# Introduction to Bayesian Network Meta-Analysis

Beth Devine, PhD, PharmD, MBA Ashley Cha, PharmD, MS CLEAR Center July 27, 2020 THE CHOICE INSTITUTE

### Outline

### > Part 1: Overview of Network Meta-Analysis (NMA)

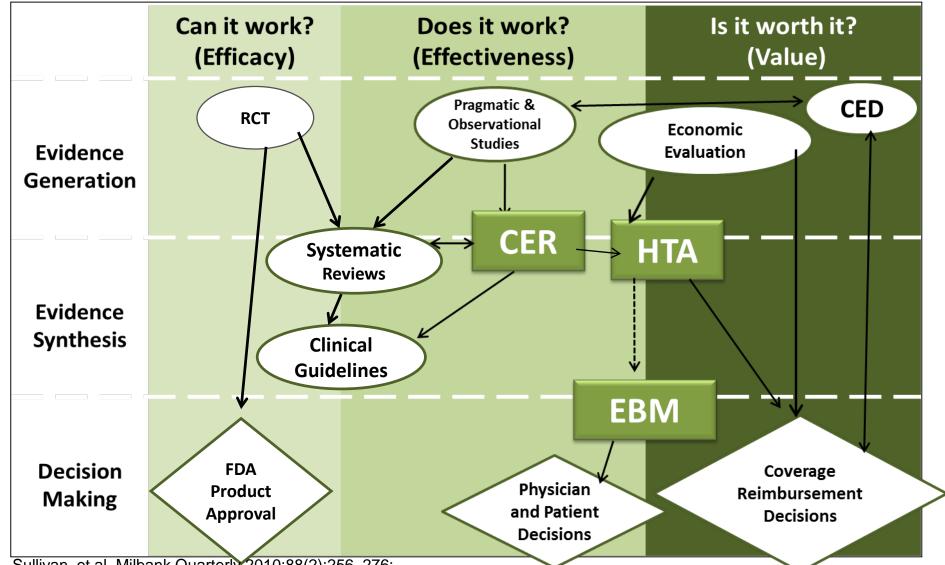
- Context for Evidence Synthesis
- From meta-analysis (MA) to NMA
- Fundamentals of NMA

### > Part 2: Case Study

Microvascular Benefits of New Anti-Diabetic Agents
> NMA of Renal Outcomes

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### Evidence Synthesis in Comparative effectiveness research (CER); Health technology assessment (HTA)



Adapted from Luce...Sullivan, et al. Milbank Quarterly 2010;88(2):256–276; CED: coverage with evidence development: EBM = evidence-based medicine: RCT = randomized controlled trial

### From Meta-Analysis to NMA

- Recall....
- Meta-analyses are useful for informing evidence-based decision-making — Quantitatively (statistically) pooling results
  - Comparable studies of the <u>same</u> intervention to the <u>same</u> comparator
  - Obtain overall estimate of effect
    - usually OR, RR, HR, or Standardized Mean Difference (SMD)
  - Each study weighted according to size and uncertainty (weighted mean)
  - Fixed effects and random effects models are used

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#### **Traditional Meta-analysis**

Educational interventions for asthma in children 23-Jun-2011 4.14 ED Visits (mean) Education Control Std. Mean Difference Std. Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% Cl Year IV, Random, 95% Cl 4.14.1 Group Interventions Lewis 1984 2.32.98 48 3.71 2.98 28 2.9% -0.47 [-0.94, 0.00] 1984 Clark 1986 1.72 4.8% 4.2 159 2.49 6.26 73 -0.16 [-0.43, 0.12] 1986 Toelle 1993 1.51 2.31 63 1.67 2.4 3.8% -0.07 [-0.44, 0.30] 1993 51 Christiansen 1997 0.3 1.2 27 0.2 0.43 15 1.9% 0.10 [-0.53, 0.73] 1997 Ronchetti 1997 0.07 0.32 0.23 0.78 4.9% 114 95 -0.28 [-0.55, -0.00] 1997 Greineder 1999 0.41 0.59 29 0.96 1.48 2.5% 28 -0.48 [-1.01, 0.04] 1999 Tieffenberg 2000 0.37 3.8% 0.3 65 0.7 0.9 52 -0.51 [-0.88, -0.14] 2000 Cicutto 2005 1.7 1.9 132 2.5 2.5 124 5.2% -0.36 [-0.61, -0.11] 2005 La Roche 2006 1.5 1.7 11 1.1 1.8 11 1.2% 0.22 [-0.62, 1.06] 2006 Bryant-Stephens 2009 1.72 2.28 4.8% 118 1.38 1.69 85 0.16[-0.11, 0.44] 2009 Espinoza-Palma 2009 0.83 1.2 36 1.78 3.0% 3 41 -0.40 [-0.85, 0.05] 2009 Indinnimeo 2009 0.8 3.78 1.59 4.0% 60 0.5 63 0.10 [-0.25, 0.46] 2009 Watson 2009 5.8% 0.45 0.96190 0.75 0.96 190 -0.31 [-0.51, -0.11] 2009 Butz 2010 1.16 2.4 100 0.95 2.6 93 4.8% 0.08 [-0.20, 0.37] 2010 Subtotal (95% CI) 1152 949 53.5% -0.18 [-0.31, -0.05] Heterogeneity: Tau<sup>2</sup> = 0.03; Chi<sup>2</sup> = 24.55, df = 13 (P = 0.03); I<sup>2</sup> = 47% Test for overall effect: Z = 2.80 (P = 0.005) 4.14.2 Individual Interventions McNabb 1985 1.9 4.72 7.4 4.72 7 0.7% -1.09 [-2.24, 0.06] 1985 Alexander 1988 0.9 0.6 2.1 10 1.0% -1.09 [-2.02, -0.16] 11 2.4 1988 Hughes 1991 0.45 1.05 44 0.6 1.05 45 3.3% -0.14 [-0.56, 0.27] 1991 2.3% Talabere 1993 0.44 0.77 25 1.08 1.32 25 -0.58 [-1.15, -0.02] 1993 Persaud 1996 0.27 0.57 18 1.2 1.7% -0.76 [-1.44, -0.08] 1996 1 18 Kelly 2000 1.7 1.85 38 2.3 1.9 40 3.1% -0.32 [-0.76, 0.13] 2000 Bartholomew 2000 1.3 1.8 64 1.2 1.7 55 3.9% 0.06 [-0.30, 0.42] 2000 Harish 2001 4.0% 0.101 0.158 60 0.3260.704 69 -0.43 [-0.77, -0.08] 2001 Krishna 2003 0.4 107 121 5.0% -0.59 [-0.85, -0.32] 2003 0.1 0.61.1 Butz 2006 27 28.4 46.5 86 4.6% -0.34 [-0.63, -0.05] 2006 95 40 Joseph 2007 5.1% 0.5 2 134 0.8 1.9 107 -0.15 [-0.41, 0.10] 2007 Garbutt 2010 0.52 0.92 154 0.48 0.77 150 5.5% 0.05 [-0.18, 0.27] 2010 Subtotal (95% Cl) 757 733 40.3% -0.32 [-0.50, -0.14] Heterogeneity: Tau<sup>2</sup> = 0.05; Chi<sup>2</sup> = 26.56, df = 11 (P = 0.005); l<sup>2</sup> = 59% Test for overall effect: Z = 3.57 (P = 0.0004) 4.14.3 Individual and Group Interventions Fireman 1981 0.08 1.14 13 1.14 13 1.3% -0.78 [-1.58, 0.02] 1981 Shields 1990 0.54 1.68 101 0.38 1.68 104 4.9% 0.09 [-0.18, 0.37] 1990 Subtotal (95% Cl) 114 117 6.2% -0.26 [-1.10, 0.58] Heterogeneity: Tau<sup>2</sup> = 0.29; Chi<sup>2</sup> = 4.10, df = 1 (P = 0.04); l<sup>2</sup> = 76% Test for overall effect: Z = 0.60 (P = 0.55) Total (95% CI) 2023 1799 100.0% -0.23 [-0.33, -0.13] Heterogeneity: Tau<sup>2</sup> = 0.04; Chi<sup>2</sup> = 58.96, df = 27 (P = 0.0004); I<sup>2</sup> = 54% -2 -1 Test for overall effect; Z = 4.37 (P < 0.0001) Favours education Favours control Test for subgroup differences: Chi<sup>2</sup> = 1.57, df = 2 (P = 0.46), l<sup>2</sup> = 0%

Agapova, Devine, Nguyen, Wolf, Inoue *J. Comp. Eff. Res.* 2014;3(4), 345–357

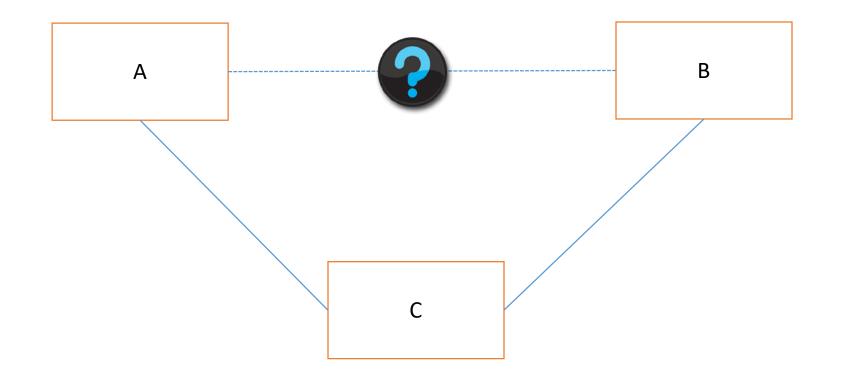
### Introduction to Network MA Methods (1)

- > But now...
- > Network of studies involves > 2 drugs
  - Drug A to C (study<sub>AC</sub>)
  - Drug B to C (study<sub>BC</sub>)
- > We wish to know how Drug A compared to Drug B can make an <u>indirect</u> <u>comparison</u>

 $study_{AB} = study_{AC} - study_{BC}$ 

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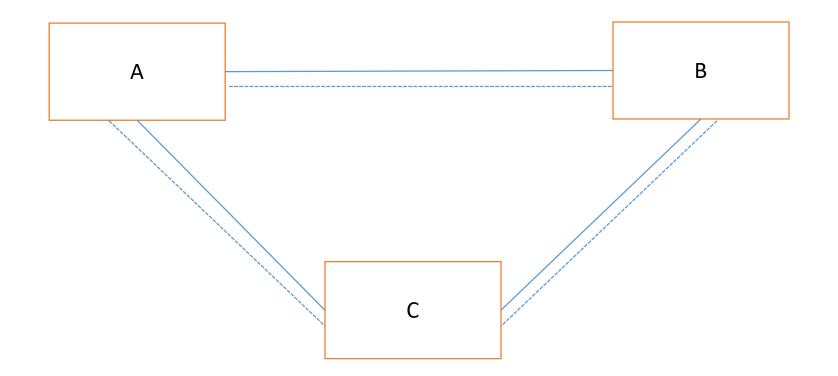
### **Introduction to Network MA Methods (2)**



#### "Indirect Treatment Comparison (ITC)"

Statistical comparison of two or more agents that have not been directly compared to each other, but that have one comparator in common, thus creating a network

### **Introduction to Network MA Methods (3)**

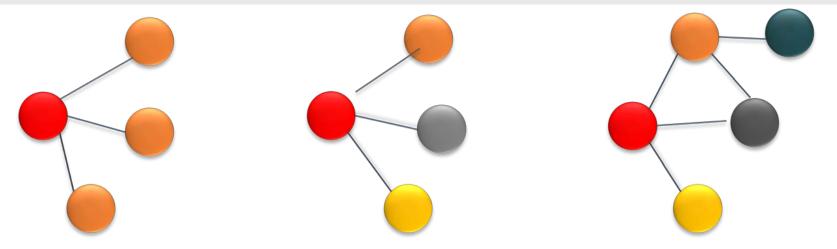


"Mixed treatment comparison (MTC)" Extension of ITC where both direct and indirect evidence is included

### Introduction to Network MA Methods (4)

#### **Network Meta-Analysis**

Meta-analysis	Indirect Treatment Comparison	Mixed Treatment Comparison
Quantitatively combined results of <u>comparable</u> studies of the <u>same agent</u> to obtain overall estimate of effect.	Statistical comparison of two or more agents that have <u>not been directly</u> <u>compared to each other</u> , but that have <u>one</u> <u>comparator in common</u> , thus creating a network	Extension of ITC where <u>both direct and indirect</u> evidence is included



Jansen. Value in Health 2008;11(5):956-64; 21:2313-24; Lu & Ades. Stat Med 2004;23:3105-24; Sutton & Ades. Pharmacoeconomics 2008;26(9);753-67

### First, must conduct all systematic review steps

- > Establish **PICOTS** criteria
  - <u>P</u>opulation, <u>Interventions</u>, <u>C</u>omparator(s), <u>O</u>utcomes, <u>T</u>iming (timing of literature search, duration of treatment, duration of follow-up), <u>S</u>etting/<u>S</u>tudy design
- > Conduct search using multiple databases
- > Dual review & reconciliation of titles, abstracts, full-text of included studies
- > Conduct quality assessment on each included study using a risk of bias tool (dual review again)
- > Extract data into evidence tables
- > Address heterogeneity in protocol/analysis pool at all? Subgroups? Meta-regression?

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### Fundamentals of NMA (1) – Preserve randomization

- > Validity of evidence synthesis relies on methods that appreciate within trial randomization
- > If within trial randomization not preserved then NMA has a fatal flaw
- > A limitation inherent in the method is risk of bias due to lack of randomization across trials

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## Fundamentals of NMA (2) - Heterogeneity

- Also recall...
  - in meta-analysis, heterogeneity of included studies must be taken into account
  - if assumption not met.....then conduct systematic review
- Similarity
  - qualitative assessment
  - compare studies on PICOTS criteria & study design
    - "P" = demographic and clinical characteristics
- Heterogeneity
  - quantitative assessment
  - percent of variation across studies due to heterogeneity, rather than chance
  - evaluate with I<sup>2</sup> statistic
  - primary goal of meta-analysis is to explore heterogeneity, rather than to calculate one effect

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## Fundamentals of NMA (3) – Two additional assumptions

### > Transitivity

- Validity of logical inference; potential modifiers of treatment effect similarly distributed across trials
- If A=B, and B=C, then A=C
- Qualitative assessment

#### > Consistency

- If direct and indirect evidence, then quantitatively check consistency
- If inconsistency.....then non-transitivity
- Quantitative (statistical) measure of transitivity
- If inconsistent, include a "Design by Treatment" interaction term in meta-regression model

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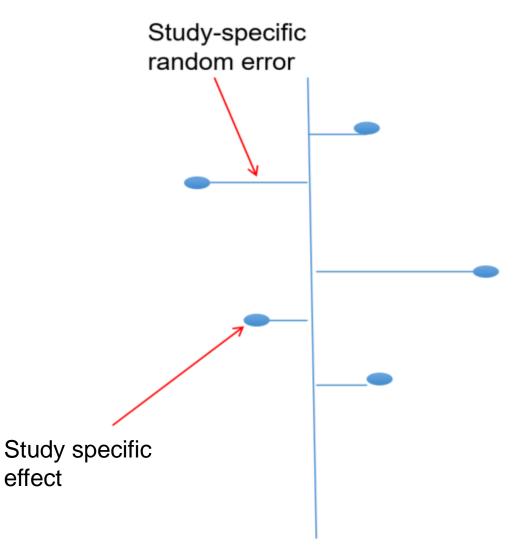
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Jansen. Value in Health 2008;11(5):956-64; 21:2313-24; Jansen, et al. Value in Health 2014;17:157-173; Neupane. NMA using R: Review of currently available automated packages. PLoS One. 2014;9(12):e115065

## Fundamentals of NMA (4): Fixed Effects (FE) Model

- No heterogeneity
- We estimate the common true effect

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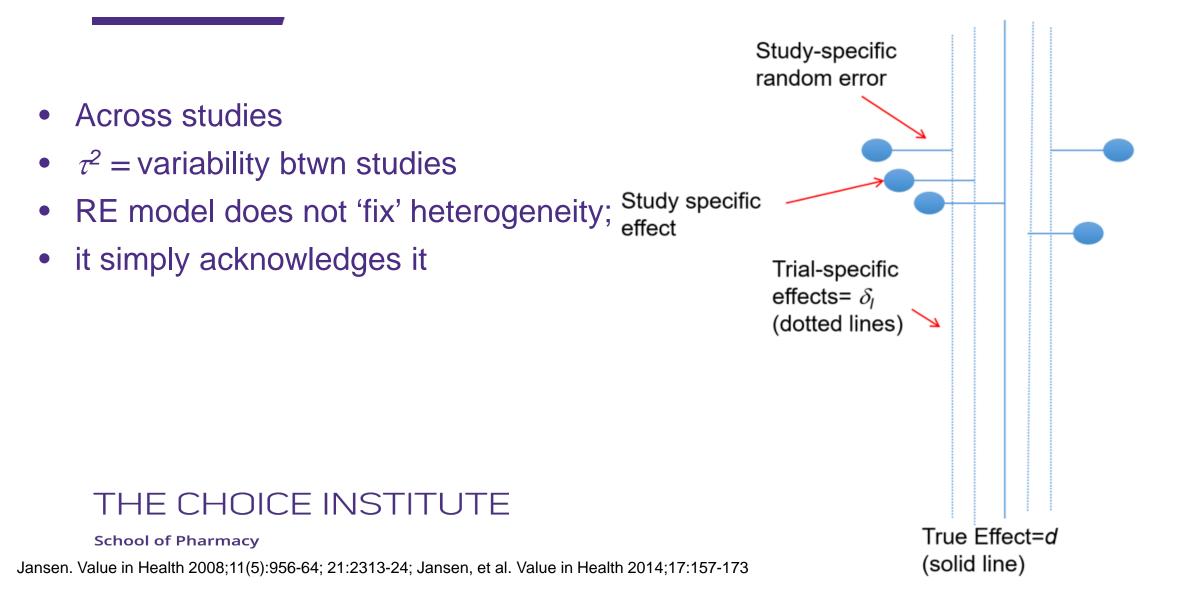


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Jansen. Value in Health 2008;11(5):956-64; 21:2313-24; Jansen, et al. Value in Health 2014;17:157-1

True effect=d

## Fundamentals of NMA (5): Random Effects (RE) Model



### **Bayesian Framework for Analysis**

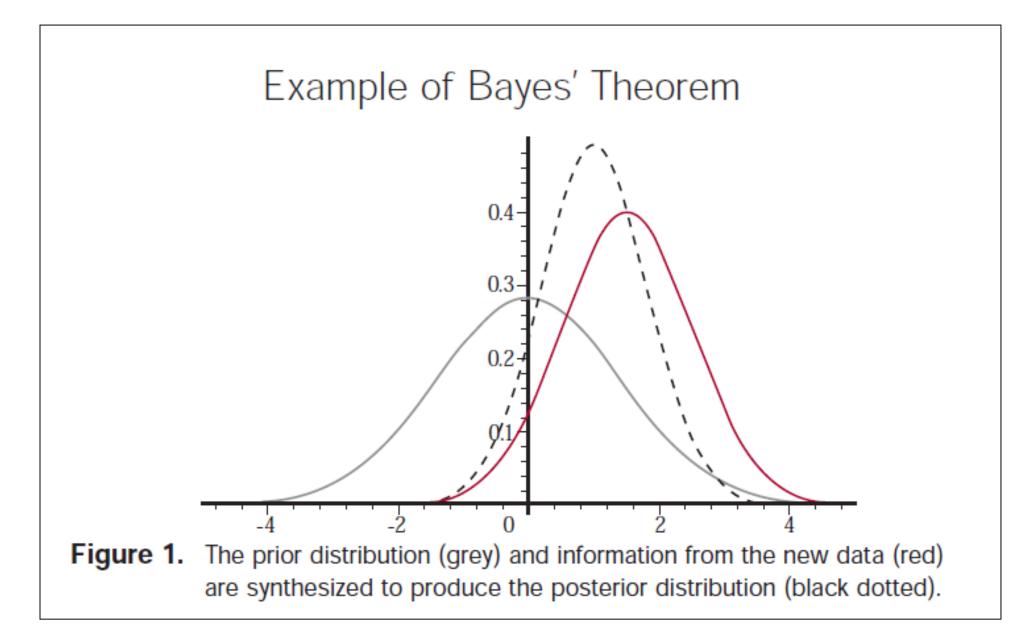
- > Start with what you know (prior information)
- > Combine with what you observe (likelihood function)
- > This gives you what you know after observing the data (posterior information)

likelihoodpriorPr(B|A) = $\frac{Pr(A|B) \times Pr(B)}{Pr(A) \text{ scaling term}}$ 

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O'Hagan & Luce. A Primer on Bayesian Statistics. Center for Bayesian Statistics in Health Economics. MEDTAP International, 2003



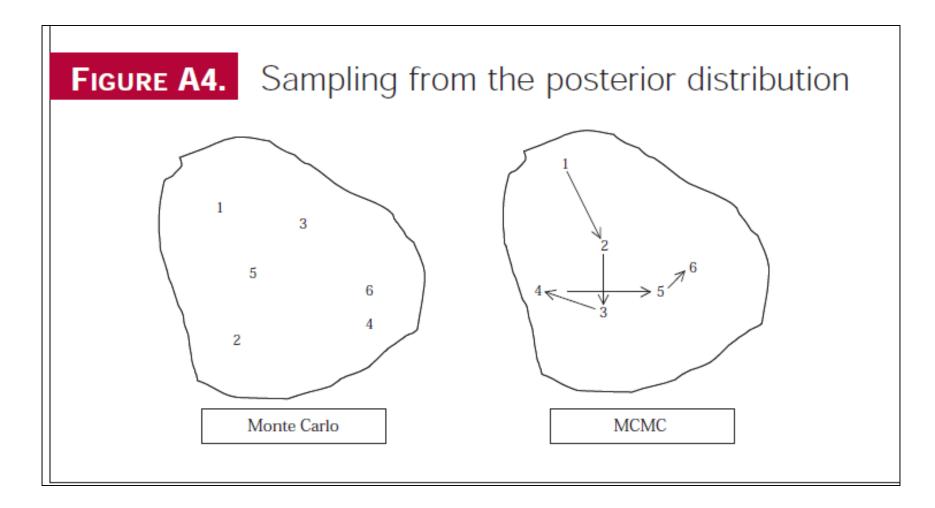
### **Bayesian Computational Methods (1) – Monte Carlo Simulation**

- > Estimates random sequence of chains, where
  - next chain relies only on its immediate predecessor Markov chain
- > Markov chain Monte Carlo simulation (MCMC)
  - set up a Markov chain whose distribution is the posterior distribution
- > Chain must run to convergence before estimating posterior probabilities <u>burn ins</u>
- > A special type of algorithm cycles through each model parameter one at a time is called <u>Gibbs sampling</u>

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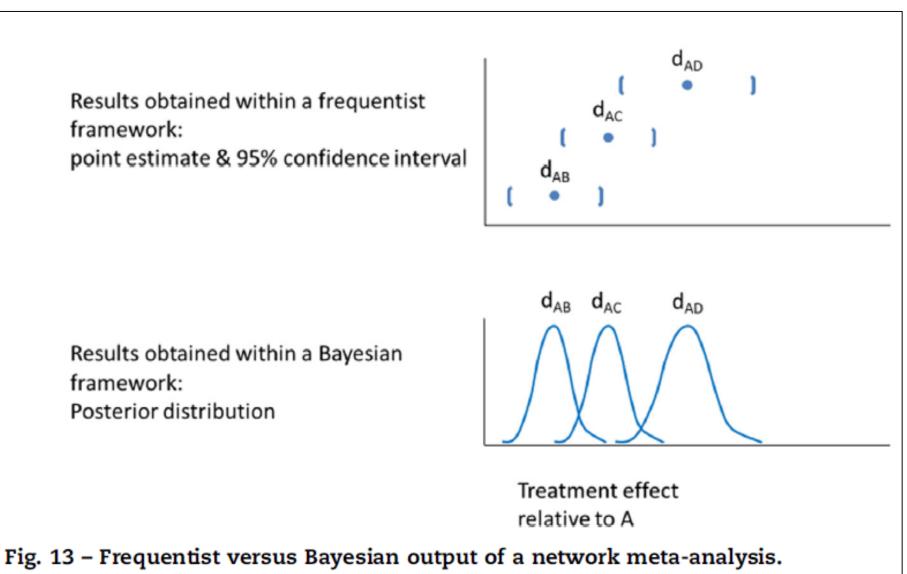
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### **Bayesian Computational Methods (2)– Monte Carlo Simulation**



O'Hagan & Luce. A Primer on Bayesian Statistics. Center for Bayesian Statistics in Health Economics. MEDTAP International, 2003

### Frequentist vs. Bayesian Results of NMA



### **Criticisms of Bayesian Approach (of NMA)**

- > Priors are subjective (differ between persons)
- > Priors difficult to specify
  - An area of active research
- > No single measure of "statistical significance "
  - No p-value
- > Computationally more challenging
  - Computers have largely solved the problem
- > Programming more challenging
  - New packages emerging

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### Advantages of Bayesian Approach (of NMA)

- > Inferences mean what you thought frequentist inferences meant!
- > Exact sample size results (no asymptotics)
- > Can incorporate prior knowledge
- > More natural in context of decision-making
  - Can calculate probability of effect of each technology
  - Can rank order technologies

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### **Evolving Methods**

Research Synthesis Methods



- > Use of individual patient data (IPD)
- > Use of partial IPD and partial aggregate data
  - Matching adjusted indirect treatment comparisons
    - > Signorovitch, et al. Comparative effectiveness without head-to-head trials. Pharmacoeconomics 2010;28:935-945
    - > Signorovitch, et al. Matching-adjusted indirect comparisons: a new tool for timely CER. Value Health 2012;15:940-947
  - Simulated treatment comparisons
    - > Caro & Ishak. No head-to-head trial? Simulate the missing arms. Pharmacoeconomics 2010;28:957-967
    - > Ishak, et al. Simulation and matching-based approaches for indirect comparison of treatments. Pharmacoeconomics 2015;33:537-549

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- > White, et al. Consistency and inconsistency in network meta-analysis: model estimation using multivariate metaregression. Res Synthesis Methods 2012;3:111-125
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- > Chaimani, et al. Graphical tools for network meta-analysis in STATA. PLOS One 2013;8(10): e76654
- > Canestaro, Forrester, Devine, et al. Drug treatment of idiopathic pulmonary fibrosis. CHEST 2016;149(3):156-66

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Thank you! Questions? bdevine@uw.edu