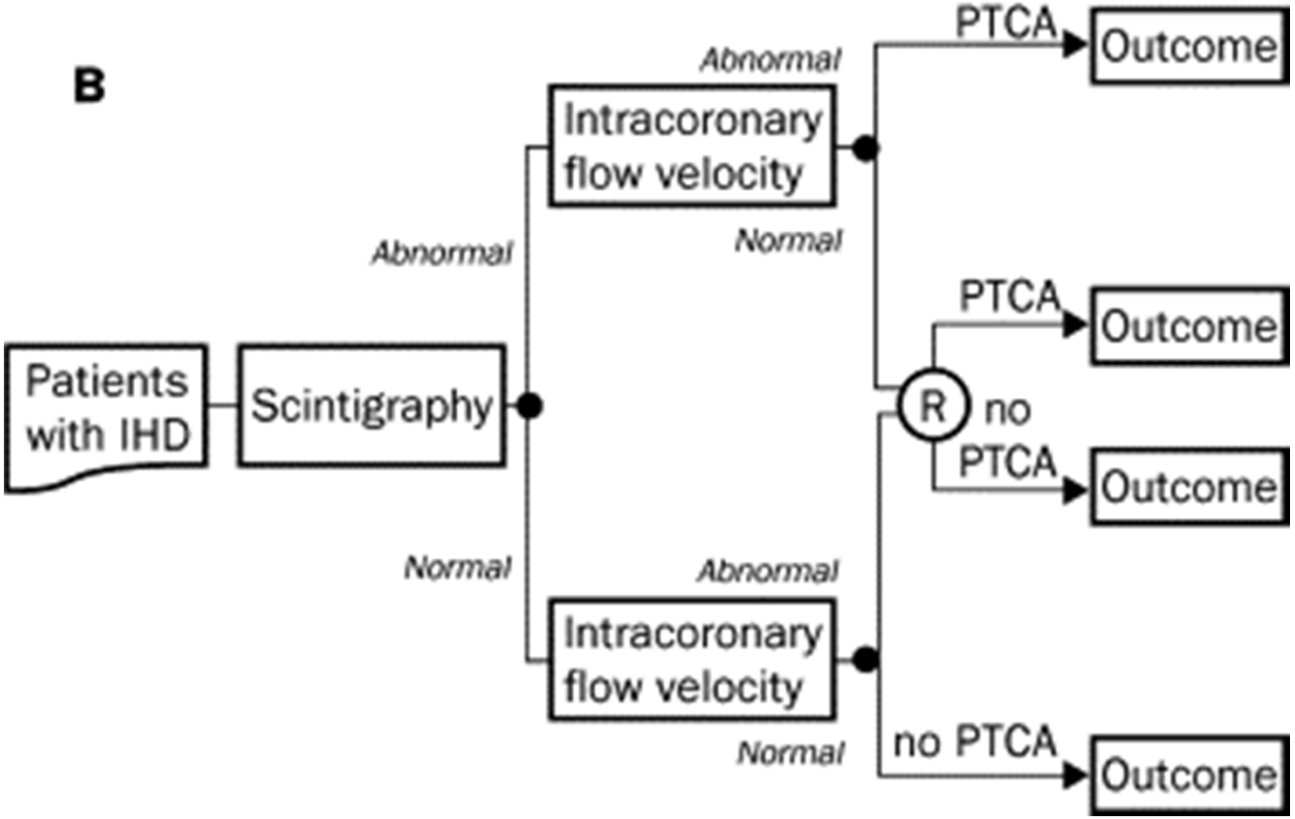
Question: Which medical test has better clinical value?

Randomized Clinical Trials Comparing Two Medical Tests



Bossuyt, Lancet. Nov 2000

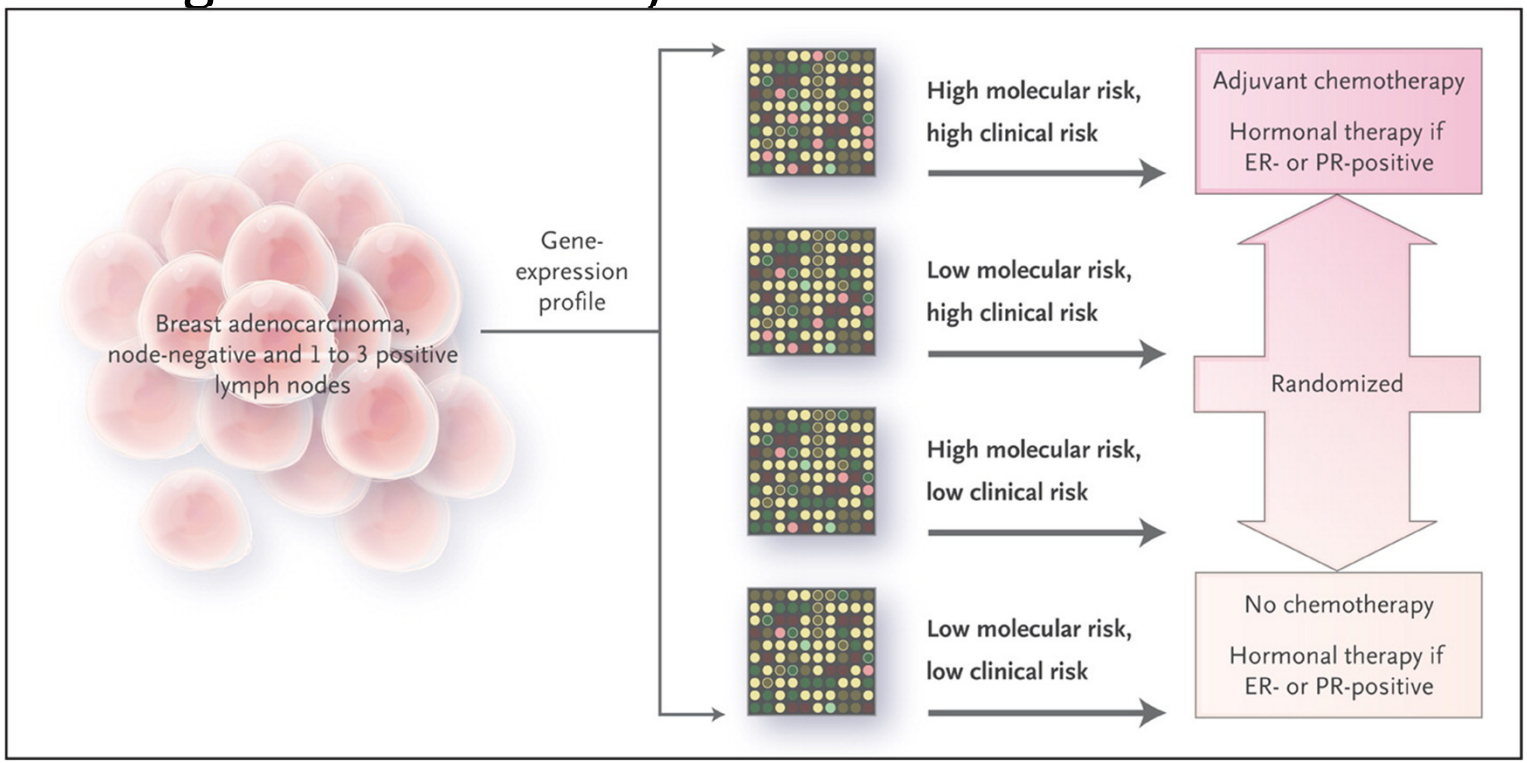
Randomized Clinical Trials Comparing Two Medical Tests



Bossuyt, Lancet. Nov 2000

Examples

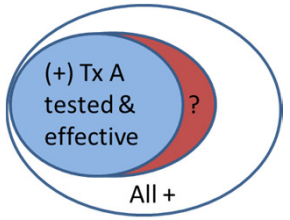
- MINDACT (Microarray in Node Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy Trial)
  - RCT for Mammaprint (70 gene sig for relapse in early stage breast cancer)

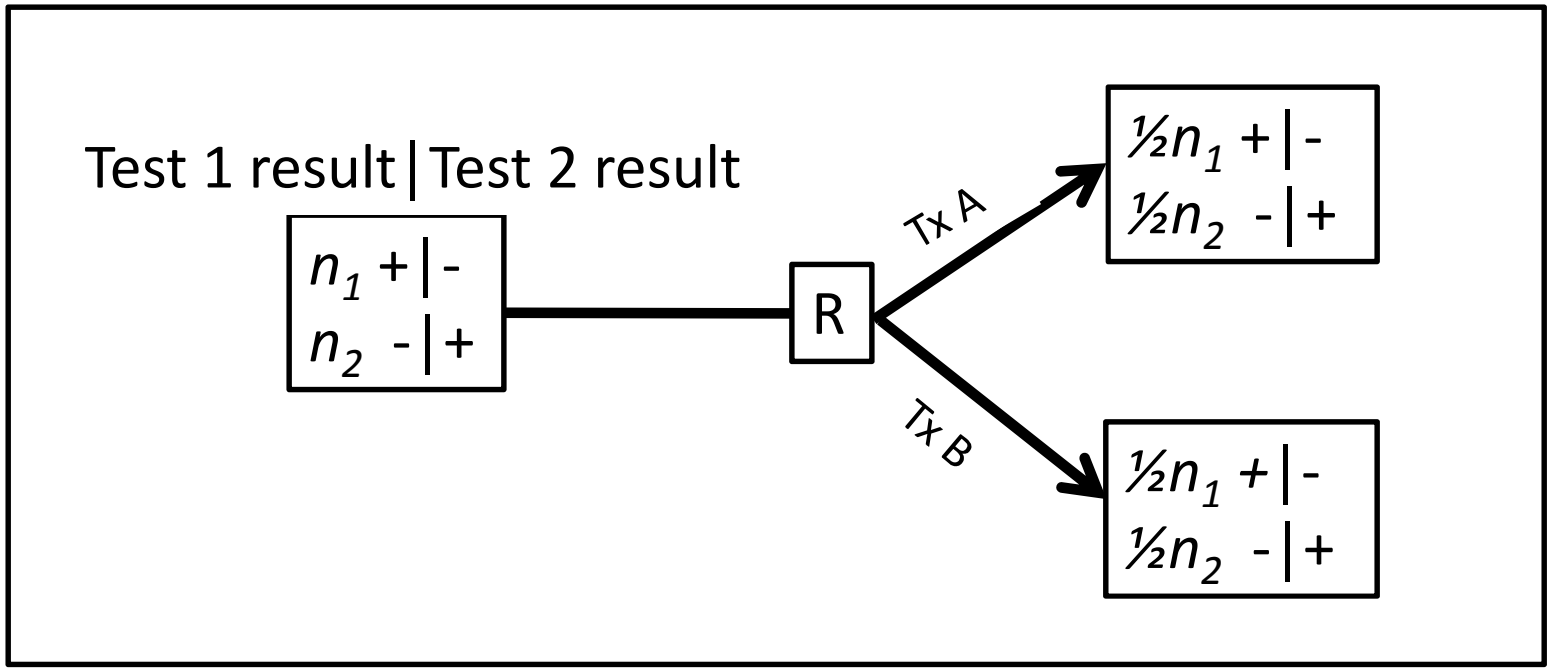


McDermott, NEJM. Jan 2011; clinicalTrials.gov NCT00433589

RCT setup

- Medical test 1, Medical Test 2
- (+) → Tx A, (-) → Tx B
  - Tx A was tested on the currently identifiable (+) patients
- Assumptions: no gold standard, order medical test irrelevant
- Outcome (binary): 5 year survival

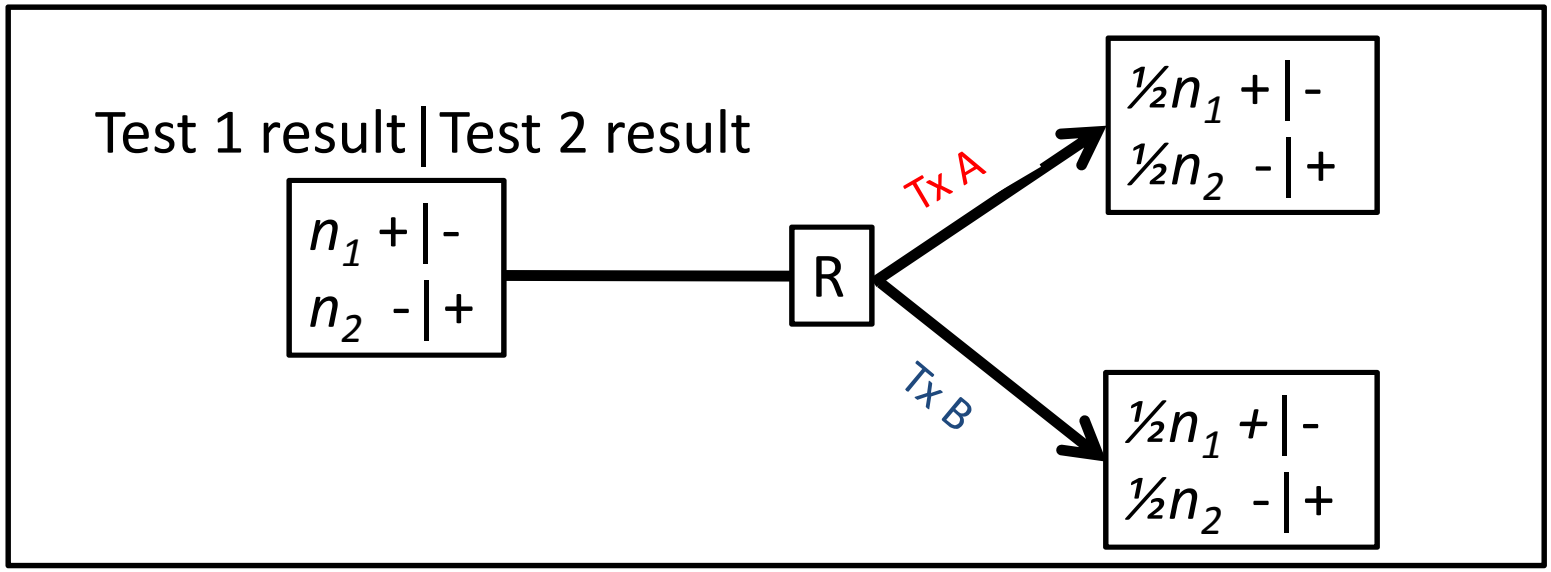




1. Statistical Analysis: Treatment

<u>Tx A versus Tx B</u>

Question: For discordant patients, which treatment is better?

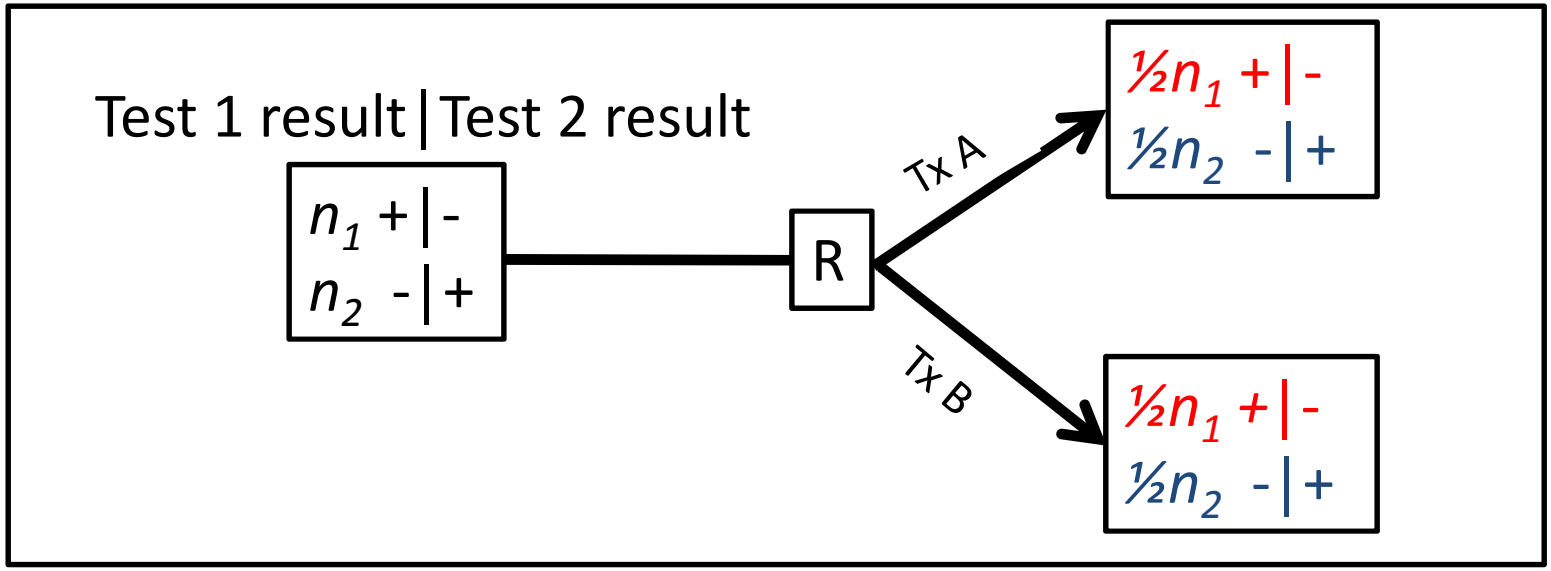


(Ligmer & Bossuyt, Evidence Base of Clinical Diagnosis, 2009)

2. Statistical Analysis: Treatment Effect of Test results

n_1 +|- versus n_2 -|+

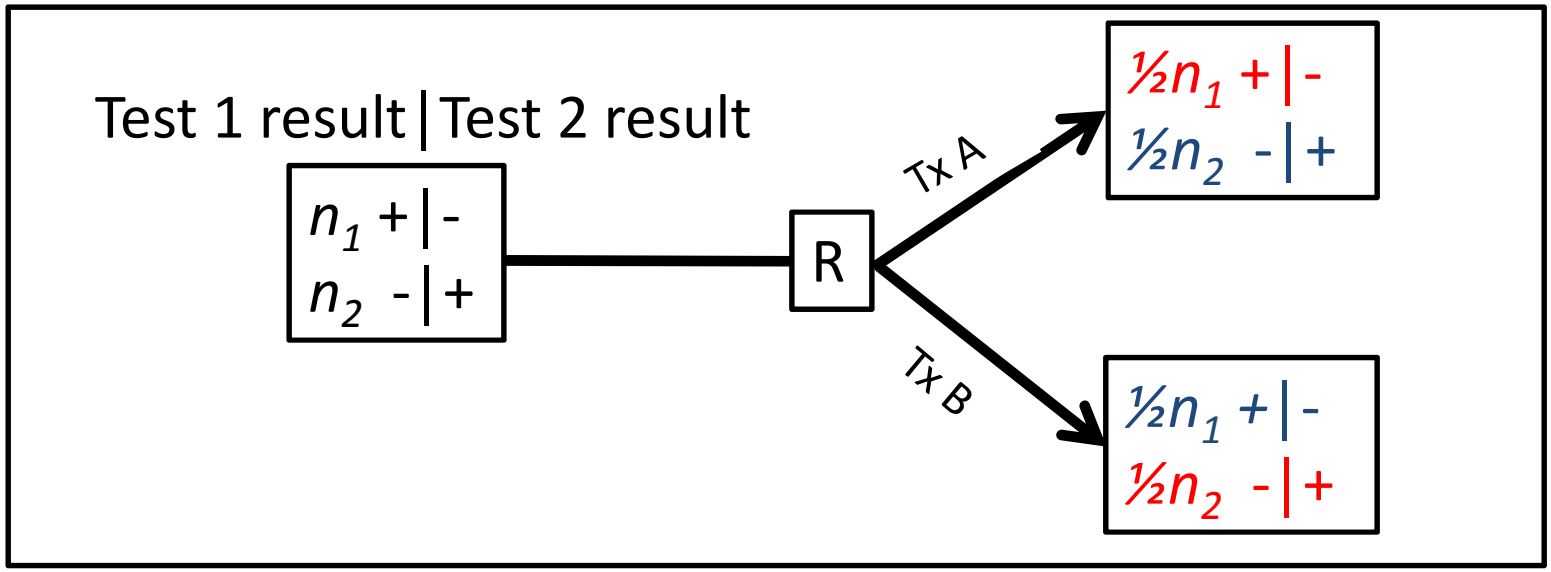
When patients with one discordant result are randomly treated with A or B, does +|- (+ Test 1) have better outcomes than -|+ (+ Test 2)?



(Ligmer & Bossuyt, Evidence Base of Clinical Diagnosis, 2009)

3. Statistical Analysis: Clinical pathway (strategy based on test method)

With appropriate treatment does Test 1 have better outcomes than Test 2?



(Ligmer & Bossuyt, Evidence Base of Clinical Diagnosis, 2009)

3. Statistical Analysis: Clinical pathway (strategy based on test method)

Another view

Strategy based on Medical Test 1

1	2	Tx	Favorable outcome	Poor outcome
+	-	A		
-	+	B		

Strategy based on Medical Test 2

1	2	Tx	Favorable outcome	Poor outcome
-	+	A		
+	-	B		

Absolute risk difference of clinical pathway Test 1 compared to clinical pathway Test 2 **=** Difference in favorable outcome rate, after correcting for frequency of discordant

Note: To calculate the RR or total risk, need outcome rate for concordant group

(Ligmer & Bossuyt, Evidence Base of Clinical Diagnosis, 2009)

3. Clinical Pathway - Example

5% discordant rate

n_1 (+|-) = 22, ½n_1 (+|-) = 11

n_2 (-|+) = 200, ½n_2 (-|+) = 100

Total patient for each clinical pathway = 111

Strategy based on Medical Test 1

1	2	Tx	Favorable outcome	Poor outcome
+	-	A	10	1
-	+	B	50	50

60/111=0.54 favorable outcome

Strategy based on Medical Test 2

1	2	Tx	Favorable outcome	Poor outcome
-	+	A	90	10
+	-	B	10	1

100/111=0.90 favorable outcome

36% absolute difference risk difference in favor of Test 2 for discordant × 5% discordant rate = 1.8% absolute risk different in favor of Test 2

Paired Diagnostic tests with 3 (*k*) treatment options

		Medical Test 2		
		Tx A	**Tx B**	**Tx C**
Medical Test 1	**Tx A**	Same	A/B	A/C
	Tx B	B/A	Same	B/C
	Tx C	C/A	C/B	Same

Strategy based on Medical Test 1

1	2	Tx	Favorable outcome	Poor outcome
A	B	A		
A	C	A		
B	A	B		
B	C	B		
C	A	C		
C	B	C		

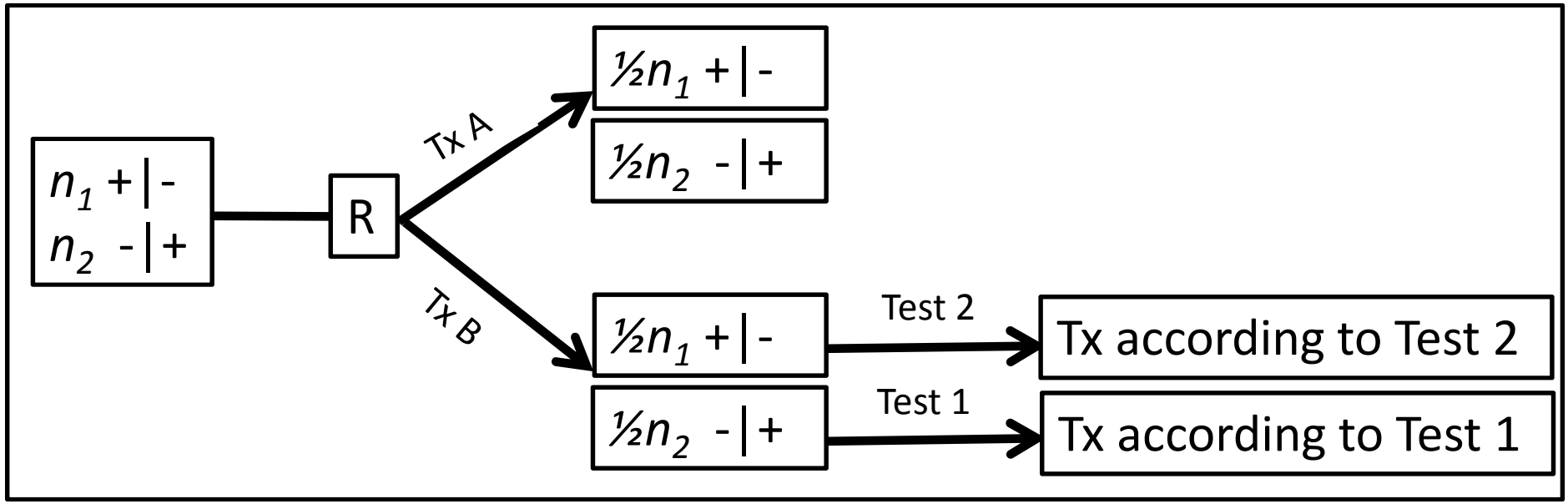
Strategy based on Medical Test 2

1	2	Tx	Favorable outcome	Poor outcome
B	A	A		
C	A	A		
A	B	B		
C	B	B		
A	C	C		
B	C	C		

Same Analysis 2 test, 2 treatment

Serial Medical Testing

- Serial Screening (mammography every 2 year)
- Therametrics – quantification of therapeutic parameters in management of disease (viral load HIV(Reed 1996), serum c-erB-2 breast cancer(Fehm 1997))



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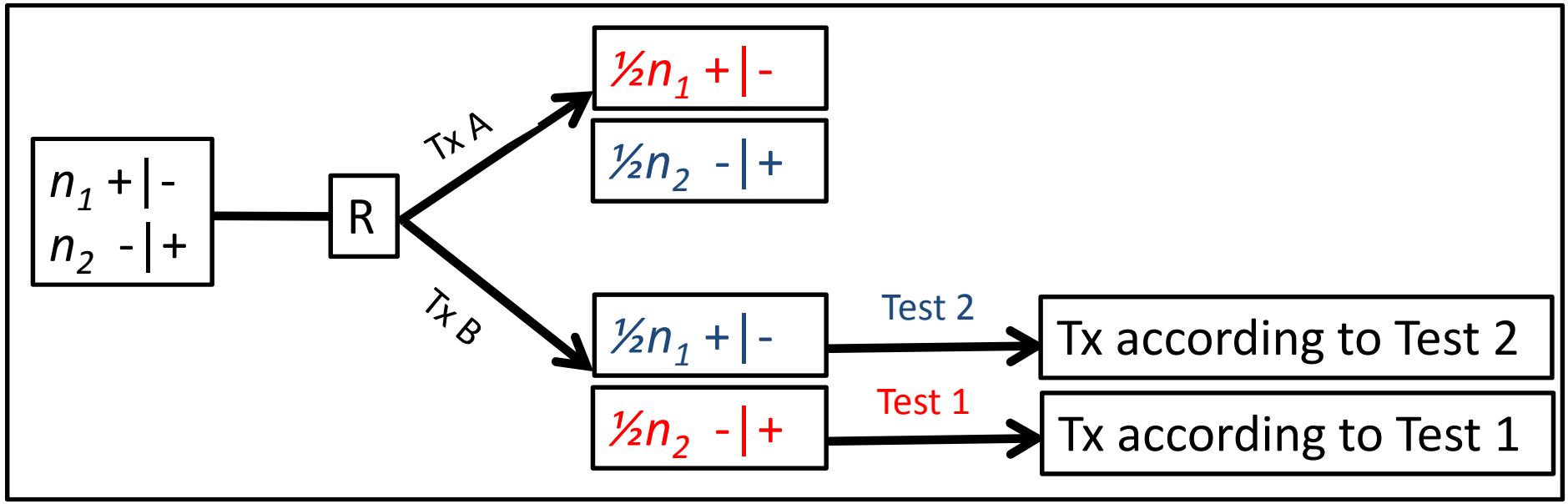
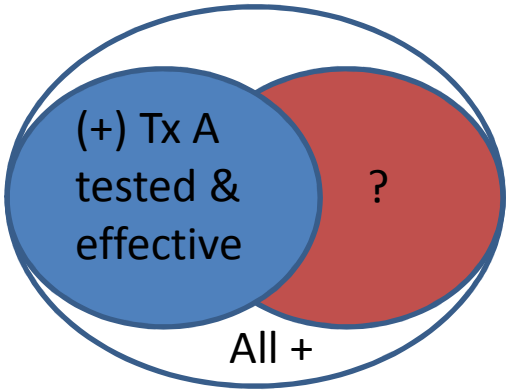


Same Analysis as 2 test, k treatment

Future direction

- This design should be performed even if a new test has the same sensitivity, but is cheaper/easier to conduct, etc.
- Continuous outcome with and without censoring
- Non-inferiority



Thank You

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Support

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