

Ethical, Legal, & Social Issues in Human Gene Therapy & PGD

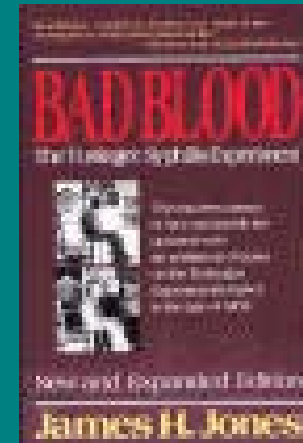
James F. Childress
University of Virginia

Medical/Genetic Interventions

- Therapy: effort to treat particular patient
- Research: systematic effort to generate generalizable knowledge

Ethical Standards for Research

- Background: Nazi experiments & the Nuremberg Code
- Standards in US were sharpened in the context of our own ethical scandals such as the Tuskegee syphilis study



The Belmont Principles

- *Beneficence*
- *Respect for Persons*
- *Justice*

Formulated by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Federal Register, 1979)

Respect for Persons

- Two components
 - Respect autonomous agents
 - Protect persons with diminished autonomy
- Application: informed consent (information, comprehension, & voluntariness)

Beneficence

- Two components:
 - Do not harm
 - Maximize possible benefits and minimize possible harms
- Application: conduct analysis to determine that probable benefits outweigh risks

Justice

- Requirement: Fair distribution of the benefits and burdens of research
- Application: fair selection of research subjects

Two Pillars of Subject Protection

- Review by Institutional Review Board (IRB)
- Informed Consent

Common Rule: Criteria for IRB Approval of Research

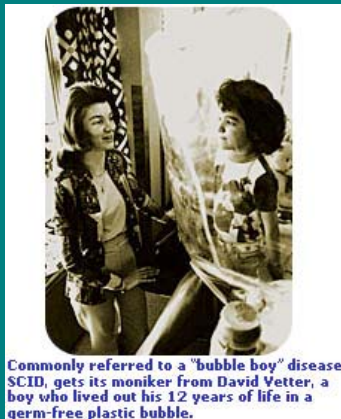
- Minimization of risks to subjects
- Determination that risks are reasonable in relation to anticipated benefits
- Equitable selection of subjects
- Informed consent & its documentation
- Appropriate monitoring to ensure safety
- Protection of privacy and confidentiality

Medical/Genetic Interventions

- Therapy
 - Routine therapy
 - Experimental therapy
- Research
 - Reasonable prospect of patient benefit (so-called therapeutic)
 - No reasonable prospect of direct benefit (so-called non-therapeutic)

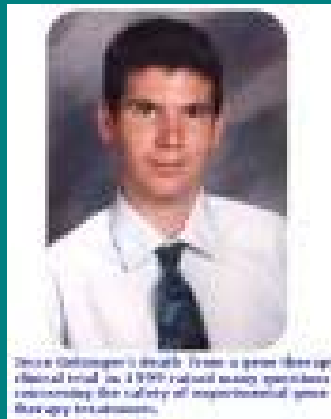
Milestones in Gene Transfer

1990 First
approved
trials



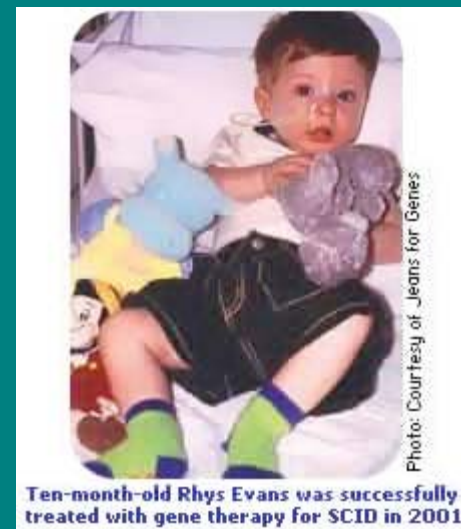
Commonly referred to a "bubble boy" disease, SCID, gets its moniker from David Vetter, a boy who lived out his 12 years of life in a germ-free plastic bubble.

Death of Jesse
Gelsinger, 1999,
in gene transfer
trial



Jesse Gelsinger is shown in a photo from a gene therapy clinical trial in a 1999 national news magazine. He was the first person to die in a gene therapy clinical trial.

SCIDS cure--
2001-- but
leukemia
developed for
some



Ten-month-old Rhys Evans was successfully treated with gene therapy for SCID in 2001.

Photo: Courtesy of Jeans for Genes

Recombinant DNA Advisory Committee

- Additional level of review of each protocol-
-public, national, etc.
- Recent guidance re informed consent
- Study: widespread therapeutic
misconception. Even language: “gene
therapy” should be “gene transfer”

Types of Genetic Intervention

	<i>Somatic Cell</i>	<i>Germline</i>
• <i>Correct Disease</i>	1	2
• <i>Enhance Qualities</i>	3	4

Concerns: Wedge & Slippery Slope Arguments

- From correction of diseases (#1) to enhancement of qualities (#3)
 - E.g., gene doping in sports--benefits/risks
 - How clear is line between 1 & 2?
- From somatic cell (#1) to germline interventions (#2 & 4)
 - Uncertain impact on future generations

Shaping the Policy Context

“now is the time for the gene transfer research community to become more involved in shaping the social policy context for their work. Desperate parents, unscrupulous coaches, and adventuresome infertility specialists will all need the aid of skilled scientists to take steps that could compromise further medical progress in genetic medicine.

Shaping the Policy Context II

“If gene transfer researchers are alert to these issues, accurate in their advertising, and articulate about the moral convictions that guide them, the field can go far to secure its pride of place in the new world of genetic medicine now beginning to emerge.”

Eric Juengst, “What next for human gene therapy?”

PGD

- Backdrop to Gene Therapy: regulation of research in light of previous abuses
- Backdrop to PGD in context of IVF: lack of regulation of practice of “reprogenetics”
 - Reproductive technologies largely unregulated in US (ct UK and other countries)
 - Genetic counseling largely “non-directive” as reaction to eugenics movement
 - Reprogenetics: largely consumer driven in US

Status of Early Embryo

- Mere tissue
- Potential human life
- Full human life

- *What does “respect” require under these different views?*

PGD: Medical Uses

- Screening for genetic conditions manifested in infancy or childhood
- Screening for susceptibility and for adult-onset disorders
- HLA matching for sibling needing cord blood or bone marrow

PGD: Non-Medical Uses

- Robertson: depends on
 - whether valid reproductive or rearing interests justify creating and destroying embryos;
 - whether selecting for a trait will harm resulting children;
 - whether it will stigmatise existing persons;
 - whether it will create other social harms
- Examples: gender selection; perfect pitch; other traits

Major Concerns

- Safety of IVF/embryo manipulation in PGD and accuracy of genetic tests
- Concerns about the creation, selection, and destruction of human embryos
- Equity--should health insurance cover?
- Impact on family relationships, people living with disabilities, and society as whole
[JHU, Genetics & Public Policy Center]

John Kilner's Opposition 1

“Using PGD as a method of weeding out undesirable offspring is unethical by its very nature. ‘Savior babies’ are just the latest (and perhaps clearest) example of how utilitarian thinking can be demeaning to human beings. Whatever the variation, the basic approach of PGD involves producing many more human beings than are wanted, selecting those deemed best, and discarding the rest.”

Kilner's Opposition 2

The only ethical purpose would be to use PGD “for the good of those tested,” e.g., “to prepare for any special supports that will be needed later.”

“...the use of PGD would be ethical in a situation where the use of [ART] is necessary and a genetic therapy is available that must be done at the embryonic state. But such is never the case today--and some say it may never be.”

Who Decides?

- US:
 - Few regulations
 - Fertility clinics; professionals involved
 - Client/consumer driven
 - Freedom reigns
- UK:
 - Human Fertilisation and Embryology Authority (HFEA)
 - Strong regulations to enforce rough societal consensus





Past, Present, & Future

- 1990-1st approved human gene transfer experiment
- 1999-Death of Jesse Gelsinger
- 2001-02-Apparently successful gene transfer & cure of children with SCIDS, but caused cancer in some children
- Story of unfulfilled promise
- Near future: Pharmacogenomics