FDA-JHU CERSI
HTE Symposium
2018-Nov-28

Session 3 Presenter and
Moderator: John Whyte

Session 3: Communication of HTE to Key Stakeholders

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Challenge Question

How can individualized treatment effect estimates and their uncertainty be communicated?

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Subgroup Analysis

- Patients enrolled into a clinical study can be heterogeneous.
- Thus, treatment effects may be heterogeneous among subgroups.
- Heterogeneity of treatment effects may be anticipated or unanticipated *a priori*.
- The individual is the most granular subgroup. Clinically, it is the most important.

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Individualized Medicine

- **Precision Medicine**: “The right dose of the right drug for the right patient at the right time”.

- **Clinical Decision Support:** “CDS provides clinicians, staff, patients, and other individuals with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care”.
  - Office of the National Coordinator for Health Information Technology (ONC). https://www.healthit.gov/policy-researchers-implementers/clinical-decision-support-cds

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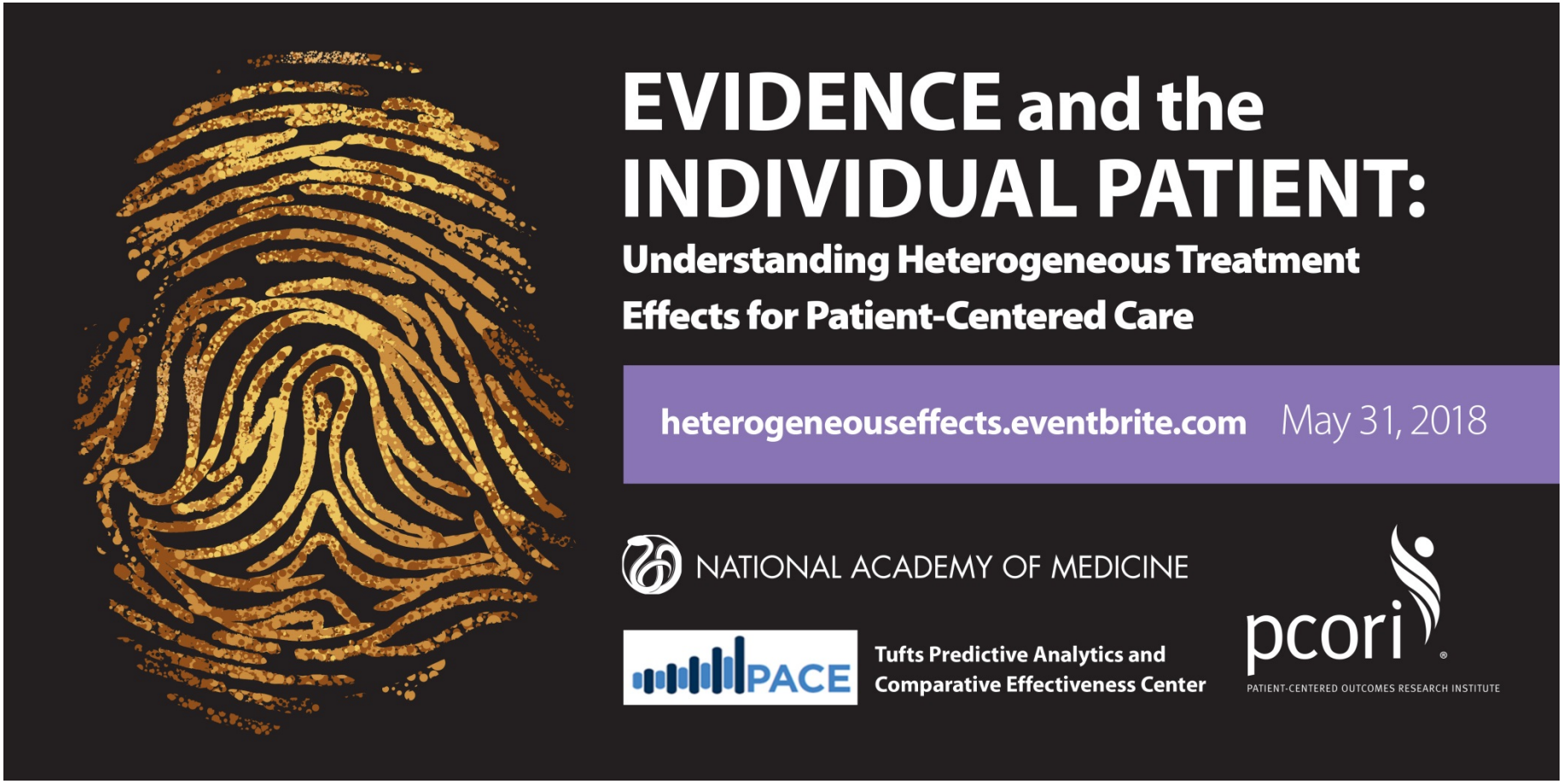
EVIDENCE and the
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Eastern North American Region (ENAR) Meeting, International Biometric Society, 2018 Mar 24-27

Individualized Evidence for Medical Decision Making: Principles and Practices

- **Scott Zeger**, PhD, Johns Hopkins University
  Bayesian models for "individualized health"
- **Laura Hatfield**, PhD, Harvard Medical School
  Personalized Bayesian minimum-risk decisions for treatment of coronary artery disease
- **Tracey Marsh**, PhD, Fred Hutchinson Cancer Res Center
  Assessing clinical impact with net benefit metrics
- **David Kent**, MD, Tufts
  Moving from evidence-based medicine to personalized/precision medicine

https://enar.org/meetings/spring2019/index.cfm

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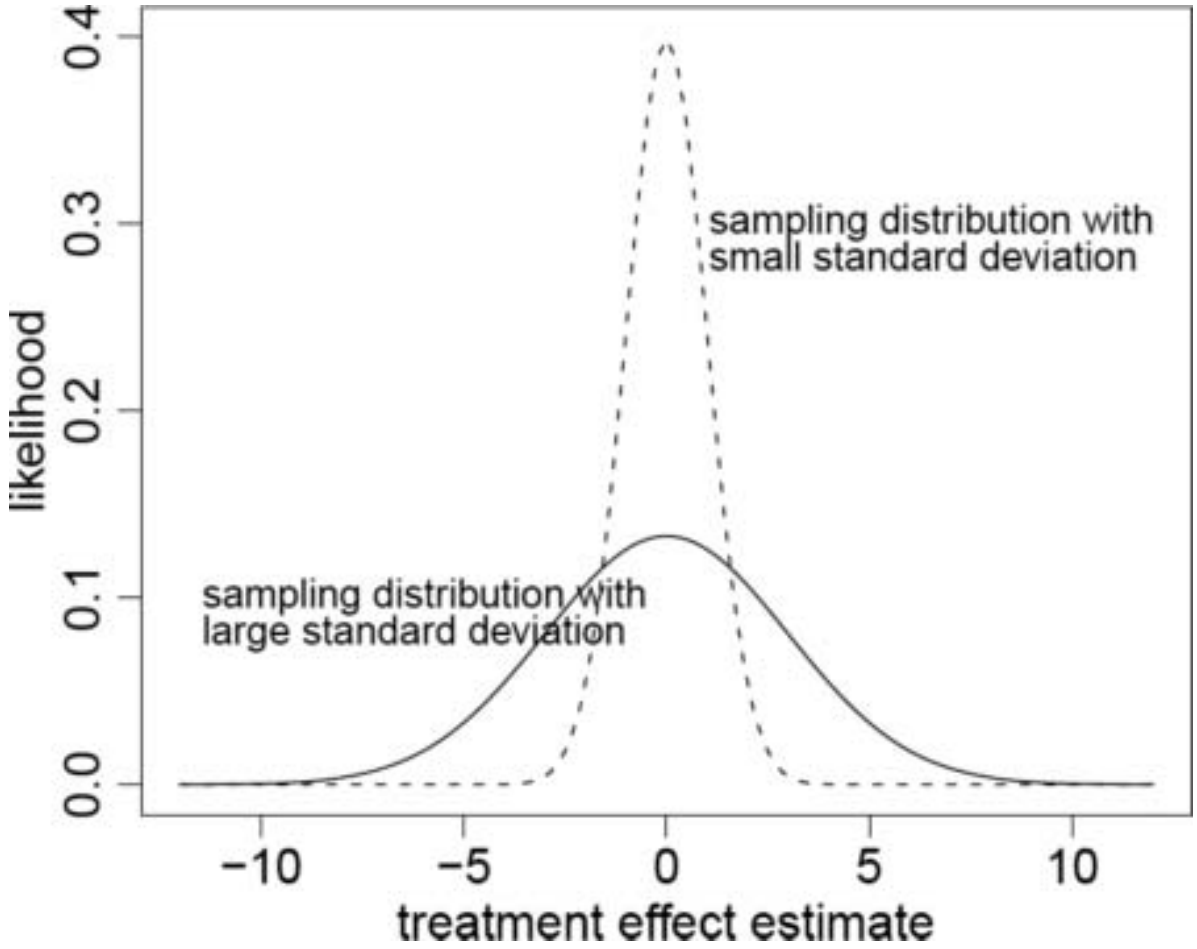
The Subgroup Problem



Gelman, Hill, Yajima, Why We (Usually) Don't Have to Worry About Multiple Comparisons. *J Res Educ Effectiveness* 2012; 5: 189–211.

- Random variation increases chance that subgroup specific treatment effects are falsely significant.

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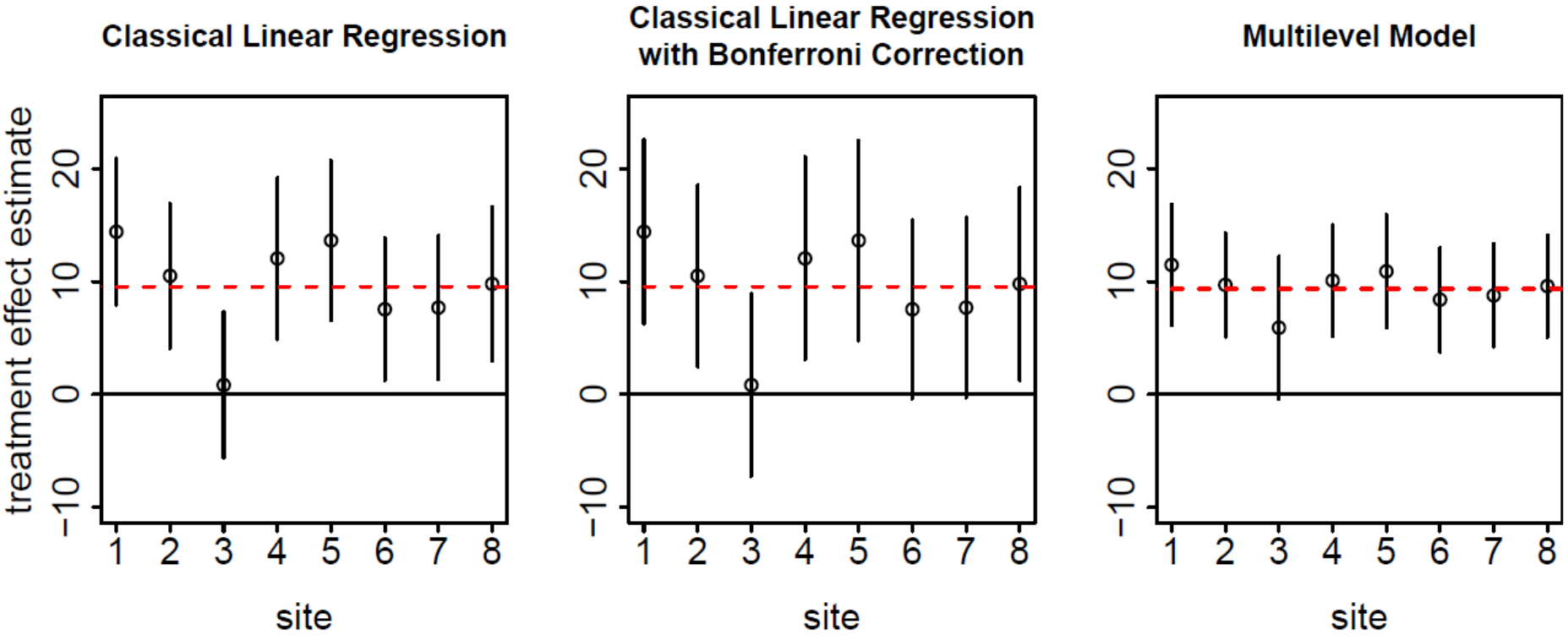
Comparison of Approaches



Gelman, A., Hill, J., and Yajima M. (2012), Why We (Usually) Don‟t Have to Worry About Multiple Comparisons, *Journal Research Education Effectiveness,* 5, 189-211.

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Warfarin Dose by Genotype

Recommended Initial Warfarin Dose (mg/day) by Genotypes CYP2C9 and VKORC1 †						
	CYP2C9					
VKORC1	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	6	5	4	4	3	2
AG	5	4	3	3	2	1.5
AA	3	3	2	2	1	1

†Other clinical factors should be considered when selecting the initial dose within the recommended range (eg, age, race, body weight, sex, smoking status, concomitant medications, and comorbidities).

International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med. 2009 Feb 19;360(8):753-64.

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Warfarin Dose by Genotype

Recommended Warfarin Dose Range (mg/day) by Genotypes CYP2C9 and VKORC1†						
	CYP2C9					
VKORC1	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7	5-7	3-4	3-4	3-4	0.5-2
AG	5-7	3-4	3-4	3-4	0.5-2	0.5-2
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2

†Other clinical factors should be considered when selecting the initial dose within the recommended range (e.g., age, race, body weight, sex, smoking status, concomitant medications, and comorbidities).

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Warfarin Dose by Genotype

Median Stable Warfarin Dose (mg/day) by Genotypes CYP2C9 and VKORC1†						
	CYP2C9					
VKORC1	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	6.1	5.0	4.3	4.1	3.4	2.6
AG	4.5	3.9	3.3	3.2	2.0	1.6
AA	2.9	3.0	2.1	1.6	1.0	2.0

†Other clinical factors should be considered when selecting the initial dose within the recommended range (eg, age, race, body weight, sex, smoking status, concomitant medications, and comorbidities).

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Warfarin Dose by Genotype

90% Prediction Interval on Stable Warfarin Dose (mg/day) by Genotypes CYP2C9 and VKORC1†						
	CYP2C9					
VKORC1	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	3-11	3-10	2-10	1-10	1-6	0.5-4
AG	2-8	2-7	2-7	1-6	1-4	0.5-3
AA	1-5	1-6	1-4.5	1-2.5	0.5-3	0.5-2.5

†Other clinical factors should be considered when selecting the initial dose within the recommended range (eg, age, race, body weight, sex, smoking status, concomitant medications, and comorbidities).

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Confounding

- Subgroup treatment effect estimates can be confounded by covariates (effect modifiers) that are distributed differently in treatment and control arms.
- Combinations of categorical covariates can generate many strata. For binary outcomes,
  - the Cochran-Mantel-Haenszel (CMH) method or conditional logistic regression can be used to adjust odds ratios, risk differences, and risk ratios for stratum effects even when data are sparse within strata.

Agresti A, Hartzel J. Strategies for comparing treatments on a binary response with multi-centre data. Stat Med. 2000 Apr 30;19(8): 1115-39.

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Multi-Way Subgroup Analysis

- Varadhan R, Wang SJ. Standardization for subgroup analysis in randomized controlled trials. *J Biopharm Stat*. 2014;24(1):154-67.

- Pennello G, Rothmann M. Bayesian Subgroup Analysis with Hierarchical Models, in *Biopharmaceutical Applied Statistics Symposium Volume 2: Biostatistical Analysis of Clinical Trials*, Eds. Karl E. Peace, Ding-Geng Chen, Sandeep Menon, Springer, 2018.

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Causal Estimands

Treatment Indicator $X = x\ (0,1)$

Potential Outcomes $\underline{T} = (T_0, T_1)$

Target Condition $\boldsymbol{D = I(T_1 > T_0)}$

$D = 1 =$ subject would live longer on investigational treatment than on control

$D = 0 =$ subject would live longer on control than on investigational treatment

Causal Predictive Values

- $PPV =$ Probability that a test positive subject would live longer on treatment than control.
- $NPV =$ Probability that a test negative subject would live longer on control than treatment.

Simon R. Sensitivity, Specificity, PPV, and NPV for Predictive Biomarkers; *J Natl Cancer Inst* 2015, Jun 24; 107(8). pii: djv153. doi: 10.1093/jnci/djv153.

Summary

- To communicate individualized treatment effects, consider
  - Bayesian shrinkage estimates
  - prediction interval
  - adjustment for confounding
  - multi-way subgroup analysis
  - causal effect estimands
- For brevity, consider reporting only subgroups in which individualized treatment effects vary significantly from overall effect.

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