Legal and Policy Considerations in the Use of New Approach Methodologies (NAMs) in Chemical Risk Assessment

Focus on "Common Law," Meaning Decisions by Judges

Virtual Webinar
American Society for Cellular and Computational Toxicology,
and European Society for Toxicology in Vitro

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LAW | SCIENCE | POLICY

Overall Message

- Implementing NAMs for chemical risk assessment will be a journey of some years as courts receive cases and learn about NAMs
- Process will be a journey because 1) today, most lawyers and courts know little about molecular science and new methods, and
- 2) court cases move slowly and a single case usually creates only incremental change
  - legislation and regulation, in contrast, sometimes create broad change, relatively suddenly

- Today, most lawyers and judges would deny knowledge of NAMs

- Journey likely will proceed first in federal courts, which usually hear regulatory cases, have smart judges with 2-3 smart young lawyers as "clerks" (researchers/writers), more time to think, and more resources, such as Reference Manual on Scientific Evidence and option to appoint neutral experts

- Federal judges in Washington, DC, inevitably will encounter and learn about NAMs because they handle the vast majority of cases involving federal regulatory agencies
  - involved lawyers may be from anywhere

- Specialty science and law courts are uncommon, but some exist and are successful in applying advanced science; e.g.
  - "vaccine" court – judges of this court hear only lawsuits involving post-vaccinations events
  - patent courts

Outline of Talk

- Overview and resource materials on common law courts and process
- Comparative database search results – big picture evidence of how far law lags science
  - links to handful of opinions where advanced methods mentioned or applied
- Example of "sealed" records from recent case (*Vanda*) in which drug maker sued FDA for requiring extended animal studies for a new drug
- Comments from senior justices on handling with science and law challenges
- Overview of US federal and state legal rules and standards for scientific evidence
- Update of federal court Reference Manual on Scientific Evidence, 3rd Ed
- Selected cases and events that reflect use of methods beyond epidemiology
- Citations to articles on use of genomics in litigation

Overview of Common Law Decisions and Courts

- "Common law" courts and decisions in the US are vestiges of ancient UK common law courts and process
- Each state has its own court system, as does the U.S. government (federal courts)
- Judges issue rulings based on facts shown by evidence, and prior precedents
- Judges and lawyers can cause change to precedents, but it's easier to follow existing precedents, and so change often is resisted
- Trials involve a fact finder "weighing evidence" and then "finding facts"
  - "Finder of fact" may be a judge or a jury
- Common law lawyers and judges are far, far behind regulatory agencies in receiving and understanding scientific evidence

Information About Litigation Processes

- American Bar Association
  - useful overall outline of steps of litigation process

- Expert witness:
  - could be a neutral expert for court
  - or, may "consult" with lawyers on one side or the other, meaning teaching/advising lawyers, without providing testimony – that person is never deposed
  - may become a "retained" expert, who provides a written opinion that explains/interprets facts and then provides an opinion about the meaning of the facts (e.g., mechanism of action for all fibers involves X, Y and Z events)
  - retained expert usually will be questioned under oath before trial in a "deposition"
  - opposing party may move to bar expert or opinions as:
  - 1) not qualified (lack of training/knowledge) or
  - 2) may seek to bar expert opinion as not admissible under applicable state or federal legal standard for admission of scientific evidence (*Daubert* or *Frye* – discussed infra)

- Non-US courts and arbitrators tend to expect more candor and less advocacy from experts
  - See generally A Brief History of the Expert Witness

- Online tools for access to briefs and other papers generated during litigation process

  - see Supplemental Materials for general principles and links

Big Picture Evidence on Disparities Between Courts and Scientists – Comparative Results of Word Searches of All U.S. Opinions v. PubMed

- Ran boolean searches in national database (Lexis) of all published opinions from all federal and state courts
- Results for the following searches:

  - "new analytic methods" – 0 hits in Lexis
    - PubMed – 46 hits

  - "in vitro assay" - 19 hits in Lexis, but only 1 involved chemicals/product risks/harms (2010 state lawsuit against big tobacco to recover money spent on tobacco induced diseases)
    - PubMed – 9,029 hits

  - "in silico" – 10 hits in Lexis – 2 relevant to risk assessment and toxicology; most were patent cases
    - PubMed – 308,192

  - "in silico analysis" – 0 hits in Lexis
    - PubMed – 123,950

  - "prediction model" – 67 hits in Lexis
    - PubMed - 553,152 hits

  - "exposomics" – 0 hits in Lexis
    - PubMed – 993 hits

More Word Searches of All US Caselaw v. PubMed

- More results:
  - "mechanism of action" – 406 hits in Lexis
    - PubMed – 76,583 hits
  - "gene expression" – 174 hits in Lexis
    - PubMed – 1,517,535
  - "gene expression regulation" – 3 hits in Lexis – all "vaccine court" opinions
    - E.g. Nunez v. Sec'y of HHS, 2019 U.S. Claims Lexis 664
    - PubMed – 1,132,874 hits
  - "transcriptomics" – 2 hits in Lexis (1 vaccine court case)
    - PubMed 111,818 hits
  - "metabolomics" – 4 hits in Lexis
    - PubMed 49,102 hits

More Word Searches of All US Caselaw v. PubMed

- More results:
  - "bioinformatics" - 85 hits in Lexis
    - PubMed – 372,038 hits
  - "Hela cells" – 6 hits in Lexis, with 2 pertinent
    - PubMed – 113,497
    - *Sarkees v. E. I. DuPont de Nemours & Co.*, 2020 U.S. Dist. LEXIS 32070, 2020 WL 906331 (lawsuit involving personal injuries alleged to arise out of workplace chemical exposure)
    - *J.M. v. Sec'y of HHS*, 2017 U.S. Claims LEXIS 2026 (lawsuits alleging autism arose from vaccination)
  - "

More Word Searches of All US Caselaw v. PubMed

- More results:
  - "epigenetics" - 19 hits in Lexis
    - PubMed - 106,686 hits
    - Of the 19 hits in Lexis, 8 were vaccine court opinions (all involved advanced scientific evidence)
    - 2 cases involved personal injuries
      - Hysell v. Raleigh Gen. Hosp., 2020 U.S. Dist. LEXIS 180646
      - Spedale v. Constellation Pharm., Inc., 2019 U.S. Dist. LEXIS 139010, 2019 WL 3858901
    - One case involved product liability/risk assessment of a drug known as Actos, alleged to cause bladder cancers in humans
    - Epigenetic mechanism testimony by a UK researcher was key – issues included whether epigenetic factors could drive manifestation of a cancer in rodents in less than 1 year, thereby validating animal study
      - Allen v. Takeda Pharms. North America, Inc. (In re Actos® (Pioglitazone) Prods. Liab. Litig.),

Confidentiality Example from Recent Case In Which Drug Maker Sued FDA For Requiring Extended Animal Studies

- Found one case in which drug maker sued FDA for requiring extended animal studies before allowing extended public trials for experimental drugs

- Vanda Pharm., Inc. v. FDA, 436 F. Supp. 3d 256, 2020 U.S. Dist. LEXIS 16623, 2020 WL 516561
  - Opinion by respected federal judge with broad experience

- Note secrecy in litigation is fairly common – filings under seal can block access to court papers

  - E.g. public version of brief filed by FDA is NOT the entire brief filed with the court

- Lack of full transparency slows change and progress

Commentaries from Senior Justices on Challenges for Courts Hearing Cases with Scientific Issues

- Some influential senior justices are keenly aware that most judges are lousy at science, and that courts face increasing volume of scientific issues

- They understand/appreciate the major differences between scientific methods and processes, and the adversary system of litigation

  - adversary process in litigation – EU in general is less extreme/more rational than US

- Lord David Neuberger – former Chief Justice of UK Supreme Court
  - raised in science focused family
  - undergraduate degree in chemistry

- His 2015 talk: Science and Law: Contrasts and Cooperation

- His 2016 Nature article: Stop needless dispute of science in the courts
  - "Primers on various scientific topics could be used across trials to avoid wasting time on debating basic points, argues David Neuberger."

- Related commentary in Nature by David Baltimore, and a science focused lawyer and judge - David Tatel (D.C Circuit) - "Science primers in the courtroom"

Comments from Justice Breyer of SCOTUS - GE v. Joiner, 522 U.S. 136 (1997)

- Comments from Justice Breyer of SCOTUS (US Supreme Court) on challenges faced in cases involving disputes between science experts, and the need for more agreements and impartial expert advisors

- **Judges act as "gatekeepers" for scientific evidence**: "The Court's opinion, which I join, emphasizes Daubert's statement that a trial judge, acting as "gatekeeper," must "'ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable.'" Ante, at 5 (quoting Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 589."

- **The gatekeeper roles means judges sometimes are reading and weighing scientific papers**: "This requirement will sometimes ask judges to make subtle and sophisticated determinations about scientific methodology and its relation to the conclusions an expert witness seeks to offer -- particularly when a case arises in an area where the science itself is tentative or uncertain, or where testimony about general risk levels in human beings or animals is offered to prove individual causation."

- **Use more neutral experts is the advice from a "friend of the court" brief**: "Yet, as amici have pointed out, judges are not scientists and do not have the scientific training that can facilitate the making of such decisions. In the present case, the New England Journal of Medicine has filed an amici brief "in support of neither petitioners nor respondents" in which the Journal writes:

  "[A] judge could better fulfill this gatekeeper function if he or she had help from scientists. Judges should be strongly encouraged to make greater use of their inherent authority . . . to appoint experts . . . . Reputable experts could be recommended to courts by established scientific organizations, such as the National Academy of Sciences or the American Association for the Advancement of Science."

Admission of Scientific Evidence in Court - "Frye" Standard - Old Federal Standard Still Used in Some States

- Old federal court standard was the "general acceptance" standard, also known as the Frye standard because it arose in Frye case in 1923 involving validity of use of systolic blood pressure as a lie detector test
  - Wikipedia – cogent lay summary with links

- Key quote: "Just when a scientific principle or discovery crosses the line between the experimental and demonstrable stages is difficult to define. Somewhere in this twilight zone the evidential force of the principle must be recognized, and while the courts will go a long way in admitting expert testimony deduced from a well-recognized scientific principle or discovery, the thing from which the deduction is made must be sufficiently established to have gained general acceptance in the particular field in which it belongs."

- Frye standard is still used in many states, albeit sometimes with a new name and more recent refinements or nuances created by the courts or legislature of that state
  - https://www.expertinstitute.com/resources/insights/daubert-v-frye-a-state-by-state-comparison/

Big Picture Perspective on Science and Law in the U.S - Agencies, Science and Law

- 1960s in the US – science started to matter more, driven by:
  - Prominent media pictures of literally burning rivers, "Love Canal," environmental "activists," Vietnam war, and race to the moon
  - President Kennedy and "activist" groups touted Rachel Carson's 1962 book, "Silent Spring"

- Over the years, Congress and court systems became interested in more repeatable process-oriented methods

- 1962 – major FDA reform through a new federal statute – statute understood to required double blind clinical trials instead of "snake oil"
  - but many products were "grandfathered" for continued sales

- 1970 - EPA and OSHA - created by Congress during term of President Nixon
  - OSHA history
  - EPA history

Current Federal Rule of Evidence 702 and "Daubert Standard"

- 1973 – federal courts developed, implemented and published "rules of evidence" to decrease dependence on ad hoc decisions

- Federal Rule of Evidence 702 changed the federal standard for admitting scientific evidence, as explained in 1993 in the first of the "Daubert trilogy" of cases that wer issued over a 6 year period (1993-1999)

  - Wikipedia - Cogent lay summary with extensive hyperlinks

- For more detailed, lawyerly histories, see:
  - David Bernstein, Frye, Frye, Again: The Past, Present, and Future of the General Acceptance Test
  - Or see this page at Cornell Legal Information Institute

Daubert's 5 Factors for Deciding if Scientific Evidence is Admissible

- Most everyone agrees on the key big picture rules drawn from the Daubert trilogy of cases; the art and challenge will be applying the criteria to NAMs

- Cornell provides a cogent summary:

- "Daubert factors that may be considered in determining whether the methodology is valid are:
- (1) whether the theory or technique in question can be and has been tested;
- (2) whether it has been subjected to peer review and publication;
- (3) its known or potential error rate;
- (4) the existence and maintenance of standards controlling its operation; and
- (5) whether it has attracted widespread acceptance within a relevant scientific community."

Update of Reference Manual on Scientific Evidence, 3rd Ed

- The Reference Manual on Scientific Evidence, 3rd Ed. is by far the most respected and neutral source to educate federal judges on scientific evidence
  - also used by most science focused lawyers and savvy state court judges

- A fourth edition update process is underway with collaboration between National Academies of Science and administrative arm of US federal courts:

  "Emerging Areas of Science, Engineering, and Medicine for the Courts: Identifying Chapters for a Fourth Edition of The Reference Manual on Scientific Evidence - Virtual Workshop

- Professor Marchant recently spoke during the 3rd workshop in the update proces;
  - full written and video materials online here

- Update process and comments also described in summary blog post in February 2021 by a science and statistics focused lawyer – Nathan A. Schachtman

Professor Marchant, ASU – Science and Law Leaders

- Professor Marchant – long and multidisciplinary view of intersections between science and law
  - in my view, the KOL in the US for science and law intersections

- Annual ASU "GET" conference –
  - Governance of Emerging Technologies and Science
  - https://events.asucollegeoflaw.com/gets/
  - Abstracts due August 2, 2021
  - Conference – October 29-30

- Mark A. Rothstein, Yu Cai, and Gary E. Marchant, et al., *The Ghost in our Genes: Legal and Ethical Implications of Epigenetics*, 19-1 Health Matrix Clevel., 1-62 (2009)(open access at PubMed)

- Gary E. Marchant, Genetic Data in Toxic Tort Litigation, The Brief, Winter 2016 (ABA Tort, Trial & Insurance Section) https://www.scribd.com/document/415652109/Marchant-Genetics-in-Toxic-Tort-Litigation-2016

Other Articles - Use of Genomics in Litigation

- Use of genomic analyses is perhaps the most advanced molecular science currently in cases involving claims that chemical exposures caused harms. See

- Scott Elder, Anderson Kemp, *Genomics in the Courtroom: The Current Landscape of DNA Technology in Criminal and Civil Litigation* (IADC Jan. 19, 2021) https://www.iadclaw.org/assets/1/6/Genetic_Paper_2.pdf
- James M. Beck, *More on Genetic Testing Orders, Drug & Device Law Blog (Feb. 20, 2020)* *https://www.druganddevicelawblog.com/2020/02/more-on-genetic-testing-orders.html)*
- Andrew Gendron & Thomas M. Morgan, M.D., *Incomplete Penetrance: Whole-Exome Sequencing and Federal Courts*, FOR THE DEFENSE, January 2019, at 23 http://digitaleditions.walsworthprintgroup.com/publication/?m=55594&i=557674&p=24
- Susan E. Brice & Dr. Whitney V. Christian, *The Use of Genetic Evidence to Defend Against Toxic Tort Claims—Part I-III*, Intell. Prop. & Tech. L.J. (2017) https://www.bryancave.com/images/content/9/9/v2/99117/IP-Reprint-Article-complete.pdf
- Christine R. M. Kain & Christin Jaye Eaton, *The Double-Edged Sword: Genomic Profiling in Drug and Chemical Litigation*, Faegre Baker Daniels (2015) https://www.faegredrinker.com/en/insights/publications/2015/5/the-doubleedged-sword-genomic-profiling-in-drug-and-chemical-litigation

NAMs Will Used:
Examples of Molecular Science Driving Notable Changes in Law

Examples of Milestone Common Law Events

- In 1993, the seminal *Daubert* ruling arose in a Bendectin case; the defense sought to exclude molecular evidence not backed by epidemiology w/ relative risk of 2.0

- 1994 – first Federal Reference Manual on Scientific Evidence generally embraces 2.0 standard – see Schachtman blog summary

- 1997 – Havner ruling – Texas Supreme Court embraces 2.0 increased risk standard as the minimum a plaintiff must show to recover money damages; epidemiology ascendant and *Frye* type standards in use in many states
  - See Bryant and Reinert, The Legal System's use of Epidemiology

- 2011 - epidemiology perhaps at its apex in Texas and some other states
  - "The Texas Supreme Court recently held that plaintiffs seeking to prove general causation with epidemiological evidence must produce two independent studies demonstrating that subjects who used the product at issue under circumstances substantially similar to those encountered by the plaintiff doubled their the risk of injury."
  - See Texas Supreme Court Imposes Strict Standards Governing Use of Epidemiological Evidence in Proving Causation

2011 - Evolution of Rule 702 and *Daubert* Standard

- Daubert and Rule 702 of the Federal Rules of Evidence evolved
- 2011 amendments to Rule 702 are notable

- **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:
- (a) 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;
- (b) the testimony is based on sufficient facts or data;
- (c) the testimony is the product of reliable principles and methods; and
- (d) the expert has reliably applied the principles and methods to the facts of the case.
  - See text and history of changes at
  - https://www.law.cornell.edu/rules/fre/rule_702

More Examples of Milestone Events

- And so, meanwhile, in federal courts using Rule 702 and *Daubert* standard:

- In 2011, in *Milward v. Acuity Specialty Products,* 639 F.3d 11 (1st Cir. 2011), one federal court of appeals held a trial judge improperly excluded molecular evidence to show leukemia caused by translocations of chromosomes 17 and 15 in case involving a specific form of leukemia (APL) attributed to benzene

  - Major defense groups asked SCOTUS to review and reverse but failed. See SCOTUS blog for briefs.
  - http://www.scotusblog.com/case-files/cases/united-states-steel-corp-v-milward/

- In 2013, another federal court of appeals also reversed a trial judge who excluded molecular evidence in a benzene case

  - *Schultz v. Akzo Nobel Paints*, *721 F.3d 426* (7th Cir. 2013).

- Since then, cases go both ways, often depending on the trial judges view of the appropriate intensity of "gatekeeping"

Prediction of Understanding of Mechanisms of Action

- There are common law precedents that anticipated the arrival of vastly improved molecular science and the ability to see and explain mechanisms of action
- The *Daubert* ruling by SCOTUS was sent back to a lower court for further proceedings
- There, in 1995, on remand to the 9th Circuit Court of Appeals, Judge Kozinski wrote:
  - "But scientists simply do not know how teratogens (chemicals known to cause limb reduction defects) do their damage: They cannot reconstruct the biological chain of events that leads from an expectants mother's ingestion of a teratogenic substance to the stunted development of a baby's limbs. Nor do they know what it is about teratogens that causes them to have this effect.
  - No doubt, someday we will have this knowledge, and then we will be able to tell precisely whether and how Bendectin (or any other suspected teratogen) interferes with limb development…"

See Daubert v. Merrell Dow Pharmaceuticals, 43 F.3d 1311 (9th Cir. 1995)

More Factors

- Courts are going to start seeing medical analyses performed by AI and algorithms
- FDA is implementing real world data and evidence standards, which will resonate with courts and judges
- 21st Century Cures Act also offers other possible inroads to reduce dependence on typical methods (see Supp. materials)
- Debates about alternatives to .05 confidence levels are filtering into legal thinking
- Rare disease groups are lobbying hard for new drugs based on biomarkers, small "n" trials, and trials with less than fully objective endpoints (see Supp. Materials)
- Update of Federal Reference Manual on Scientific Evidence will be very important, over time

Conclusion

- History shows that science and law changes occur, but take time
- Federal judges inevitably will see NAMs as art of evidence in regulatory challenge cases such as *Vanda*
- Vaccine court opinions show that science and law can be done well
- Implementing NAMs can be done, but it will be a journey
- More multidisciplinary science and law programs are underway and will help
  - ASU is by far the leader in innovative multidisciplinary thinking as to science and law intersections
  - University of Illinois and others are playing catch up

Questions or follow-up?

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Background and Disclosures

- Trial lawyer in U.S. for 35+ years with strong lay knowledge of genomics, but no formal training
- Since 2016, principal in an alliance with several Ph.D.s in national consulting group (ToxicoGenomica.com) focused on the use of genomic analyses to assess causation of cancers in product liability lawsuits involving asbestos, benzene, radiation and other substances
- Service as pro bono director of not for profit focused on legal rights of persons with cancer (TriageCancer.org), and pro bono legal advocacy against insurance payors regarding access to advanced genomic diagnostics and therapies for persons with cancer, and access to continuous glucose monitors for persons with type 1 diabetes
- 1984 - 2011, commercial litigation and mass tort trial lawyer working as partner at national law firms involved in cases for large corporations involved in manufacturing (no work for insurers)
  - numerous cases taken to final judgment, including jury verdict and final judgements in federal and state cases, arbitration cases and asbestos-related chapter 11 cases
  - final judgements involved issues in excess of $1 billion
- Since 2011, practicing lawyer at my own law firm - LSP Group LLC
- GlobalTort blog on law and science intersections

GlobalTort Blog

- GlobalTort blog is located at www.GlobalTort.com
- Focus is on intersections between science, law, and other disciplines
- Numerous articles on asbestos and other toxic tort litigation
- Frequency of posts is lagging these days

Access to Legal Papers from Lawsuits

- Lawsuits can produce interesting rulings and legal papers presenting the issues
- Most papers from U.S. federal court lawsuits are available – for modest fees – via PACER
- Court papers often also available via Lexis and Westlaw databases
- Most regulatory litigation in U.S. in D.C. Circuit Court of Appeals
  - not much information available for free online from D.C . Circuit
  - other federal circuit courts provide more free information – e.g. 7th Circuit
    - United States v. Dellinger, 472 F.2d 340 (7th Cir. 1972)
- State supreme and intermediate appellate opinions generally available
  - Legal papers (briefs) available in a few states
  - Increasing free access services for opinions and briefs – see lists and links here
- State trial court papers are usually very hard to obtain for most states
  - most courts lack funds for well organized online systems
  - massive needs and size drive lead to online access for courts in some large metro areas

21st Century Cures Act – An Avenue to Import Genetic and Other Molecular Data into FDA and Tort System Decision Making?

21st Century Cures Act

- The 21st Century Cures Act holds implications for use of genetic and other molecular information for decision making by FDA, and for product liability litigation

- Sections of the Act expand the categories of data and information FDA must or can utilize in decision making, and open more paths for use of genetic and other molecular data

Expansions in Approval Criteria - 21st Century Cures Act

- Examples of the Act's expansions or/future changes in FDA approval criteria
- Section 3012 allows more use of past data for new uses of previously approved rare disease drugs that are genetically targeted or variant protein targeted drugs
- Sections 3033 – 3036 specifically address "regenerative medicine" including stem cell therapies and gene alteration therapies, and require consultation with stakeholders on data and evidence standards for this category
- Section 3021 focuses on clinical trial design and requires additional guidance from FDA on "adaptive designs" and "novel statistical modeling" for new drug applications
- Sections 3001-3002 allow use of qualitative "patient experience" data; this may include groups of persons in a basket or umbrella clinical trial based on an inherited or somatic mutations

More Companion Diagnostic Tools - 21st Century Cures Act

- The Act also expands the process for creating "companion diagnostics" that can be used to identify a gene or biomarker that identifies a subset of persons who may benefit more than others
- **Sec. 3011 Qualification of Drug Development Tools**
- "For example, a drug intended to treat a rare genetic condition would benefit from a test that would validate the presence of that genetic marker in a patient-a so-called biomarker
- See http://www.raps.org/regulatoryDetail.aspx?id=9809
- Section 3011 "actually establishes a review pathway at FDA for such biomarkers and other development tools that can be used to help shorten drug development times, aiming to help reduce the high failure rate in drug development.
- Under this section, FDA would be required to make publicly available on at least a biannual basis on its website, the following:
- All drug development tools qualified, including all surrogate endpoints which were the basis of approval or licensure (as applicable) of a drug or biological product;"

"Real World Evidence" Pushed More into the Mix - 21st Century Cures Act

- **"Sec. 3022 Real World Evidence**
- This section requires FDA to evaluate the use of "real world evidence" to help support the approval of a new indication for a previously approved drug and to help support or satisfy post-approval study requirements."

- What is "real world evidence" ?

- Section 3022 states: ‘‘(b) REAL WORLD EVIDENCE DEFINED.—In this section, the term ‘real world evidence’ means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.

- Standard appears to include privately compiled data, such as data compiled by hospitals using genetic data in treating patients, as well as data compiled by drug companies or companies that perform in genetic testing or other “forms” of “omic” analysis

"Real World Evidence" Pushed into the Mix - 21st Century Cures Act

- "Real World Data" is to be defined over the next two years, with a draft to be provided at that point.
- In a summer 2016 FDA guidance document, at 4, FDA provided some insights into its thinking on what is "real world evidence" http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM513027.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery

- "Real-World Data (RWD) is data collected from sources outside of traditional clinical trials. These sources may include large simple trials, or pragmatic clinical trials, prospective observational or registry studies, retrospective database studies, case reports, administrative and healthcare claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries (e.g., device, procedural, or disease registries). The data is typically derived from electronic systems used in health care delivery, data contained within medical devices, and/or in tracking patient experience during care, including in home-use settings."

There are Practical Reasons Why We See New Clinical Trial Designs

- FDA approval process has changed over the years

- Major statutory changes to FDA in 1962 and 1963 produced focus around three stage randomized clinical trials to prove "efficacy"
  - History up to 2008 at: http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm
- Arguments about use of placebo arose, including through Helsinki human rights accords
  - "In 1964, the topic of ethics in clinical trials was a major issue during the 18th World Medical Association General Assembly in Helsinki, Finland. In June of that year, the WMA Declaration of Helsinki was adopted with the subtitle Ethical Principles for Medical Research Involving Human Species."
  - http://rxethics.org/Niemiec%20Edited%20PDF.pdf
- Today, arguments and ethical debates about use of placebo are even more in the forefront of trial design. E.g.
  - Gupta U, Verma M. Placebo in clinical trials. *Perspectives in Clinical Research*. 2013;4(1):49-52. doi:10.4103/2229-3485.106383

Reading on Eteplirsen and FDA

- A letter written by FDA Commissioner Robert Califf laid out in remarkably frank terms the heated internal debate at the agency, which may have led to the departure of one key scientist who was opposed to approving the drug.
  - http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf

- "It is inevitable that in some of these situations, highly qualified experts will disagree," Califf wrote, and he praised Dr. Janet Woodcock, the head of the FDA division that reviews new drugs, who made the call "in the face of profound changes in science and social interactions related to drugs.""

- http://www.npr.org/sections/health-shots/2016/09/24/495174472/controversy-continues-over-muscular-dystrophy-drug-despite-fda-approval