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Network meta-interpolation: a fast, novel NMA approach accounting for effect modification

Panelist

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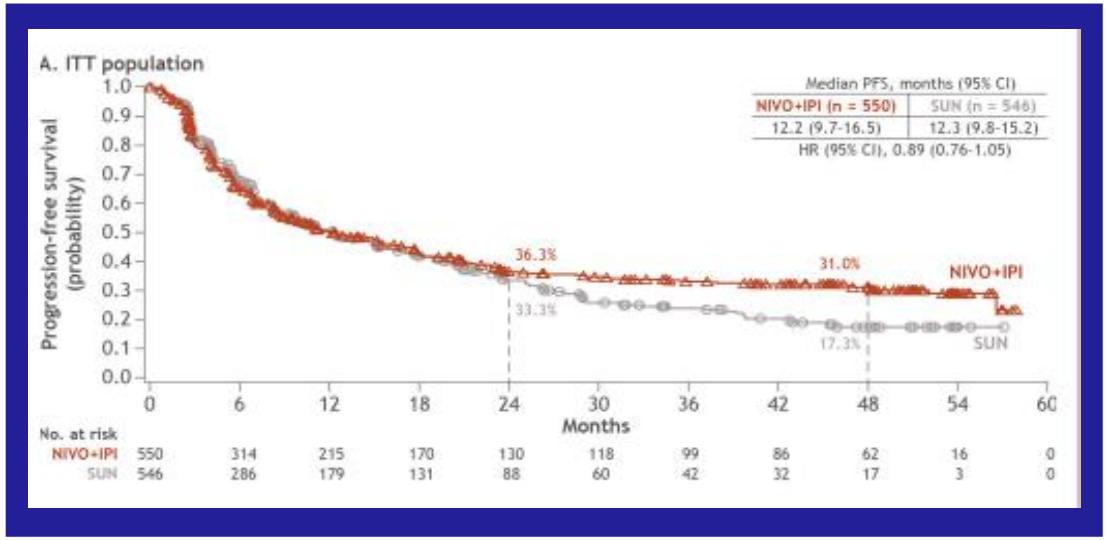
To Adjust or Not to Adjust for Effect Modifiers in HTA Submissions; Considerations in Population-Adjusted Indirect Treatment Comparisons

What is effect modification?



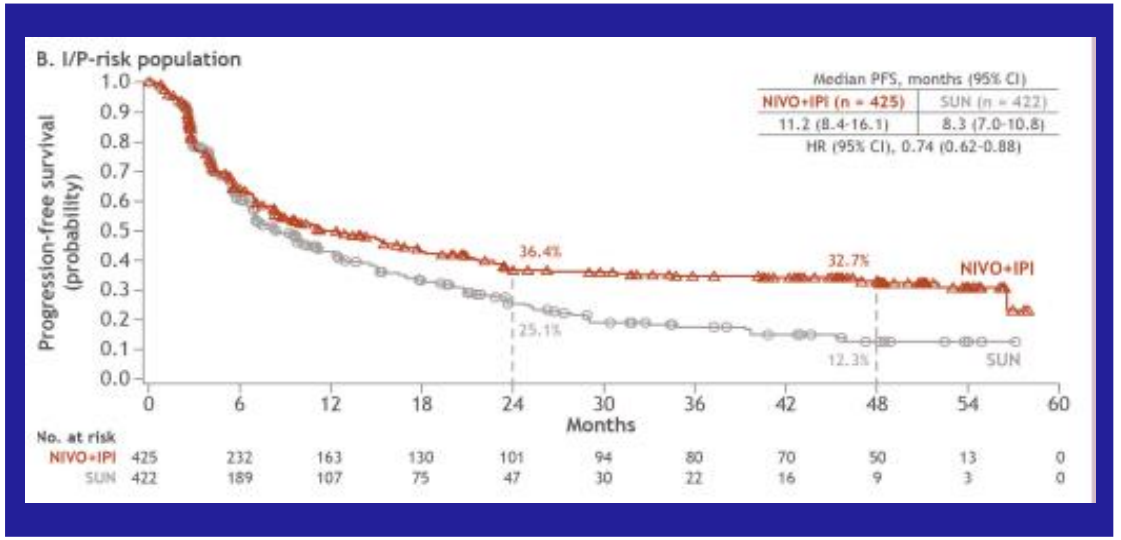
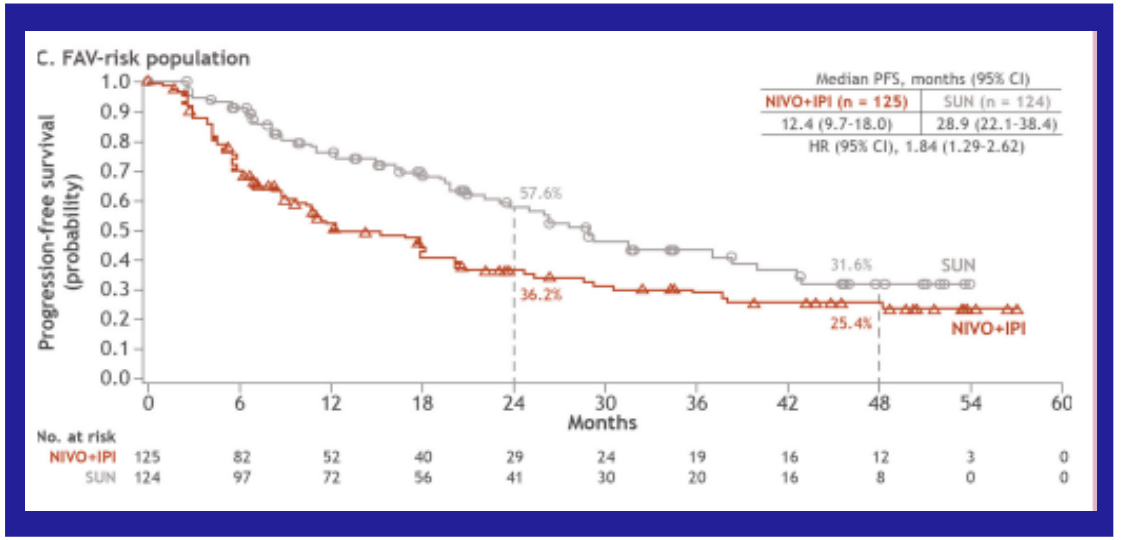


Illustration source: Cochrane UK



Violation of shared effect modification?

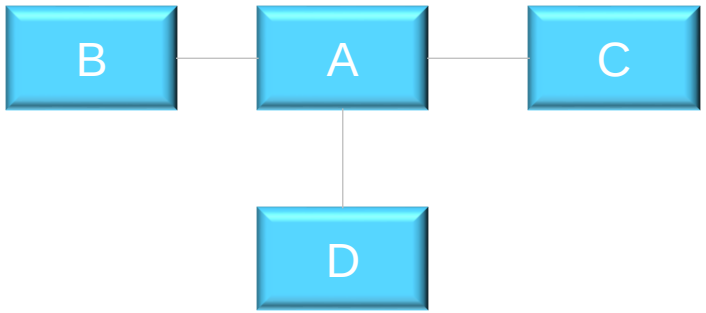
Returning to the previous renal cell carcinoma (REF,REF) example.

		Hazard ratio		
		Intention to treat	Favorable	Intermediate and poor
Renal cell carcinoma progression-free survival	Lenvatinib + pembrolizumab vs. sunitinib	**0.39**	**0.41**	**0.37**
	Nivolumab + ipilimumab vs. sunitinib	**0.89**	**1.84**	**0.74**
			With brain metastasis	**Without brain metastasis**
Non-small cell lung cancer (overall survival)	Atezolizumab trial		**0.57**	**0.77**
	Nivolumab trial		**0.81**	**0.66**
			Males	**Females**
Heart failure (overall survival)	Dapagliflozin trial		**0.73**	**0.79**
	Empagliflozin trial		**0.80**	**0.59**

A quick search shows shared effect modification (SEM) assumption may be questioned even for therapies of the same class.

Problem

Study	Trt1	Trt2	% age > 65	% high severity	TE	SE
1	A	B	62.8	45.7	1.387	0.188
2	A	B	84.3	61.8	1.475	0.183
3	A	B	78.7	59.2	1.612	0.187
4	A	C	73.3	50.3	2.757	0.204
5	A	C	70.5	46.8	2.526	0.198
6	A	C	60.0	40.5	2.134	0.191
7	A	D	53.3	30.3	0.667	0.187



Study	Trt1	Trt2	x1	x2	TE	se
1	A	B	0.675	0.475	1.439	0.189
2	A	B	0.675	0.475	1.370	0.216
3	A	B	0.675	0.475	1.480	0.196
4	A	C	0.675	0.475	2.786	0.200
5	A	C	0.675	0.475	2.571	0.195
6	A	C	0.675	0.475	2.540	0.209
7	A	D	0.675	0.475	0.289	0.221

Description of data

Individual patient data (IPD)

- All the necessary data are here (study 7 A-D).

Aggregate data (AgD)

- Data for the intention-to-treat (ITT) population (first row) includes (study 1-6 A-B, A-C):
  - x1 and x2
  - Treatment effect (TE)
  - Standard error (SE)

Subgroups

- Data includes:
  - TE
  - SE
  - But not x1 corresponding to x2 subgroup and vice versa

Trt1	Trt2	x1	x2	TE	se
A	B	0.628	0.457	1.387	0.188
A	B	1		1.829	0.242
A	B	0		0.492	0.319
A	B		1	1.363	0.267
A	B		0	1.464	0.270

Three-step approach to NMI

Step 1: Based on IPD for the AgD, the x2 is estimated as belonging to x1 and vice versa

Original AgD

Trt1	Trt2	x1	x2	TE	se
A	B	0.628	0.457	1.387	0.188
A	B	1		1.829	0.242
A	B	0		0.492	0.319
A	B		1	1.363	0.267
A	B		0	1.464	0.270

Imputed AgD

Trt1	Trt2	x1	x2	TE	se
A	B	0.628	0.457	1.387	0.188
A	B	1.000	0.538	1.829	0.242
A	B	0.000	0.321	0.492	0.319
A	B	0.739	1.000	1.363	0.267
A	B	0.535	0.000	1.464	0.270

Three-step approach to NMI (cont.)

Step 2: Treatment effect estimation by x1 and x2 by AgD study

ITT and subgroup data

- Using the ITT and the subgroup data:
  - Relative TE is defined as a linear function of x1 and x2.
  - SE is defined as a (more complex) function of x1 and x2.

Imputed AgD

Trt1	Trt2	x1	x2	TE	se
A	B	0.628	0.457	1.387	0.188
A	B	1.000	0.538	1.829	0.242
A	B	0.000	0.321	0.492	0.319
A	B	0.739	1.000	1.363	0.267
A	B	0.535	0.000	1.464	0.270

Evaluate TE and SE at certain value of x1 and x2

Trt1	Trt2	x1	x2	TE	se
A	B	0.628	0.457	1.387	0.188
A	B	1.000	0.538	1.829	0.242
A	B	0.000	0.321	0.492	0.319
A	B	0.739	1.000	1.363	0.267
A	B	0.535	0.000	1.464	0.270

Trt1	Trt2	x1	x2	TE	se
A	B	0.675	0.475	1.44	0.189

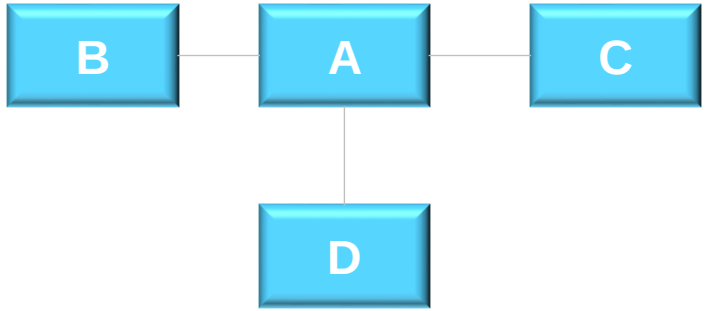
Using functions TE and SE (previous slide)

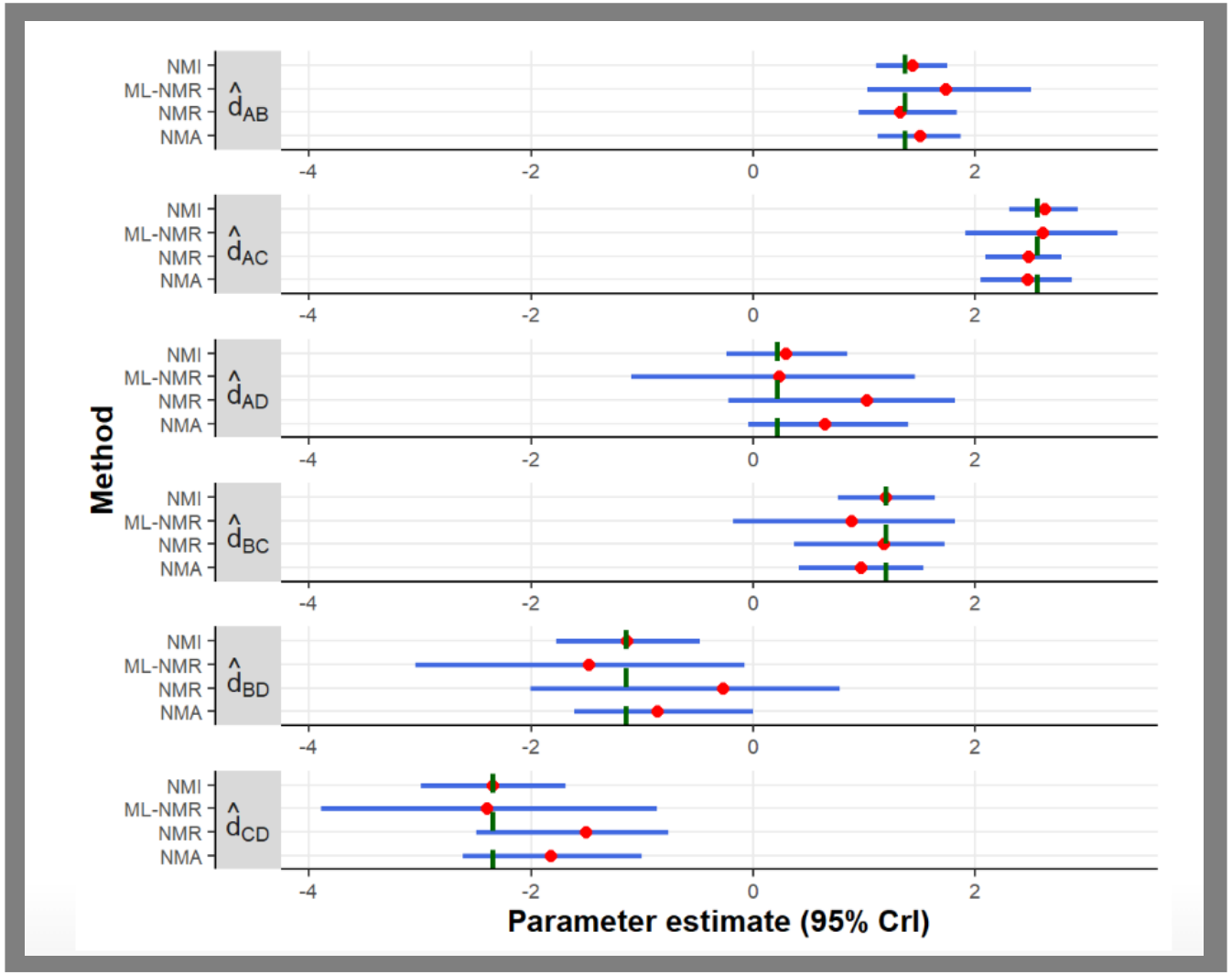
Study	Trt1	Trt2	x1	x2	TE	se
1	A	B	0.675	0.475	1.439	0.189
2	A	B	0.675	0.475	1.370	0.216
3	A	B	0.675	0.475	1.480	0.196
4	A	C	0.675	0.475	2.786	0.200
5	A	C	0.675	0.475	2.571	0.195
6	A	C	0.675	0.475	2.540	0.209
7	A	D	0.675	0.475	0.289	0.221

Three-step approach to NMI (cont.)

Step 3: Results simulation study comparing NMA and NMR ML-NMR and NMI at x1=0.675 and x2=0.475

- Green line is the true estimate.
- dAB
  - NMI and network meta-regression give the lowest bias ().
- dAC
  - All methods show similar results ().
- dAD
  - NMI and ML-NMR give the lowest bias ().
- NMI seems to predict well for indirect comparisons (dBC, dBD, dCD).





Conclusion

NMI is a novel population-adjusted indirect comparison (PAIC) method.

NMI requires:

- IPD of one trial, otherwise assumptions on correlation covariates needed
- Subgroup data (%, TE and SE) that are consistently reported over the evidence netrwork

Considerations

- Before choosing a PAIC method, consider all subgroup data available in the evidence network to identify effect modifiers (EM) and evaluate SEM.
- Consider the impact of immature data and sample size (chance findings) on conclusion of EM/SEM.
- Justify the considerations on EM, SEM and chosen PAIC method carefully.
- Guidance would be helpful on choice between PAIC vs. network meta-analysis.
  - Number of potential EMs
  - Size of distributional differences in EMs over evidence network
  - Strength association EM and relative TE
- If EM is present in evidence network, ideally the PAIC is conducted on covariate estimates reflecting clinical practice.
  - NMI
  - ML-NMR
- Present findings are based on simulation studies, which require assumptions; ideally the study can be replicated based on evidence networks with large trials for which IPD are available.

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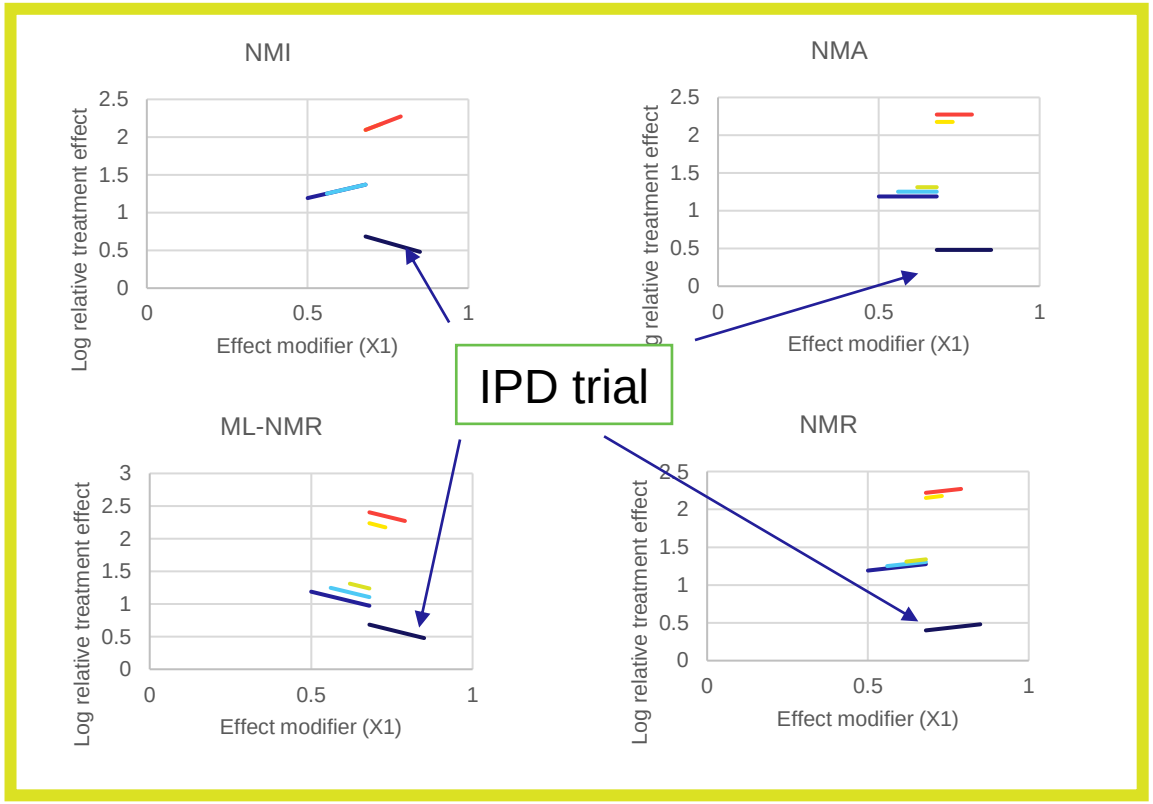
Thank you

NMI

Network meta-interpolation (NMI), network meta-analysis (NMA), network meta-regression (NMR), and multi-level network meta-regression (ML-NMR) deal differently with effect modifiers (EM).



- Even for therapies of same class, SEM might be debatable based on subgroup data
  - HR on PFS by sex show in the pembrolizumab is 0.77 [0.61;0.97] for males and 0.54 [0.37;0.81] for females. The corresponding numbers in the avelumab are 0.56 [0.42;0.75] for males and 0.90 [0.55;1.47] for females. (Motzer et al., 2019; Rini et al., 2019).
  - HR on OS for the dapagliflozin of 0.73 [0.63;0.85] for males and 0.79 [0.59;1.06] for females, corresponding empagliflozin trial shows 0.80 [0.68;0.93] for males and 0.59 [0.44;0.80] for females (McMurray et al., 2019; Packer et al., 2020).
- Despite this NMR, ML-NMR and NMA assume SEM (all lines on left same direction)
- NMI (top left) is only method that allows the association found between EM and RTE in individual studies to be leveraged to adjust for EM