ACE in Action: The Role of Epidemiology in Law

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About Me

- ACE Ethics and Policy Committee
- ACE Foundation Board of Directors
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Acknowledgements

- **American College of Epidemiology**
  - Melinda Aldrich, M.D., M.P.H.
  - Sandy Sulsky, Ph.D., M.P.H.
  - Endia Crabtree, Ph.D., M.L.A., M.S.
  - Jennifer Salerno, Ph.D.
  - WayWay Hliang, Ph.D., M.S., M.B.B.S.
  - Brian Buff and Katie Hertel
- **Keller Postman LLC**
  - Ashley Keller, J.D., M.B.A.
  - Ashley Barriere, J.D.
  - J.J. Snidow, J.D.
  - Amanda Hunt, J.D.
- **Boston Congress of Public Health**
  - Candice Carpenter, M.D., M.B.A., M.P.H., Ed.M.
  - Circe Le Compte, Sc.D., M.S.
- **Kershaw Talley Barlow, P.C.**
  - Bill Kershaw, J.D.
  - Ian Barlow, J.D., M.P.P.
  - Vinh Le, J.D.

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Agenda

- Primers on Litigation, Complex Litigation, and Expert Work
- Epidemiology in Law 101
  - General Causation
  - Specific Causation
  - Liability and Notice
- Causal Inference in Law
  - Preponderance and Equipoise Legal Standards
  - Bradford Hill v. Newer Models
  - Disproportionality Analysis
  - Triangulation
- Expert Admissibility
  - *Daubert* and Federal Rule of Evidence 702
  - *Daubert* v. *Frye* Jurisdictions
- Recent Trends in Federal Courts
- Q&A

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Litigation and Complex Litigation

- Civil litigation, not criminal litigation
  - Torts = an act or omission that gives rise to harm to another, for which the courts impose liability and relief
- Common law, not civil law
- Adversarial process, each party presents its case
  - Fact discovery
  - Expert discovery
- Trial by jury
- Complex litigation is procedurally, not substantively, more complex.
  - Class action v. mass tort (aka multidistrict litigation or MDL)
  - Coordination motion → Judicial Panel on Multidistrict Litigation or JPML → MDL → leadership appointments → discovery → bellwether selection → bellwether trials → settlement or verdict

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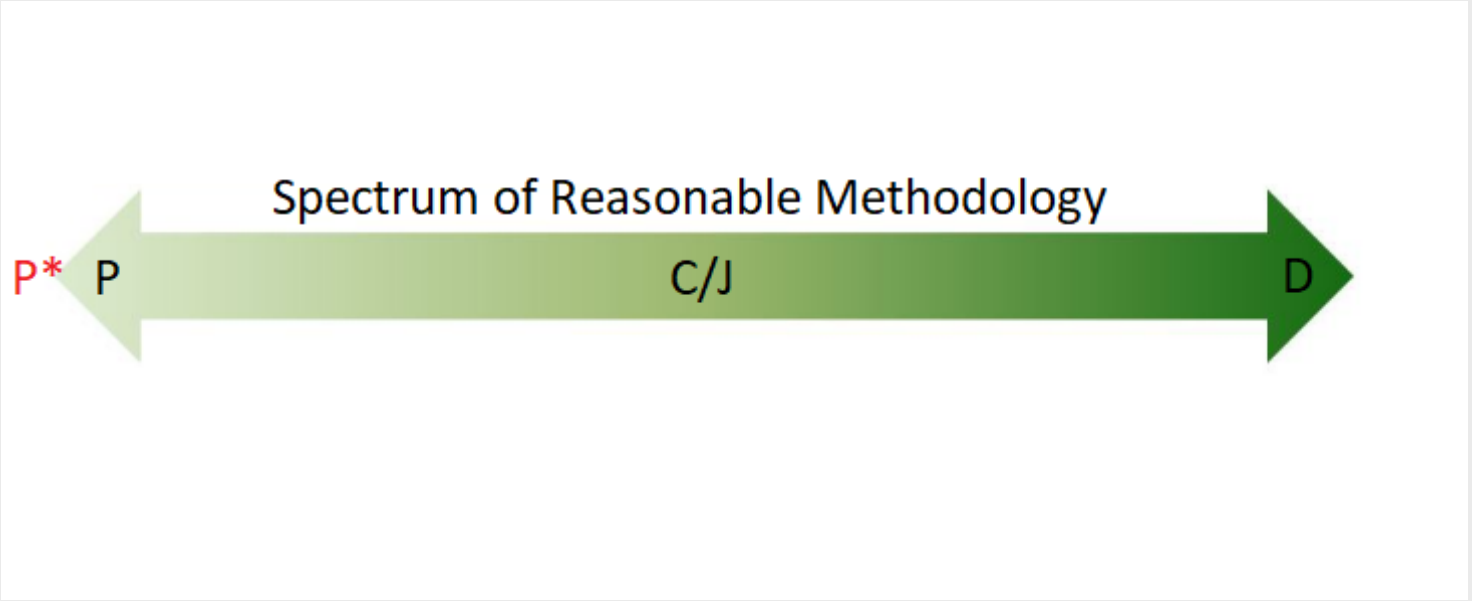
Expert Work

- Expert work is an exercise in advocacy, bounded by the limits of reasonable methodology.
- Interactive process between experts and lawyers



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General v. Specific Causation

- General Causation = a particular exposure (more likely than not/as likely as not) can generally cause or contribute to a particular outcome.
  - Can establish legal causation using epidemiological studies and data if rule out bias, confounding, and chance within legal standards
    - Statistical associations greater than 1.0 are probative, but not dispositive, of general causation.
- Specific Causation = a particular exposure (more likely than not/as likely as not) caused or contributed to a particular outcome in a specific person.
  - Statistical associations greater than 2.0 are probative, but not dispositive, of specific causation.
  - Differential diagnosis
- *See generally* Reference Manual on Scientific Evidence, 3rd Ed. (2011)
  - Study designs
  - Statistical significance
  - Bradford Hill "criteria"
  - Non-epidemiological lines of evidence

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Liability and Notice

- Litigation requires more than finding that an exposure is unsafe or ineffective.
- It also requires liability or culpability on the part of a defendant.
- Potential causes of action:
  - Neglience = duty, breach, causation, and damages
  - Failure to warn
  - Strict products liability
  - Fraud or concealment
  - Intentional, negligent, or strict liability misrepresentation
  - Breach of implied or express warranties of merchantability
- Notice = when a defendant knew or should have known
  - Based on public knowledge
  - Based on internal documents produced in discovery, e.g., PV and literature reviews
  - Based on third party documents, e.g., FDA and CROs
  - Based on expert testimony, e.g., DPA using FAERS, MAUDE, or internal databases

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Preponderance and Equipoise

- Preponderance = more likely than not
- Equipoise = as likely as not
  - Non-SS but elevated point estimate?
  - SS at 90% confidence level?
- How does this translate to statistical significance?
  - Some Circuits have established a gating factor insofar as only SS results are admissible, e.g., 4th
  - Most Circuits, at the judge's discretion, have translated SS at 95% confidence level as meeting preponderance, e.g., 2nd
    - Non-SS results are significantly downgraded or used only for "context" to corroborate SS findings.
  - At least one Circuit has embraced a more progressive reading of statistical significance, i.e., 7th

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Causal Inference Models

- Bradford Hill criteria: strength of association, consistency, specificity, biological gradient or dose-response, biological plausibility, coherence, analogy, temporality, and experiment
  - *See, e.g.,* Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol. 2015 Sep 30;12:14.
- Jurists commonly misapply and misinterpret the BH criteria.
  - In epidemiology:
    - "Viewpoints" to be considered
    - Neither exclusive nor dispositive (*but see* temporality)
    - Consideration of non-SS results
    - Integration with newer technologies and models
  - In law:
    - "Requirements" to be applied in checklist
    - Exclusive and dispositive
      - Arbitrary weighing arising from WoE jurisprudence (not contemplated by BH)
    - General exclusion of non-SS results
    - Slow to adopt newer technologies and models
      - Criticism of epigenetics and omics

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Equipoise Example

- *In re: Camp Lejeune Water Litigation* (No. 7:23-CV-897)
- Manuscript under review: Bove FJ. Evaluation of cancer incidence among Marines and Navy personnel and civilian workers exposed to contaminated drinking water at USMC Base Camp Lejeune: a cohort study. DOI: 10.1101/2024.01.27.24301873.
- Some findings inconsistent with existing CDC (ATSDR) and academic literature
  - Plaintiffs may use to elevate non-presumptive injuries
  - Defense may use to downgrade presumptive injuries
- Recalculations to establish SS at 90% (or lower) confidence level

Injury	Unadjusted 95% HR (per Bove)	Unadjusted RR Recalculation (per WJL)
Esophageal Cancer	1.23 (1.00, 1.51)	1.1972, P = 0.0852
Laryngeal Cancer	1.20 (0.98, 1.48)	1.1768, P = 0.1276
Non-Small Cell Lung Cancer	1.22 (0.96, 1.55)	1.1962, P = 0.1395
Rectal Cancer	1.12 (0.96, 1.30)	1.0996, P = 0.2115
Multiple Myeloma	1.22 (0.99, 1.51)	1.1985, P = 0.0917
Myeloid Cancers (Including Polycythemia Vera)	1.21 (1.00, 1.45)	1.1849, P = 0.0716
Pancreatic Cancer	1.07 (0.91-1.27)	1.0486, P = 0.5683

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Other Common Issues

- Misinterpretation of multiplicity-corrected P-values
  - *See, e.g.,* Lee S, Lee DK. What is the proper way to apply the multiple comparison test? Korean J Anesthesiol. 2018 Oct;71(5):353-360.
- Sibling-controlled analyses v. negative control exposures
  - *See, e.g.,* Frisell T. Invited Commentary: Sibling-Comparison Designs, Are They Worth the Effort? Am J Epidemiol. 2021 May 4;190(5):738-741.
  - *See also* Sjölander A, Zetterqvist J. Confounders, Mediators, or Colliders: What Types of Shared Covariates Does a Sibling Comparison Design Control For? Epidemiology. 2017 Jul;28(4):540-547.
- Across jurisdictions, legal causation is out of step with modern causal inference models by Rothman, VanderWeele, et al.
  - *See, e.g.,* Höfler M. Causal inference based on counterfactuals. BMC Med Res Methodol. 2005 Sep 13;5:28.
  - *See also* Invited Commentary: The Continuing Need for the Sufficient Cause Model Today. Am J Epidemiol. 2017 Jun 1;185(11):1041-1043.

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Disproportionality Analysis

- DPA has been used as notice evidence and supplemental line of causation evidence.
- Advantages: real-world use, captures rare and/or latent AEs
- Disadvantages: spontaneous reporting data, case law against AERs
- Frequentist v. Bayesian approaches, e.g., ROR v. EBGM
- Refine methods by employing bi-level controls, i.e., comparator drug and negative control events
- Seminal literature:
  - Duggirala HJ, Tonning JM, Smith E, et al. Use of data mining at the Food and Drug Administration. J Am Med Inform Assoc. 2016 Mar;23(2):428-34.
  - Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004 Aug;13(8):519-23.
  - Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology. 2011 Jul;141(1):150-6.

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DPA Example

- Context: growing MDL, plausible mechanism, lack of traditional epidemiological data
- Seminal study: Woods RH. Dental Disorders Reported to the FDA Adverse Event Reporting System in Association with Buprenorphine: An Analysis by Ingredient Composition and Route of Administration. Curr Drug Saf. 2024;19(2):261-267.
- Manuscript in preparation by WJL et al.
- Comparison of dental problems (tooth loss, tooth erosion, and dental caries) between oral suboxone (buprenorphine/naloxone) and oral methadone
- ROR = 6.14 (95% CI = 4.93-7.66), EBGM = 1.86 (EB05 = 1.54)

Comparison of Injuries (Tooth Loss, Tooth Erosion, or Dental Caries*) Between Cases (Suboxone) and Controls (All Methadone)**

	Injury (+)	Injury (-)	Row Totals
Suboxone	467	19340	19807
All Methadone	96	24417	24513
Column Totals	563	43757	44320***

*MedDRA Preferred Terms in FAERS
**Includes Methadone (Intensol), Diskets, Methadose, and Dolophine and excludes Ketalgin (a methadone analgesic)
***Excludes adverse events reporting cases and controls as Suspected Products

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Triangulation

- Particularly important in litigations based exclusively on observational data, e.g., Tylenol litigation
- *See, e.g.*, Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. Int J Epidemiol. 2016 Dec 1;45(6):1866-1886.
  - "Triangulation is the practice of obtaining more reliable answers to research questions through integrating results from several different approaches, where each approach has different key sources of potential bias that are unrelated to each other."
  - "With respect to causal questions in aetiological epidemiology, if the results of different approaches all point to the same conclusion, this strengthens confidence in the finding."
  - "This is particularly the case when the key sources of bias of some of the approaches would predict that findings would point in opposite directions if they were due to such biases."

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FRE 702

- [Amended] Rule 702. Testimony by Expert Witnesses
  - A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if the proponent demonstrates to the court that it is more likely than not that:
    - the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
    - the testimony is based on sufficient facts or data;
    - the testimony is the product of reliable principles and methods; and
    - the ~~expert has reliably applied~~ expert's opinion reflects a reliable application of the principles and methods to the facts of the case.

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Daubert v. Merrell Dow Pharmaceuticals Inc., 509 U.S. 579 (1993)

- *Daubert* introduced a five-factor test that requires judges to scrutinize not only the expert's methodology but also the underlying scientific principles.
- Under the *Daubert* standard, the trial court considers the following factors to determine whether the expert's methodology is valid:
  - Whether the technique or theory in question can be, and has been tested;
  - Whether it has been subjected to publication and peer review;
  - Its known or potential error rate;
  - The existence and maintenance of standards controlling its operation; and
  - Whether it has attracted widespread acceptance within a relevant scientific community.

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Frye v. United States, 293 F. 1013 (D.C. Cir. 1923)

- The *Daubert* standard applies in all federal jurisdictions.
- In most state jurisdictions, the *Frye* standard has been superseded by the *Daubert* standard.
  - States still following *Frye* include: CA, IL, MN, MY, PA, WA, and, until recently, NJ.
- *Frye* focuses on only one prong of *Daubert* inquiry: "general acceptance" of expert's methodology, ideas, and/or strategies.
- Practical considerations

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Recent Trends in Federal Courts

- Working with, *inter alia*, the Boston Congress of Public Health to bring light to these issues
  - Forthcoming manuscript entitled "Revisiting *Daubert*: Ensuring Equity and Integrity in the Admissibility of Scientific Testimony" in the *HPHR Journal* (formerly the *Harvard Public Health Review*)
- Courts have, alarmingly and increasingly, applied the peer-review prong of *Daubert* as a *sine qua non*.
- Moreover, courts have circumscribed expert testimony insofar as it cannot exceed express limitations identified in the literature.
  - Discordance between scientific and legal writing wrt limitations, next steps, and causal language
  - Precludes litigation for emergent safety issues for which the science is still developing
- Defense experts can generally rely on industry-sponsored studies not available to plaintiffs' experts.
- The admissibility of scientific testimony should turn on whether the expert reliably applied generally accepted methodologies to analyze the scientific data, not whether they were the first to do so.
- Experts routinely apply established methodologies to underlying scientific data when performing original research in their ordinary practice.

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