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TIMELINE: RECENT HISTORY OF HUMAN SUBJECTS RESEARCH

1947: Nuremberg Code was drafted. Comprised of ten principles for the conduct of research involving human subjects, the Nuremberg Code included the fundamental principle that the voluntary consent of the human subject is essential.

1964: Declaration of Helsinki was adopted by the World Medical Association, providing guidelines for physicians conducting biomedical research on human subjects.

1966: Public Health Service developed a policy requiring peer review of all research that held a possible risk to human subjects.

1966: Dr. Henry Beecher published a landmark survey of 22 questionable research studies.

1972: Tuskegee Syphilis Study was exposed, in which 400 African American men with syphilis were left untreated to try to gain a scientific understanding of progression of the disease (study began in the 1930s).

1974: National Research Act was enacted to regulate the protection of human research subjects through Institutional Review Boards ("IRB"). IRBs, rather than investigators, became responsible for determining whether potential research subjects were "at risk" and, if so, whether the risks outweigh the benefits. The Act led to the establishment of the Office of Protection from Research Risks ("OPRR") and the National Commission for the Protection of Human Subjects, which were charged with examining problems in humans subjects research and suggesting guidelines for protection of human subjects.

1978: The National Commission for the Protection of Human Subjects released a draft of the Belmont Report, which laid out the ethical principles guiding research involving human subjects.

1981: The Department of Health and Human Services (then the Department of Health, Education and Welfare) revised the regulations codified at 45 C.F.R. §46, which regulates the protection of human research subjects.

1983: Subpart D was added to the 45 C.F.R. §46 to provide additional protections for children participating in research.

1983: FDA issued human subjects regulations at 21 C.F.R. §§ 50 and 56.

1991: Regulations codified at 45 C.F.R. §46 were adopted by fifteen federal agencies and became known as the Common Rule; FDA adapted its human subjects regulations to comport with Common Rule.

Jan. 8, 1997: IRB at University of Oklahoma Health Sciences Center - Tulsa ("UOHSC-T") approved protocol for Phase I study of melanoma cancer vaccine ("Melanoma Vaccine Study").

1998: Department of Health and Human Services ("DHHS") Office of Inspector ("OIG") General report, *Institutional Review Boards: A Time for Reform*, concluded that "the effectiveness of IRBs is in jeopardy" and delineated six challenges for IRBs:

(1) Major changes in the research environment;
(2) Too much to review, too quickly, with too little expertise;
(3) Minimal continuing review of approved research;
(4) Conflicts that threaten independence;
(5) Little training for investigators and board members; and
(6) Not giving sufficient emphasis to evaluating effectiveness.

September 17, 1999: Jesse Gelsinger, an 18-year old with a mild form of ornithine transcarbamylase, a genetic liver disorder ("OTC"), died while participating in a Phase I clinical research study for the treatment of OTC ("OTC Study") led by Dr. Michael McGee at the University of Pennsylvania's Institute for Human Gene Therapy.

April 2000: OIG released a status report finding some improvement in the enforcement of federal regulations, but also finding that most of the Inspector General's 1998 recommendations regarding human subjects research protections had not been implemented.

April 3, 2000: Study participants in Melanoma Vaccine Study at UOHSC-T informed that study was being closed due to an insufficient amount of vaccine being available.

June 12, 2000: Cherlynn Mathias, nurse coordinator of Melanoma Vaccine Study at UOHSC-T brought her concerns about the Study to attention of Office for Human Research Protections ("OHRP").

June 29, 2000: OHRP suspended all federally funded research at UOHSC-T following finding that "IRB failed to conduct substantive and meaningful continuing review" of Melanoma Vaccine Study.

September 18, 2000: Gelsinger family filed suit against University of Pennsylvania, lead investigator, sponsor, former medical school Dean and bioethicist.

November 3, 2000: Undisclosed settlement reached in *Gelsinger* case; claims against former medical school Dean and bioethicist dismissed.

January 29, 2001: Numerous Melanoma Vaccine Study participants and estates filed complaint (*Robertson v. McGee*) against lead investigator, individual IRB members, the IRB chairman, the IRB bioethics consultant, the IRB supervisor, the University President, the former Dean of the College of Medicine, the Chairman of the Department of Surgery and five co-sponsoring institutions.

February 8, 2001: Trial court dismissed *Grimes v. Kennedy Krieger Institute* case on summary judgment, holding that a corporation conducting a non-therapeutic scientific

study of lead paint abatement ("Lead Paint Study") did not have a duty to warn minor volunteer participants and/or their legal guardians regarding dangers present when the researcher had knowledge of the potential for harm and the subjects were unaware of the danger.

March 26, 2001: William Wright, Sr., both individually and in his capacity as personal representative of the estate of Becky Wright, filed a class action suit on behalf of participants in Protocol 126, the purported goal of which was to prevent an immune system reaction known as graft-versus-host disease ("GVHD") in recipients of bone marrow transplants ("GVHD Study"), against the Fred Hutchinson Cancer Research Center, four physicians and a corporation involved in the GVHD Study.

March 30, 2001: Complaint amended in Melanoma Vaccine Study case (*Robertson v. McGee*) to include additional plaintiffs.

May 4, 2001: Ellen Roche, a healthy 24-year old, volunteered to participate in an asthma study directed by Dr. Alkis Togias of The Johns Hopkins Bayview Medical Center ("JHBMC") (the "Asthma Study"). Shortly after commencing her participation, Roche began complaining of shortness of breath and flu-like systems that ultimately escalated to adult respiratory distress.

May 18, 2001: Allan Berman, both individually and in his capacity as personal representative of the estate of Kathryn Hamilton, who allegedly died as a result of her participation in a chemotherapy trial known as Protocol 681 ("Chemotherapy Study"), filed suit against the Fred Hutchinson Cancer Research Center and four physicians involved in the Chemotherapy Study.

June 2, 2001: Following her participation in the JHBMC Asthma Study, Roche dies of progressive hypotension and multiorgan failure.

August 16, 2001: Appellate Court filed its opinion in the *Grimes* Lead Paint Study case, reinstating the case and holding that parents may not consent to non-therapeutic research that poses a risk to a child.

September 17, 2001: KKI requested that the Maryland Court of Appeals modify its decision in the *Grimes* Lead Paint Study case and lift the ban on parental consent for non-therapeutic research that poses "any risk" to children, arguing that all research poses at least some risk to participants.

October 11, 2001: Maryland appellate court denied motion of KKI to lift the August 16, 2001 ban on parental consent for non-therapeutic research.

CASE SUMMARIES

***Jesse Gelsinger v. Regents of the University of Pennsylvania*:** Jesse Gelsinger, an 18-year-old male, died on September 17, 1999 while participating in research study conducted by UPenn's Institute for Human Gene Therapy ("IHGT"). The study in which Gelsinger participated was a Phase I clinical trial testing a new approach to the treatment of ornithine transcarbamylase deficiency ("OTC"), a rare metabolic disorder (the "OTC Study"). Gelsinger suffered from mild case of OTC. His death was not from disorder, but from multiple organ system failure triggered by the virus used to carry new genetic material into his system. Researchers and other named defendants held the patent on the viral vector used in the study. The Gelsinger family filed suit September 18, 2000 seeking actual and punitive damages from the University, the lead investigator, the sponsor, the former medical school dean and the bioethicist involved in the OTC Trial. No IRB members were named in suit. An undisclosed settlement was reached in the case on November 3, 2000.

***Robertson v. McGee*:** In early 1997, the University of Oklahoma Health Sciences Center - Tulsa ("UOHSC-T") IRB approved a protocol for a Phase I study of melanoma cancer vaccine ("Melanoma Vaccine Study"). Cherlynn Mathias ("Mathias"), a nurse coordinator assigned to the Melanoma Vaccine Study, served as a "whistleblower" when her repeated attempts to address issues of quality control, patient care, reporting of adverse events, and adherence to protocol were not internally addressed. An outside consultant produced a highly critical report of the Melanoma Vaccine Study, finding violations of good manufacturing practice, good clinical practice and FDA requirements. Three years later, after the negative audit report, the study's lead investigator advised study participants that the trial was being closed due to an inadequate supply of the vaccine. The subjects and the FDA were not informed of the safety concerns raised during the external audit. Mathias therefore brought her concerns to the Office for Human Research Protections ("OHRP") in June 2000. Following an investigation, OHRP closed down all clinical research at OUHSC-T, finding that review procedures at the University were severely deficient. In January 2001 a complaint was filed against the lead investigator, **individual IRB members**, the IRB Chairman, the IRB bioethics consultant, the IRB supervisor, the University President, the former Dean of the College of Medicine, the Chairman of the Department of Surgery and five co-sponsoring institutions. The case is currently pending.

***Wright v. Fred Hutchinson Cancer Research Center*:** Seattle's Fred Hutchinson Cancer Research Center conducted a study designed to prevent an immune system reaction known as graft versus host disease ("GVHD Study"). In early 1981, the GVHD Study was first presented to the Center's IRB. IRB members expressed concern about the protocol, including the appropriateness of a jump from trials with mice to human trials. Despite these concerns, the IRB approved the protocol in December 1981. In 1985, Becky Wright went to the Center to undergo a bone marrow transplant. Within weeks after receiving her transplant, Becky Wright died, allegedly as a result of the GVHD Study rather than her underlying disease. On March 26, 2001, a class action suit was filed by William Wright against the Center, four physicians and a co-sponsoring institution involved in the GVHD Study. Neither the IRB nor any of its members was named as a defendant in the suit. The case is currently pending.

Ellen Roche: Ellen Roche, a 24-year-old technician in the Johns Hopkins University ("JHU") Asthma and Allergy Center, was recruited as a healthy volunteer in an NIH-funded study of asthma directed by Dr. Alkis Togias ("Asthma Study"). The purpose of the study was to understand how the lungs of healthy people protect against asthma attacks. Roche consented to participate in the study in mid-April 2001. In early May, she took part in the Asthma Study protocol. Almost immediately after her participation, Roche began complaining of shortness of breath and flu-like symptoms, which ultimately progressed to the stage of adult respiratory distress. On June 2, 2001, Roche died of progressive hypotension and multiorgan failure. A subsequent investigation by OHRP cited 31 deficiencies in the JHU IRB procedure and led to the suspension of JHU's MPA, resulting in a three-day shut down of all federally-funded research projects at JHU and its affiliated institutions. A lawsuit was never brought related to Roche's death. In mid-October 2001, JHU reached an undisclosed financial settlement with the Roche family that eliminated the possibility of a lawsuit against JHU and the Asthma Study's lead investigator.

***Berman v. Fred Hutchinson Cancer Research Center*:** Seattle's Fred Hutchinson Cancer Research Center conducted a study designed to find the maximum amount of chemotherapy that patients could tolerate ("Chemotherapy Study"). Under the study protocol, a chemotherapy dose was tested on four women and then was escalated if none of the women died or suffered life-threatening complications from the dosage. If two women died or suffered serious complications, the protocol called for the researchers to reduce the dose or cease the clinical trial. Plaintiff's decedent, Kathryn Hamilton, participated in the Chemotherapy Study in 1985, and allegedly died as a result of the clinical protocol. On May 18, 2001, a lawsuit was filed against the Center and four doctors involved in the clinical protocol. Neither the IRB nor any of its members was named as a defendant. The case is currently pending.

***Grimes v. Kennedy Krieger Institute*:** Researchers at the Kennedy Krieger Institute ("KKI"), an affiliate of JHU, designed a study to find cheaper techniques for removing lead paint so that Baltimore landlords who had complained about high abatement costs would not abandon many of the city's signature row houses in low-income neighborhoods ("Lead Paint Study"). Landlords participating in the study were encouraged by researchers to rent to families with small children, as children are more susceptible to lead poisoning. KKI researchers were to measure the accumulation of lead in children's blood to gauge the effectiveness of partial lead-paint removal. The children's parents were never informed that their children were likely to ingest lead. Indeed, despite the fact that the researchers had knowledge of the hazards to children due to lead dust exposure, the informed consent document given to parents simply stated that "lead poisoning in children is a problem" and that exposure to lead in paint, dust and soil is a major source of lead exposure for children. On summary judgment, the trial court dismissed the two companion complaints (*Grimes* and *Myron*) related to the Lead Paint Study, the court holding that KKI owed no duty to warn plaintiffs or otherwise prevent a child's exposure to lead. On Aug. 16, 2001 the Maryland Court of Appeals, highly critical of the role of the reviewing IRB, reinstated the negligence suits holding that the consent agreement imposed special duties and that the plaintiffs had the expectation of warnings as to potential risks inherent in the study. The case is currently pending.

CASE BY CASE: CAUSES OF ACTION

Cause of Action	*Gelsinger*[1]	*Robertson*[2]	*Wright*[3]	*Berman*[4]
Wrongful Death	x			
Survival Action	x			
Strict Products Liability	x	x	x	
Intentional Assault and Battery, Lack of Informed Consent	x	x		
Assault, Battery and Violation of Health Care Provider Act			x	x
Intentional and Negligent Infliction of Emotional Distress	x	x		x
Common Law Fraud/Intentional Misrepresentation	x	x	x	x
Punitive Damages	x	x		
Fraud on the Food and Drug Administration	x			
Breach of the Right to be Treated with Dignity		x	x	x
Violations of 21 CFR §210, 211, 601, 610 and 45 CFR §46		x	x	x
42 U.S.C. §1983		x		x
The Belmont Report: Breach of Assurance Agreement		x	x	x
Negligence		x		
Violation of Consumer Protection Act			x	x
Monitoring of Survivors and Offspring		x		
Spousal Claims		x		

[1] Counsel for plaintiff was Sherman, Silverstein, Kohl, Rose & Podolsky, P.A. of Pennsauken, New Jersey ("SSKRP") and Saltz, Mongeluzzi, Barrett & Bendesky, P.C. of Philadelphia, PA.
[2] Counsel for plaintiffs was SSKRP and Seacat & Seacat of Okmulgee, OK.
[3] Counsel for the plaintiffs was SSKRP and Short, Cressman & Burgess, P.L.L.C. and Thomas R. Dreiling, both of Seattle, Washington.
[4] Counsel for the plaintiffs was SSKRP and Short, Cressman & Burgess, P.L.L.C. and Thomas R. Dreiling, both of Seattle, Washington.

ANALYSIS OF POTENTIAL CAUSES OF ACTION

Breach of right to be treated with dignity

- Grounded in Nuremberg Code and Declaration of Helsinki
- Alleges that Codes provide "minimum international standards of conduct governing biomedical research on humans"
- Alleges that the common law recognizes Codes as establishing the right of every human subject to be treated with dignity in the conduct of a clinical trial
- Alleges that the conduct of defendant researchers fell below the "minimum international standard," thereby effectuating the breach of the right to be treated with dignity

Violations of 21 CFR §§210, 211, 601, and 610

- Regulates the manufacture and control of investigational biological drugs for clinical use

Violations of 45 CFR §46

- The so-called "Common Rule"
- Regulates the protection of human research subjects
- Provides guidance on IRB membership, functions, operations; review of research, both standard and expedited; criteria for approval of research; and recording requirements

42 U.S.C. §1983

- Alleges that defendants were acting under the authority of their offices within a state-operated University
- Alleges that defendants were acting under color of state law
- Alleges that defendants, by their actions, deprived plaintiffs of their constitutional rights to liberty, to be treated with dignity and to privacy, all without due process of law

The Belmont Report: Breach of MPA

- Alleges that study participants are third party beneficiaries to a research institution and OHRP's Multiple Project Assurance ("MPA") Agreement
- Alleges that the purpose of an MPA is to protect all participants in clinical trials conducted at the institution
- Alleges that defendants breached their MPA in failing to follow the ethical principles delineated in the Belmont Report and 45 C.F.R. §46 (The Common Rule)

Intentional and Negligent Infliction of Emotional Distress

- Alleges that defendants willfully, recklessly and/or negligently caused the plaintiffs severe emotional distress by knowingly making false statements with knowledge that the plaintiffs would rely on them

Common Law Fraud/Intentional Misrepresentation

- Alleges that defendants knowingly committed common law fraud in intentionally misrepresenting the risks associated with participating in a research trial
- As a direct and proximate result of plaintiffs' reliance on defendants' intentional and willful misrepresentations, plaintiffs participated in the clinical trial and subsequently suffered harm

Negligence

- Alleges that defendants were responsible for rendering care and treatment to the plaintiffs properly and carefully evaluating the plaintiffs' medical conditions, carefully administering the trial protocol in a careful and prudent fashion, and for assuring that proper medical care and attention was provided to all plaintiffs during all periods of the trial
- Alleges that as a result of defendants' carelessness or negligence, plaintiffs suffered harm

Intentional Assault, Battery, Lack of Informed Consent

- Alleges that defendants failed to inform plaintiffs of the risks of the treatment, care, therapy and procedures performed as part of a clinical trial
- Alleges that plaintiffs were not permitted to make an informed decision with regard to the performance of the clinical trial procedures and that the performance of such procedures constituted a battery

Strict Products Liability

- Grounded in Restatement of Torts, 2d, Section 402(a)
- Alleges that lead investigator, sponsoring corporations and others were negligent in the manufacture and supply of product used in the study

Fraud on the U.S. Food and Drug Administration

- Alleges that defendants intentionally made numerous fraudulent misrepresentations to the FDA concerning their clinical protocol
- Alleges that defendants intended that the FDA approve the clinical study based on the fraudulent misrepresentations and that the FDA did, ultimately, provide such approval
- Alleges that defendants altered the FDA-approved consent form for the study and falsely represented that they would report adverse or unexpected events
- Alleges that the FDA was without knowledge of the fraudulent nature of the misrepresentations and that, if the FDA had been aware, the study would not have been approved
- Alleges that it is only because of the approval that the study was performed; without performance of the study, study participants would not have been subjected to an experimental procedure that resulted in death

WHAT DOES ALL THIS MEAN FOR AN IRB?

Stresses on an IRB

- Quick turn-around time
- Pressure from sponsors
- Heavy workload (both initial and continuing reviews)
- Significant time commitment needed to comply with procedural and administrative requirements
- Narrowly defined expedited review process
- Average board has gone from reviewing 40 to 300 protocols per year
- Close scrutiny by both federal regulators and the public

Common Mistakes an IRB Can Make

- Failure to protect vulnerable subjects
- Failure to adequately examine the design of the protocol
- Failure to adequately examine the qualifications of an investigator
- Failure to adequately review proposed amendments to the informed consent forms provided to the patients
- Failure to adequately review amendments to a clinical protocol
- Failure to approve advertisements for a trial
- Failure to ensure proper reporting
- Failure to make certain that a trial comports with ethical standards
- Over-reliance on administrative or expedited review procedures
- Reliance on administrative or expedited review for required changes to protocols
- Failure to comply with requirements established in 45 CFR §46
- Failure to document that IRB reviewed or considered investigator brochures, case report forms, or subject recruitment information
- Reliance upon pre-review of documentation by sponsored programs administrator, recommendation for approval, followed by administrative approval by the chairman
- Lack of final protocols in IRB records
- Failure to maintain historical membership lists of IRB members
- Approving study enrollment before required alterations are made to a study
- Retroactive approval of deviations from IRB -approved enrollment specifications
- Lack of protections for vulnerable subjects
- Failure to satisfy requirements for continuing review
- Insufficient information to make determinations required for approval of research

RESOURCES

- OHRP Web Site - *http://ohrp.osophs.dhhs.gov/*

- FDA Web Sites:

    - Good Clinical Trials in FDA-Regulated Clinical Trials can be found at *http://www.fda.gov/oc/gcp/default.htm*

    - Web Sites of Interest For Good Clinical Practice and Clinical Trial Information can be found at *http://www.fda.gov/oc/ohrt/irbs/websites.html*

- The Sherman, Silverstein, Kohl, Rose & Podolsky, P.A. Web Site (*http://www.sskrplaw.com/gene/*)has detailed information about the *Gelsinger*, *Robertson*, *Berman* and *Wright* cases

- Mary R. Anderlik and Nanette Elster, Currents in Contemporary Ethics in *The Journal of Law, Medicine & Ethics*, Vol. 29, N0. 2 (Summer 2001)

- The text of the Court of Appeals ruling in *Grimes v. Kennedy Krieger Institute* can be found at *http://www.courts.state.md.us/opinions/coa/2001/128a00.pdf*

A. Common problems identified by the Office for Human Subjects Protections (OHRP) in its investigations of research programs.

- OHRP's Division of Compliance Oversight published *OHRP Compliance Activities: Common Findings and Guidance*, in September 2000. This document lists common OHRP findings of noncompliance in the following categories: (i) initial and continuing review; (ii) expedited review procedures; (iii) reporting of unanticipated problems and IRB review of protocol changes; (iv) application of exemptions; (v) informed consent; (vi) IRB membership, expertise, staff, support, and workload; and (vii) documentation of IRB activities, findings, and procedures.

Highlights from the OHRP *Common Findings* list include:

1. Inadequate informed consent document, such as:
    - lack of required or additional elements of informed consent
    - complex language
    - inappropriate boilerplate
    - failure to minimize the possibility of coercion or undue influence
2. Lack of sufficient information to make determinations required for initial and continuing approval of research, such as:
    - privacy protections
    - equitable selection of subjects
    - vulnerable subjects (i.e., pregnant women, prisoners, children, illiterate/undereducated, decisionally impaired, economically disadvantaged)
    - lack of prisoner representative
3. Research conducted without initial or continuing IRB review, or without IRB review of protocol changes
4. Inappropriate use of expedited review procedures
5. Contingent approval of research with no additional review by the convened IRB
6. Failure of IRB to review grant applications
7. Inadequate IRB resources and overburdened IRB
8. Inadequate or poorly organized IRB minutes and other records, such as:

- failure to document consideration of safeguards for vulnerable subjects
- failure to document required findings in minutes (e.g., required findings for a waiver of one or more of the elements of informed consent; required findings for children, prisoners, illiterate subjects, economically disadvantaged)

9. Failure to report unanticipated problems to institution, sponsor, and OHRP
10. Lack of quorum and conflicts of interest

B. The most common problems identified by MW&E in responding to a recent OHRP investigation of twelve research studies.

1. Utilization by the principal investigator of letters, advertisements, questionnaires, and other study materials prior to IRB approval of the materials or changes thereto
2. Failure of the IRB to note and address discrepancies among a grant application, IRB application and research materials (e.g., consent form)
3. Approval by the IRB, and utilization by the principal investigator, of inadequate consent forms:
    - inadequate sections on voluntary participation
    - absence of a validation box
    - incomplete description of procedures and risks attendant to the study
    - failure to mention subjects' ability to omit specific procedures or withdraw samples
    - inadequate contact information
    - incomplete/misleading description of benefits
4. Implementation by the principal investigator of protocol changes prior to IRB approval of the changes
5. Failure of the IRB to document its discussion, consideration and findings with respect to vulnerable subjects (i.e., pregnant women, prisoners, children, illiterate/undereducated, decisionally impaired, economically disadvantaged)
6. Failure of the principal investigator to submit all requisite materials for a substantive and meaningful continuing review
7. Failure of the principal investigator to ensure that all initial and continuing review applications are complete, accurate, and up-to-date (e.g., submission of an out-dated version of the informed consent form)

8. Failure of the IRB to follow-up with a principal investigator in a timely manner to ensure that outstanding issues have been adequately addressed by the principal investigator

C. Identification and correction of common problems.

1. Internal Audit.

    - Paper Audit.

      Purpose: To review submissions to the IRB with respect to a sample of protocols for compliance with Common Rule requirements. This review would include: grant application, informed consent form, protocol, and IRB minutes.

    - Interviews.

      Purpose: To interview principal investigators and their staff to determine whether the protocol was implemented as approved by the IRB.

    - Audit Findings.

      Purpose: To use the audit findings to improve future IRB operations by means of a quality improvement plan ("QIP")

2. QIP, Manual, and Training.

    - QIP.

      Purpose: To guide the IRB through an ongoing process of self-assessment and correction. Its initial objectives are the result of an internal audit of a sample of protocols approved by the IRB. Subsequent objectives are identified by the IRB in its review of protocols submitted to it, as well as from any subsequent internal audits or outside investigations.

    - Updated IRB Manual.

      Purpose: To provide researchers, the IRB and its staff with a convenient and comprehensive collection of IRB policies, procedures, forms and worksheets, as well as summaries of relevant law, regulations and ethical guidelines (e.g., OHRP, FDA, the Belmont Report). The manual should be updated at least annually to incorporate QIP findings, changes in federal or state law, and best practices.

- Training.

  Purpose: To provide IRB members, staff and researchers with regularly-available mandatory and optional training. This can include: in-house programs, on-line tutorials and external programs like PRIM&R's "IRB 101 on the Road" and its "Investigator 101 CD-ROM".

D. Contemporary compliance issue: Informed Consent in population-based genetics studies

1. Population-based genetics studies contribute to knowledge about the interaction between gene variants and personal environmental factors, and how those interactions relate to disease incidence.

    - Population-based genetics studies are important to improving medicine's ability to use genetic information to improve health and prevent disease.

    - Often focus on low-penetrant gene variants (i.e., those with an expected low predictive and clinical value for individual participants)

2. Genetic information is susceptible to mis-use:

    - employment and insurance discrimination

3. Genetic information can cause psychological distress and social harm, and may stigmatize entire communities.

4. While the risks to research subjects if their privacy is breached are great, the benefits to them from participation are typically low, at best.

5. Because of these features of population-based genetics studies, the structure and content of the informed consent process requires special considerations. Researchers and IRBs, in addition to their usual informed consent concerns, should consider the following issues when designing the consent process for population-based genetics studies:

    - What benefits accrue to the population being studied? If any benefits accrue, how will they be shared with the population being studied? This is especially problematic when conducting population-based studies in developing countries, where even proven interventions may be unavailable or unaffordable.

    - How will researchers protect identifiable information from disclosure outside the research team? Will the consent process explain the possibility that study subjects and their communities might be subject to discrimination, social stigma, and psychological upset because of their participation in the study, or because of individual or group findings from the study? How likely are these possibilities?

    - Will subjects be "quizzed" to ensure their understanding of the nature and purpose of the research, the risks involved (including privacy risks and community risks), and the benefits (if any), before they are asked for their consent to participate or continue participation?

- How will researchers solicit community input and incorporate community objections or suggestions into the research design and informed consent process?

- Study subjects should understand how their genetic samples will be used, stored and shared for the current and possible future research studies.

- Study subjects should understand that they have the right to withdraw their samples from research at any time, unless the samples are made anonymous and their identification and destruction, impossible.

- How will samples and other individually identifiable research materials be kept secure? Who will have access to identifiable materials and/or identifying links?

- Is the reporting of genetic test information to participants advisable? How would participants benefit from learning this information? Will counseling and treatment be available if test information is reported to participants? If disclosure to participants is contemplated, study subjects should affirmatively consent to receiving their genetic test information (some participants won't want to know).

6. The Centers for Disease Control website includes a model consent form language for population-based genetics studies. Go to: www.cdc.gov/genetics/info/reports/policy/consent.htm.

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Christopher M. Jedrey is a partner in the Boston office of McDermott, Will & Emery and national co-chairman of its Academic Medical Center Affinity Group. Mr. Jedrey's practice is concentrated in the areas of federal and state health care regulatory matters, including anti-kickback and Stark law requirements. His practice also focuses on federal, state and local tax exemption requirements, and charitable trust and corporation law.

Mr. Jedrey represents clients in hospital mergers and physician practice mergers, joint ventures among health care providers, purchases and sales of physician practices, and sales of non-profit assets and operations to for-profit companies. He has also assisted hospitals and health maintenance organizations with the organization, restructuring and "spin off" of affiliated group practices. He represents academic medical centers for a variety of matters, including compliance with HHS requirements for human subjects research and IRS requirements for tax-exempt organizations, including incentive compensation plans for physicians. Mr. Jedrey advises hospitals, colleges, universities, museums and other tax-exempt organizations with respect to the requirements for tax-exempt status and also provides regulatory and tax advice with respect to incentive compensation plans for executives.

Mr. Jedrey's notable recent projects include: advising the Northeast Permanente Medical Groups on their separation from Kaiser Health Plan; advising Partners HealthCare System on the consolidation of seven faculty practice foundations affiliated with Brigham & Women's Hospital; acting as special counsel to Blue Cross and Blue Shield of Massachusetts on its plan of reorganization; advising Harvard Pilgrim Health Care on the formation of Harvard Vanguard Medical Associates, which now employs the clinical staff at Harvard Pilgrim's health centers; and providing regulatory and tax advice on the formation and implementation of Dana-Farber/Partners Cancer Care, a path-breaking clinical and financial collaboration for adult medical oncology services among Dana-Farber Cancer Institute, Brigham & Women's Hospital, and Massachusetts General Hospital.

Mr. Jedrey is Co-Chairman of the Health Care Law Subcommittee of the American Bar Association Exempt Organizations Committee, a Fellow of the American Bar Foundation, and a member of the Massachusetts Attorney General's Advisory Committee on Public Charities. He is a frequent lecturer at programs sponsored by Massachusetts Continuing Legal Education, Massachusetts Medical Society, HealthCare Financial Management Association, Massachusetts Hospital Association, American Bar Association, Boston Bar Association and other organizations, and has been a visiting lecturer at Harvard Law School and Northeastern Law School. He is also a fellow of the Massachusetts Historical Society.

Mr. Jedrey received a B.A., *magna cum laude*, from the University of Massachusetts, Amherst in 1971, where he was elected to *Phi Beta Kappa*; an A.M. from Harvard University in 1972; a Ph.D. from Harvard University in 1977; and a J.D., *cum laude*, from Boston College Law School in 1984. He was a Liberal Arts Fellow at Harvard Law School in 1980-1981.

MONTE DUBE

Monte Dube is a partner in McDermott, Will & Emery's Chicago office and Head of the Firm's Health Law Department. Mr. Dube represents hospitals and community health systems nationwide and has served as counsel in connection with numerous sales, affiliations and acquisitions of hospitals and academic medical centers, hospital restructurings, public hospital privatizations, joint ventures, certificate of need and reimbursement litigation and hospital and medical staff operational legal issues of all types.

Mr. Dube was a Bigelow Teaching Fellow and Lecturer in Law at the University of Chicago School of Law in 1981 and 1982. He regularly lectures and publishes on hospital-physician relations, hospital merger and affiliation transactions, fiduciary duties of not-for-profit trustees, and rural health care issues.

Mr. Dube is a member of the American Health Lawyers Association, and the American, Illinois and Chicago bar associations. He is admitted to practice before the Illinois Supreme Court, the U.S. District Court for the Northern District of Illinois and the U.S. Court of Appeals for the Third Circuit.

Mr. Dube received his bachelor's degree, *magna cum laude*, in law and psychology from Boston University in 1977. He graduated from the Benjamin N. Cardozo School of Law in 1981.