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Efficient use of microsatellite analysis and immunohistochemistry in molecular diagnosis of Hereditary Nonpolyposis Colorectal Cancer

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Background and Questions

Microsatellite instability analysis (MSA) and Immunohistochemistry (IHC) are diagnostic methods to enrich patients who are likely to have a deleterious MMR gene mutation.

- IHC is less expensive than MSA
- IHC indicates the affected gene, MSA does not

Can IHC replace MSA without losing sensitivity?

If not, how can both methods be combined efficiently in a stepwise diagnostic strategy?

- Shall either IHC or MSA be used in the first step?
- What are the costs of stepwise strategies?
- Can clinical information be used to optimise the stepwise strategy?

Patients and Methods

We analysed data of 1119 unrelated index patients from the central registry of the German HNPCC Consortium

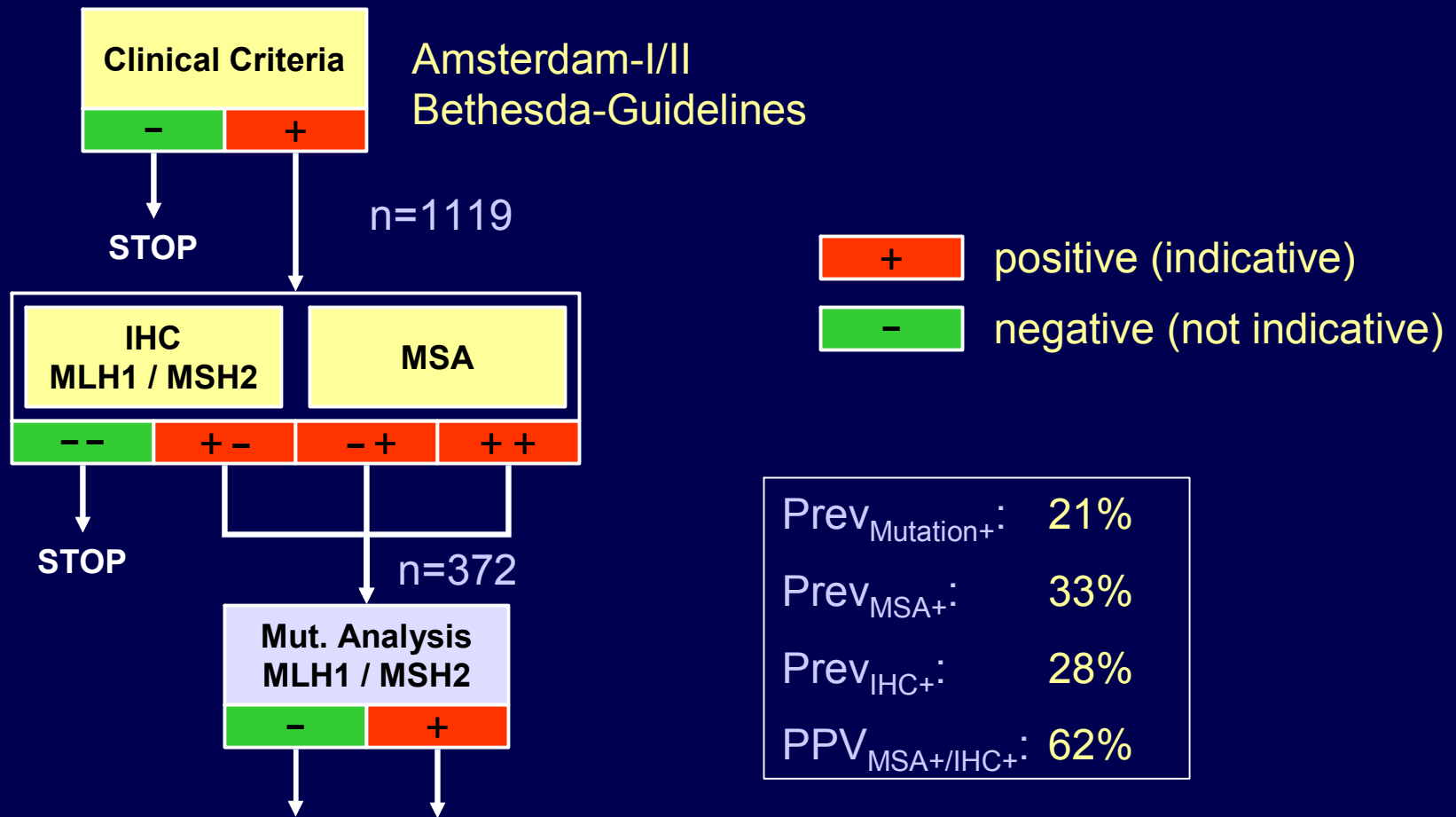
All patients fulfilled Amsterdam I/II criteria or Bethesda Guidelines

Tumour tissue was subjected independently to MSA (5/10 markers) and IHC (MLH1 and MSH2)

MSI-H and/or loss of protein expression were considered indicative for MMR deficiency. In this case, mutation analysis was performed in *MLH1* and *MSH2*

Diagnostic Strategy

using IHC and MSA in parallel



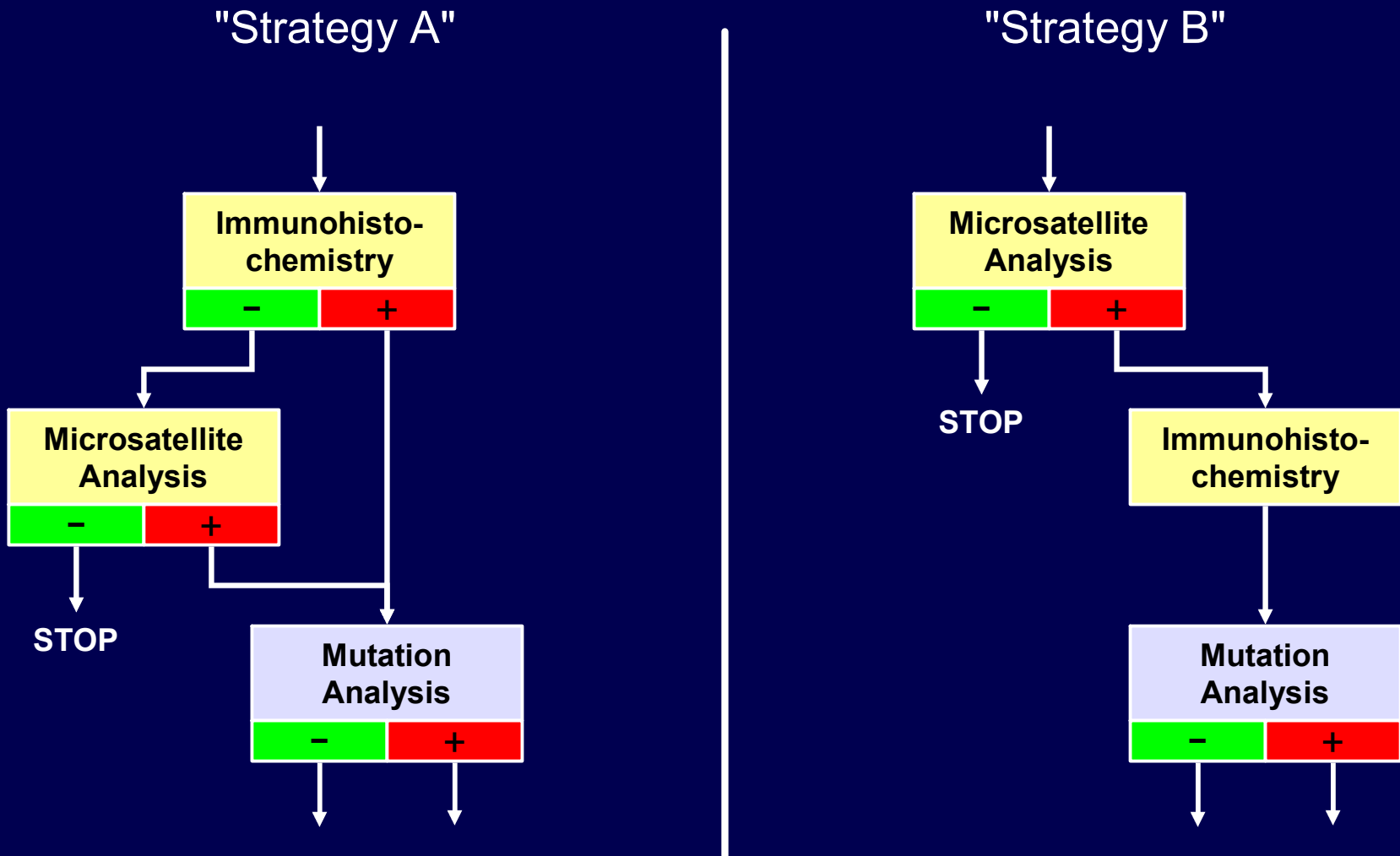
Results of MSA, IHC and mutation analysis

IHC MLH1 / MSH2	MSA	n	%	Mutations MLH1 / MSH2
-	-	747	66.8	(0 of 49)
-	+	58	5.2	14
+	-	3	0.3	0
+	+	311	27.7	216
<i>Sum</i>		1119		230

- MSA provides almost no further information in case of IHC+
- 14 mutations escaped detection by IHC!

Conclusion: IHC cannot replace MSA without losing sensitivity!

How to apply MSA and IHC sequentially?



Which strategy is more cost-effective?

Costs

for the different strategies

"Strategy P" (IHC + MSA)

$$C_P = C_{MSA} + C_{IHC}$$

"Strategy A" (IHC first)

$$C_A = C_{IHC} + (1 - p_{IHC}) \cdot C_{MSA}$$

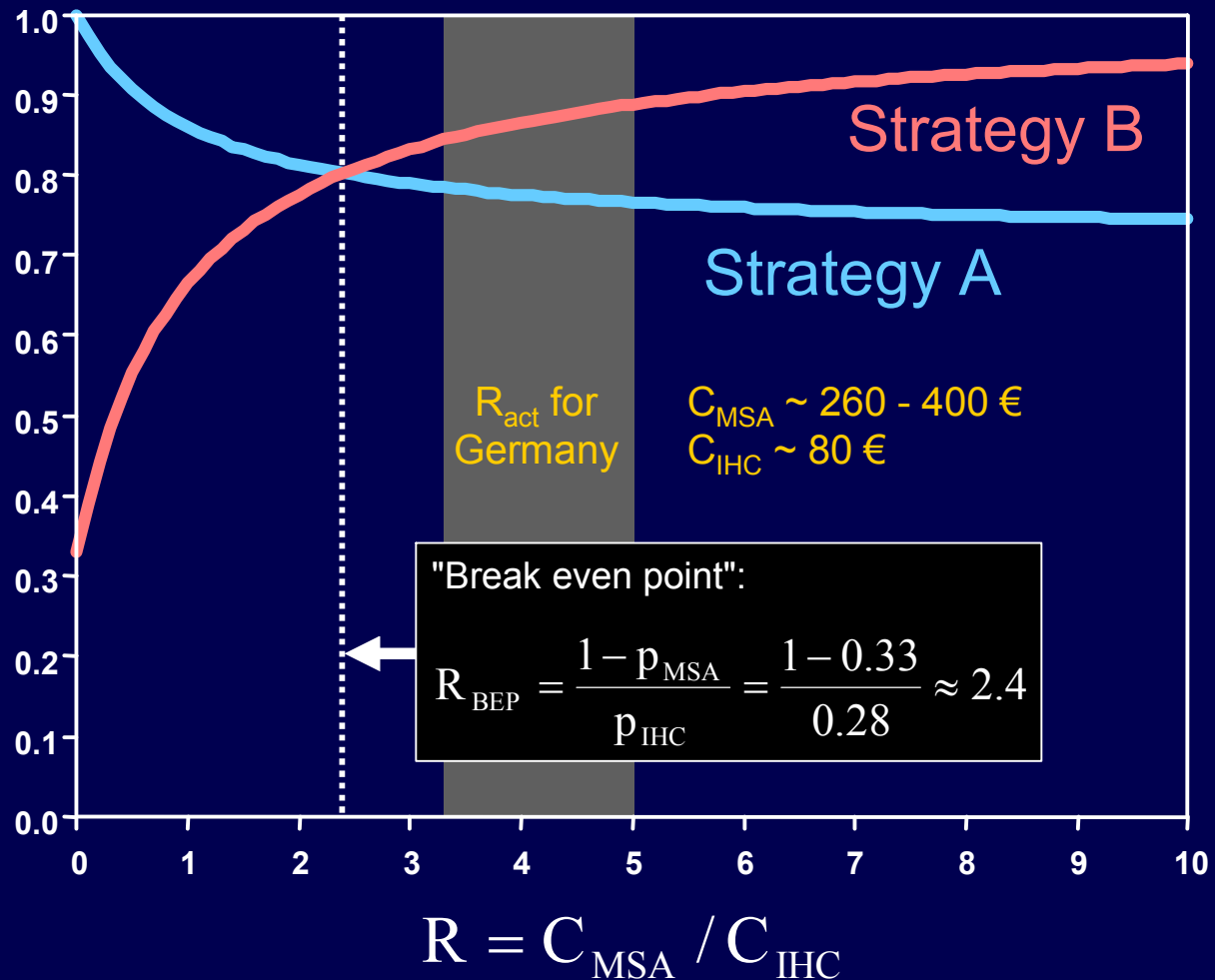
"Strategy B" (MSA first)

$$C_B = C_{MSA} + p_{MSA} \cdot C_{IHC}$$

Comparison of sequential strategies

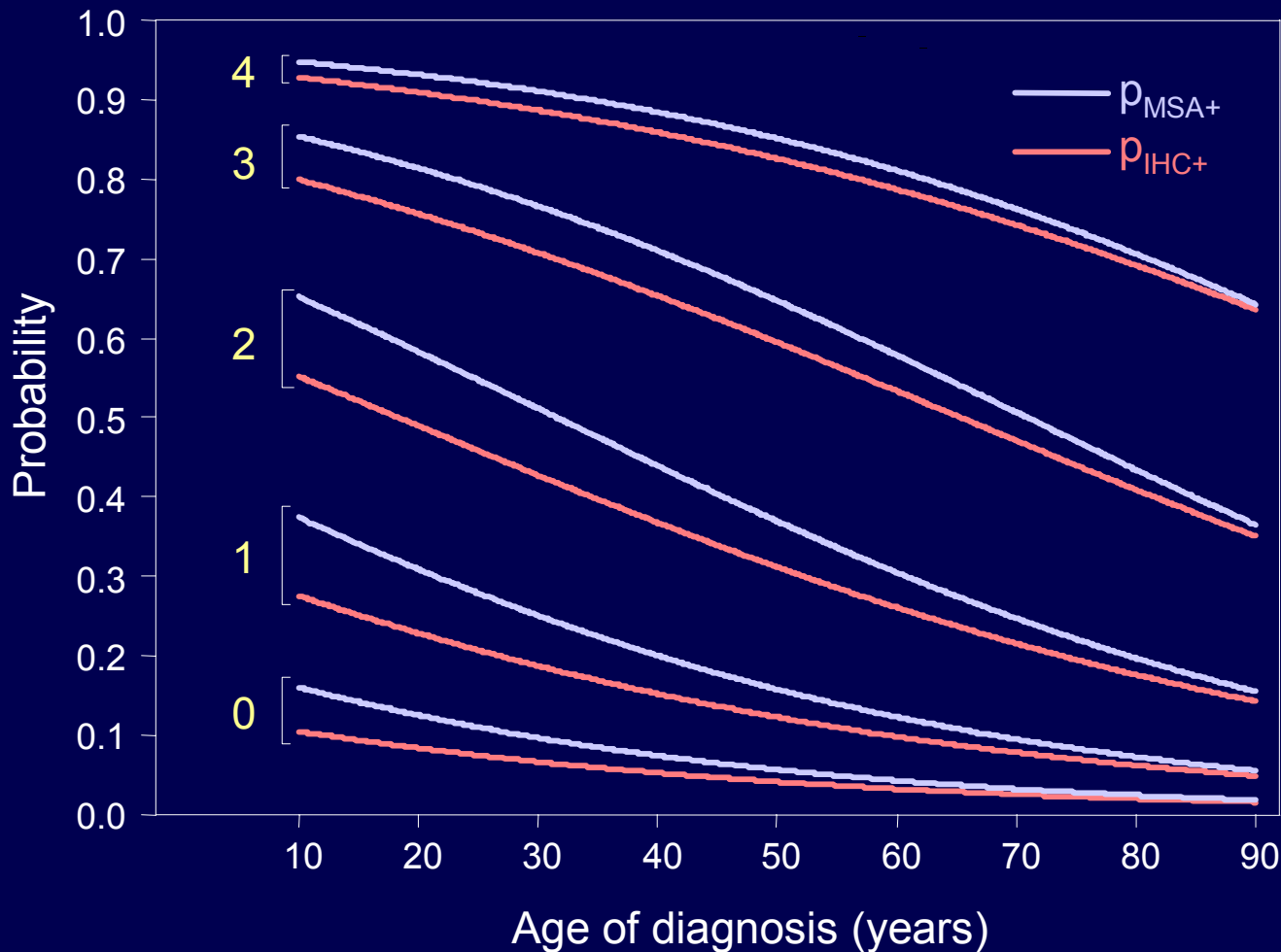
(relative to Strategy "P")

Costs
(relative to
Strategy "P")



Predictive model for $p_{\text{MSA}+}$ and $p_{\text{IHC}+}$

Logistic regression

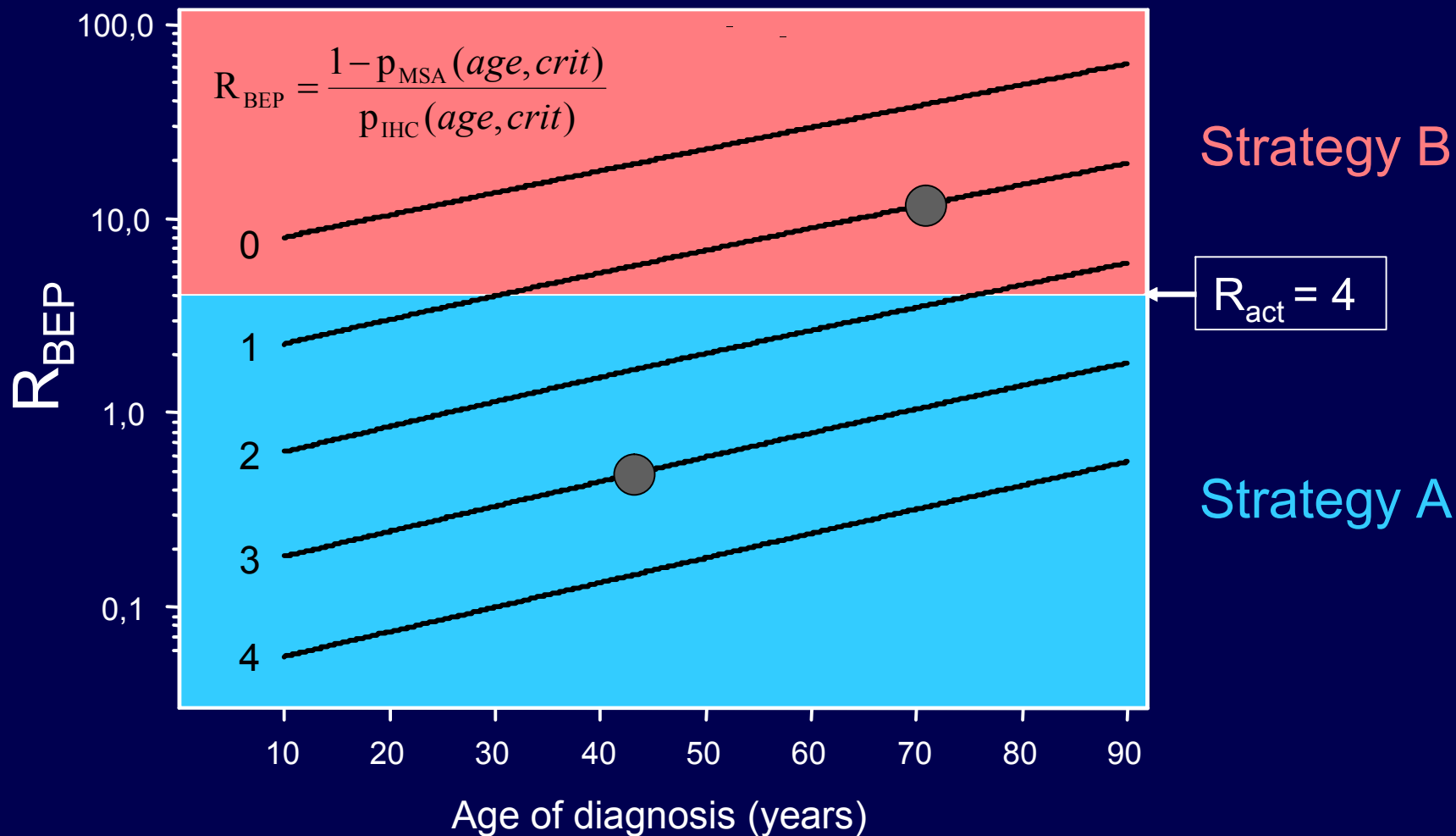


Predictors (index patient):

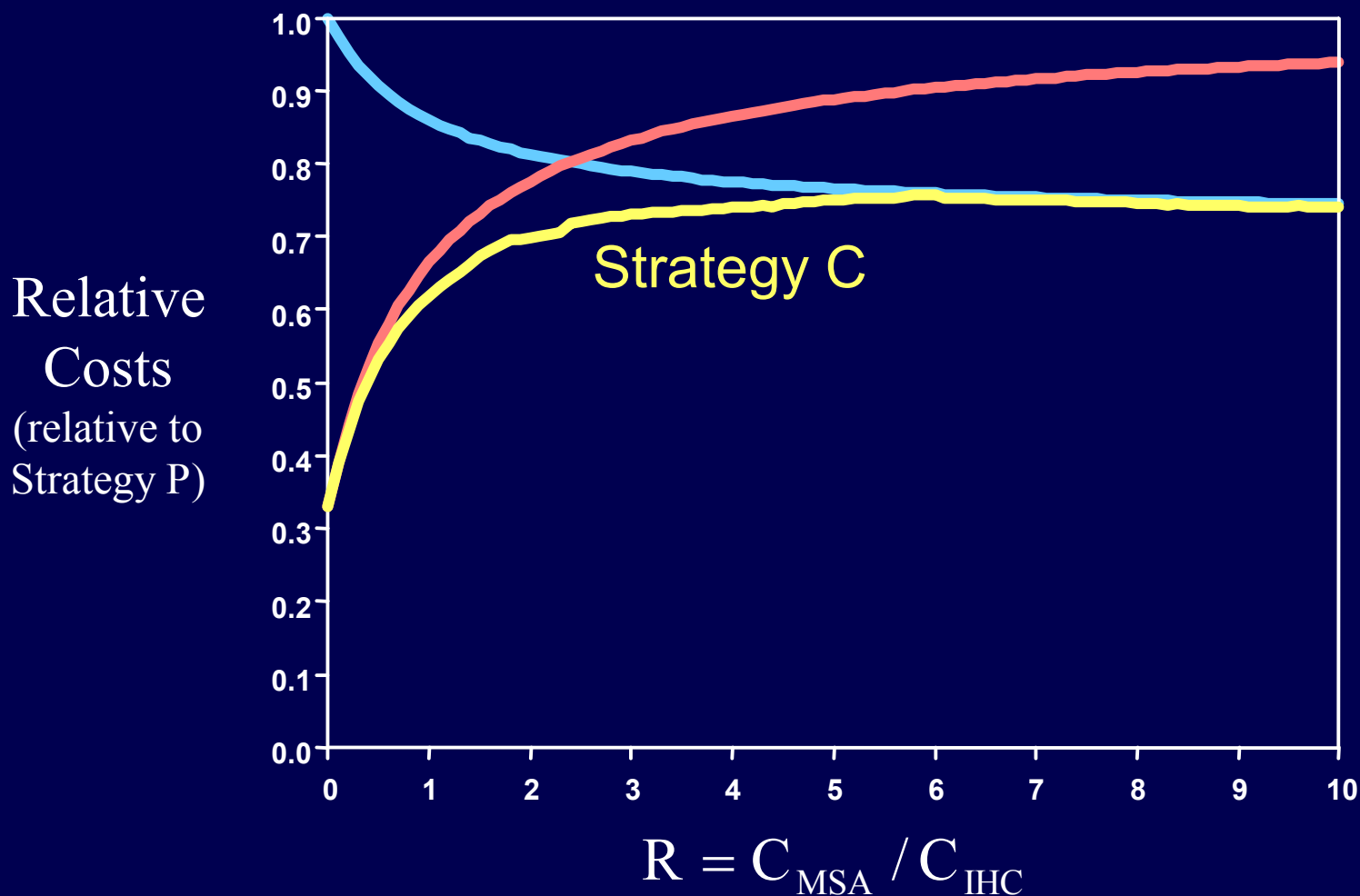
- Age of diagnosis
- Number of fulfilled clinical criteria:
 - Amsterdam 2
 - Bethesda Gl. 2
 - Bethesda Gl. 3
 - Bethesda Gl. 4

Individual allocation to strategy A or B

Calculation of expected R_{BEP}



Costs of individual allocation strategy



Conclusion

- We do not recommend IHC as a replacement for MSA
- Stepwise application of MSA and IHC is equally effective but less expensive than parallel application
- We propose a "two-way" sequential prescreening strategy, in which clinical parameters are used as a "track switch" to allocate patients to the pathway which is expected to be least expensive
- With this new strategy, a cost reduction of ~25% would be achieved for tumour screening in our patient population
- Clearly, the parameters of the decision model (actual costs for MSA and IHC, predicted probabilities of MSA and IHC positivity) may be different in other populations and other countries!

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