

An Ethics Roadmap to Translational Research

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Disclosures

- I have nothing to disclose

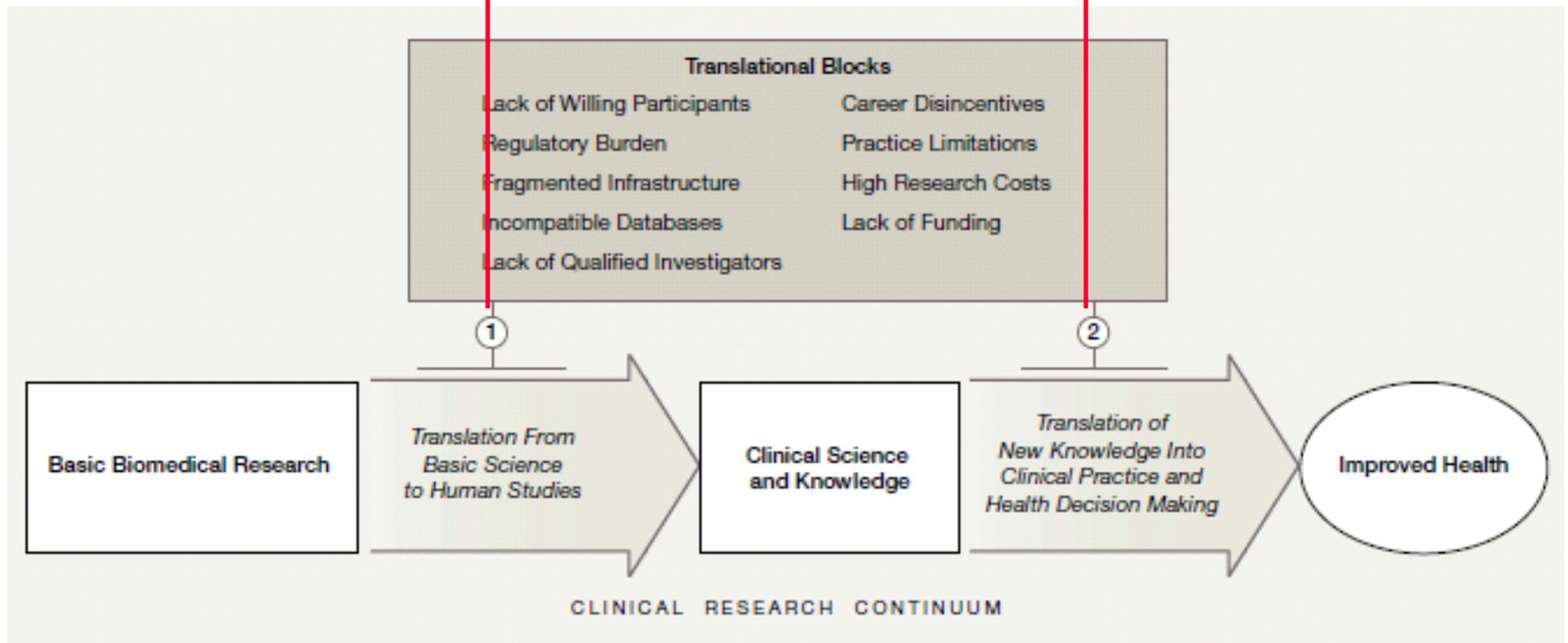
OBJECTIVES

- 1) Define the translational research pathway and the ethical challenges that arise
- 2) Consider ethical challenges along the translational pathway
- 3) Examine intended and unintended consequences of health policies

The CTSA Translational Pathway

*Ethical challenges in the
Translational pathway*

Figure 1. The 2 Translational Blocks in the Clinical Research Continuum



Sung et al. Central Challenges Facing the National Clinical Research Enterprise. *JAMA*. 2003; 289 (10): 1278-1287

Ethical Challenges in Translational Research involving Human Subjects

- Study design and research methods
- Informed Consent
- Conflicts of Interest
- From research results to policy

STUDY DESIGN and RESEARCH METHODS

First Step of Translation: Phase I Clinical Trial

- First use of drugs in humans
 - Goal: Safety
 - Usually involve a small number of subjects
 - Usually takes place in a clinical setting for careful monitoring
- Participants may be healthy volunteers;
- For oncology drugs, often individuals with advanced cancer for whom no other therapeutic modalities are available.
- MOTIVATION
 - Healthy volunteers do not seek clinical benefit.
 - Do it for the \$\$
 - (and to advance science)
 - Why do Cancer patients enroll?
 - Virtually 100% claim to do it for the possibility of clinical benefit
 - Also state they do it to advance science.

*IMAGINE THE FOLLOWING AD ON A
BULLETIN BOARD AT YOUR
HOSPITAL*

WANTED HEALTHY VOLUNTEERS

Study of TGN1412, a
humanized agonistic anti-
CD28 monoclonal antibody

TGN1412 in the UK

- What do you need to know to decide whether or not to volunteer?
- What is the purpose?
 - It is being developed by TeGenero to treat various diseases in which T cells are involved, such as chronic inflammatory disorders or hematological malignancies.
- What are the benefits?
 - As a healthy volunteer, it will not benefit you clinically
 - You will help advance science
 - You will be paid!

What are the RISKS?

● PRE-CLINICAL STUDIES

- The experimental animals experienced swollen lymph nodes after administration of the study drug.
 - What the consent form said: Experiments with animals have some predictive value for human safety. Preliminary data from animal studies demonstrated that the study drug was safe and well tolerated in the experimental animals.
- In contrast to other antibodies in clinical use, TGN1412 directly stimulates the immune response in vivo.
- In preclinical models, the stimulation of CD28 with TGN1412 preferentially activated and expanded type 2 helper T cells and, in particular, CD4+CD25+ regulatory T cells, resulting in transient lymphocytosis with no detectable toxic or proinflammatory effects.

● CONSENT FORM RISK

- “Drugs of this type can also cause swelling of the lymph glands, so you will be regularly checked for this.”
 - This may have taken on more significance if the pre-clinical results had been mentioned.

What are the real RISKS (known post facto)?

- Risk that administration could lead to T-cell activation and massive cytokine release
 - Preliminary data in monkeys had cytokine release
- Risk that antibody could result in a strong expansion of regulatory T cells and non-specific immunosuppression

TGN1412 Phase 1 Study

- 8 men were enrolled to participate on March 13, 2006.
 - Infusions begun virtually simultaneously
 - What is wrong with that?
- Within hours those receiving the drug experienced serious side effects caused by a severe inflammatory response, resulting in multiorgan failure due to a “cytokine storm,” for which they were managed in intensive care; some spent more than three months in hospital.
- Longer term effects for all of the volunteers remain unknown.

TGN1412 in the UK

- How could the risks have been minimized?
 - Study of TGN1412 with human and animal blood ex vivo could have given information about cytokine release or T-cell expansion.
 - Not done.
 - Because side-effects not ruled out prior to clinical trial, first human dose needed to be low!
 - Particularly important because the drug has a half-life of 8 days.
 - So one should wait a few weeks between first and second subject...
 - Want a good “Contingency plan” in case something goes wrong.
 - Investigator's brochure provided little guidance on control of side-effects.

Phase 3 Clinical Trial

Phase III Clinical Trials

- Placebo-controlled trials versus active controlled trials?
 - Declaration of Helsinki, the international standard of research ethics, article 29:
 - The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
 - Clarification in 2002 in response to U.S.: 2 situations in which placebos are permitted:
 - - Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
 - - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

How should one design asthma studies in the late 1990s?

- Standard of Care: NHLBI Guidelines
 - 1991 Guidelines for the Diagnosis and Management of Asthma
 - Anti-inflammatory medications (AIM) for all children and adults with more than mild asthma
 - Inhaled corticosteroids (ICS) for children and adults with severe asthma
 - ICS for adults with moderate asthma
 - 1997 Guidelines, reaffirmed 2002 guidelines
 - First line of choice for all children and adults with more than mild intermittent asthma is an ICS.
- Are placebo-controlled trials ethical?

Study Design: Placebo-Controlled Asthma Trials

- Shapiro et al. Dose-Related Efficacy of Budesonide Administered via a Dry Powder Inhaler in the Treatment of Children with Moderate to Severe Persistent Asthma. *Journal of Pediatrics*. 1998; 132: 976-82.
 - Letter by Ferdman and Church to the journal editors: No questions about the data; why was a placebo necessary?
 - Shapiro's response:
 - needed to study a new delivery device.
 - It was an ethical compromise in that we accomplished this protocol without incurring serious consequences in the subjects...

Ethical Questions

- How often do children enrolled in clinical asthma trials [CAT] receive anti-inflammatory medication [AIM] in accordance with NHLBI guidelines?
- Are subjects, particularly children subjects, enrolled in placebo-controlled trials (PCT) harmed more than subjects enrolled in other types of CAT?
- Are children enrolled in the placebo arm of a PCT harmed more frequently than children enrolled in active-treatment arms?
- Is generalizable knowledge about children as a class procured when children are enrolled in studies with adult subjects?

Results: Study Characteristics 1

Asthma studies 1998-2001	450
Eligible asthma studies	70
Trials using placebos	50
Placebo vs. experimental drug (PCT)	45
Placebo as add-on vs. experimental drug (add-on) study	5
PCT	45
Trials involving children and adults	31
Trials involving ONLY children	14

Results: Study Characteristics 2

Trials involving children and adults	52
Trials differentiating between children and adults at baseline	8
Trials differentiating between children and adults in results	1
Avg duration of trials (excl. run-in) in weeks	26.8
Trials documenting withdrawal information	62
PCTs documenting withdrawal info	40
Trials documenting IRB review and approval	67
Trials documenting procurement of consent	68

Subject Withdrawals by Trial Design

	All Trials (n=62)	Add-on and Active controlled Trials (n=22)	PCT (n=40)
Subjects analyzed #	24,953	11,690	13,263
Withdrawn #(%)	4,653 (19)	1,849 (16)	2,804 (21)*
asthma exacerb'n	1,605 (34)	358 (19)	1,247 (44)*
adverse event	518 (11)	277 (15)	241 (9)*
other	2,069 (44)	1,177 (64)	892 (32)*
not discussed	461 (10)	37 (2)	424 (15)

Were the Placebo Controlled Trials Ethical?

- “Asthma symptoms would be expected to worsen in the placebo group during the treatment period because these patients were dependent on inhaled steroids but were not allowed treatment with inhaled steroids while in the study.”
 - Shapiro et al. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol.* 1998; 102:789-96
- I doubt this was part of the informed consent process!

Ethics and Placebo-Controlled Trials

- Placebo-controlled trials are ethical if
 - no standard of care exists.
 - the commonly accepted therapy is of questionable efficacy, carries a high frequency of undesirable side-effects, or generates greater risks than benefits.
 - to determine incidence and severity of undesirable side-effects of add-on treatment to an established regimen.
 - disease process is characterized by frequent spontaneous exacerbations and remissions, and the efficacy of the therapy has not been established

Committee on Drugs, American Academy of Pediatrics. "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations." *Pediatrics* 1977; 60: 99. Reaffirmed and restated in *Pediatrics* 1995; 95: 294. Statement reaffirmed September 2005

- Why use a placebo when a standard of care exists?
 - FDA approval
 - Studies are cheaper and cleaner

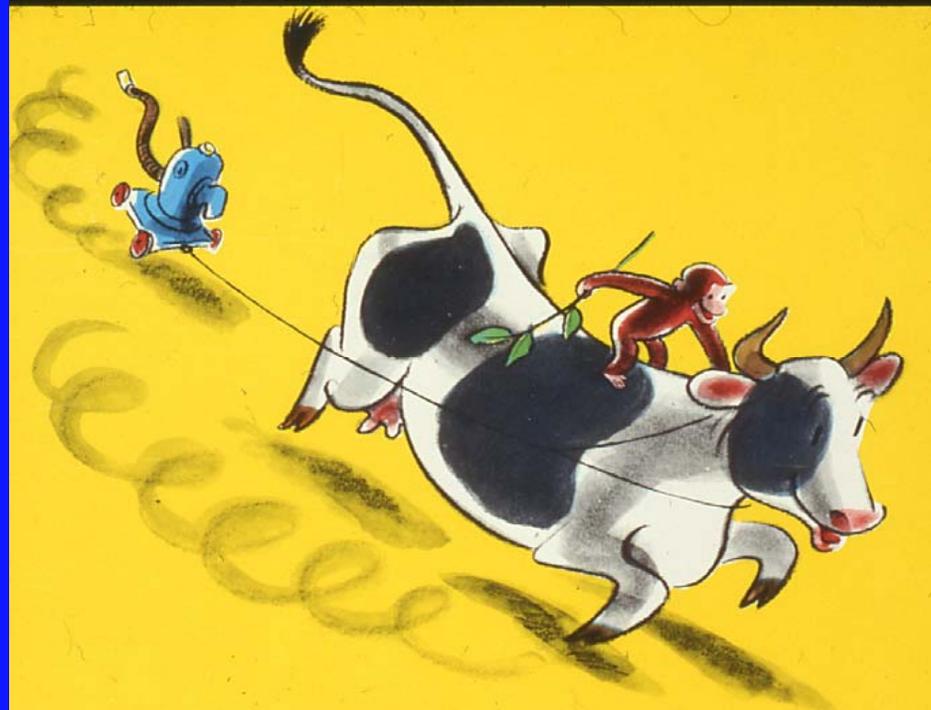
Informed Consent

Informed Consent Process

- ***Cornerstone*** of human subjects research
- ***Process*** and not just a form
 - Consent form is only the documentation that the consent process has taken place

Basic Elements of Informed Consent

- Statement that study involves research, description of procedures, duration, identification of experimental procedures
- Foreseeable risks and discomforts
- Anticipated benefits to subject or others
- Statement re: voluntary nature of participation
- Ability to withdraw at any time
- Disclosure of alternatives
- Statement regarding confidentiality/anonymity
- Statement regarding compensation/medical treatment
- Statement regarding appropriate contact for inquiries related to subject rights, research concerns, and for research-related injury
- Oral and written info at 7th grade level



*Curious George
gets a medal*

by

H.A. REY

CURIOUS GEORGE
SLIDES REMOVED

Lessons from Curious George

- The wrong lesson: Curious George is a successful astronaut, he is hailed as a hero, and (as the title foretells), he earns a medal!
- The real lessons:
 - Illiteracy makes you a vulnerable subject.
 - Informed consent documents should describe the RISKS as well as the benefits.
 - Subjects may feel coerced for many reasons.
 - “An experiment is ethical or not at its inception...ends do not justify means.” (Beecher, 1966).

Therapeutic Optimism in the Consent forms of phase 1 gene transfer trials: an empirical analysis. Kimmelman and Palmour, J Medical Ethics, 2005; 31: 209-214.

- Therapeutic misconception
 - Do the patient-subjects misunderstand?
 - Or are the health care providers also confused?
- Inclusion criteria: All consent documents for phase 1 human gene transfer protocols between 1989-2001 from NIH Office of Biotechnology Activities
 - Excluded phase 1/2 (1=safety; 2=efficacy)
 - Excluded feasibility experiments
 - 277 consent forms

Benefit Language in the Consent Forms

- Coded as positive (+1)
 - The drug may result in tumor shrinkage
 - You may experience relief of your symptoms
 - Results in animals are promising
 - This may induce an immune response to your cancer
- Coded as neutral (0)
 - You may or may not benefit
 - Direct benefit cannot be guaranteed
 - You may not benefit from this procedure
- Coded as negative (-1)
 - You are the first person to receive this drug
 - You are unlikely to benefit from the drug
 - This treatment is not a cure
 - Despite treatment, your condition will likely worsen
 - Any improvement will stop when study ends

Benefit Language

- 87% of Phase 1 consent forms had a “benefit paragraph”
 - Average rating was 0.5
- To be fair, most of these paragraphs discussed uncertainties rather than future benefits
- Forms were generally more emphatic about their optimism than about their caution.
 - Genetic trials were more cautious than cancer and HIV trials where much greater optimism

CONFLICTS OF INTEREST

Conflicts of Interest

- Definition: set of conditions in which professional judgment concerning a primary interest tends to be (or has serious potential to be) unduly influenced by a secondary interest, consciously or subconsciously.
 - primary interest: patient care or research
 - secondary interest: financial gain, academic prestige, etc.

Dennis Thompson, "Understanding Financial Conflicts of interest," *NEJM*: 1993;329: 573-6

Jesse Gelsinger, 1981-1999

Death of a research subject in a case in which subject selection, informed consent and conflicts of interest are all ethically problematic.

Jesse Gelsinger, Phase 1 Gene Transfer trial

- 18 year old with partial ornithine transcarbamylase (OTC) deficiency.
- September 1999: Enrolled in a phase 1 study to determine the safety of adenoviral vector for gene transfer.
 - Jesse was the 13th subject.
 - Within 4 days, Jesse had died.
- December 1999: Jesse's family and other families of infants with OTC went before the Recombinant DNA Advisory Committee to support the continuation of research.
- January 2000: FDA investigation found numerous lapses in Penn's research

Was Jesse Gelsinger an appropriate research participant?

- Phase 1 study
 - 10th and 12th subjects exhibited signs of significant liver stress
 - 2 other subjects may have suffered severe adverse effects as well
 - NOT REPORTED TO FDA (as required) which would have halted enrollment.
- Jesse Gelsinger's labs were abnormal at the time of enrollment and he should have been excluded.

Lapses in the Consent Process of Jesse Gelsinger

- RAC (Recombinant DNA Advisory Committee) had argued that the infusion into a vein and not hepatic artery. U Penn researchers agreed to this change, but at the time of the study, had decided to directly infuse but did not inform RAC or Penn's IRB.
- Information about deaths from liver injury in earlier animal studies had been withdrawn from the patient information sheets without IRB approval.
 - According to Jesse's father, Jesse had understood that the gene therapy worked.
 - Website had overly misleading information about the research's success to-date.

Conflicts of Interest

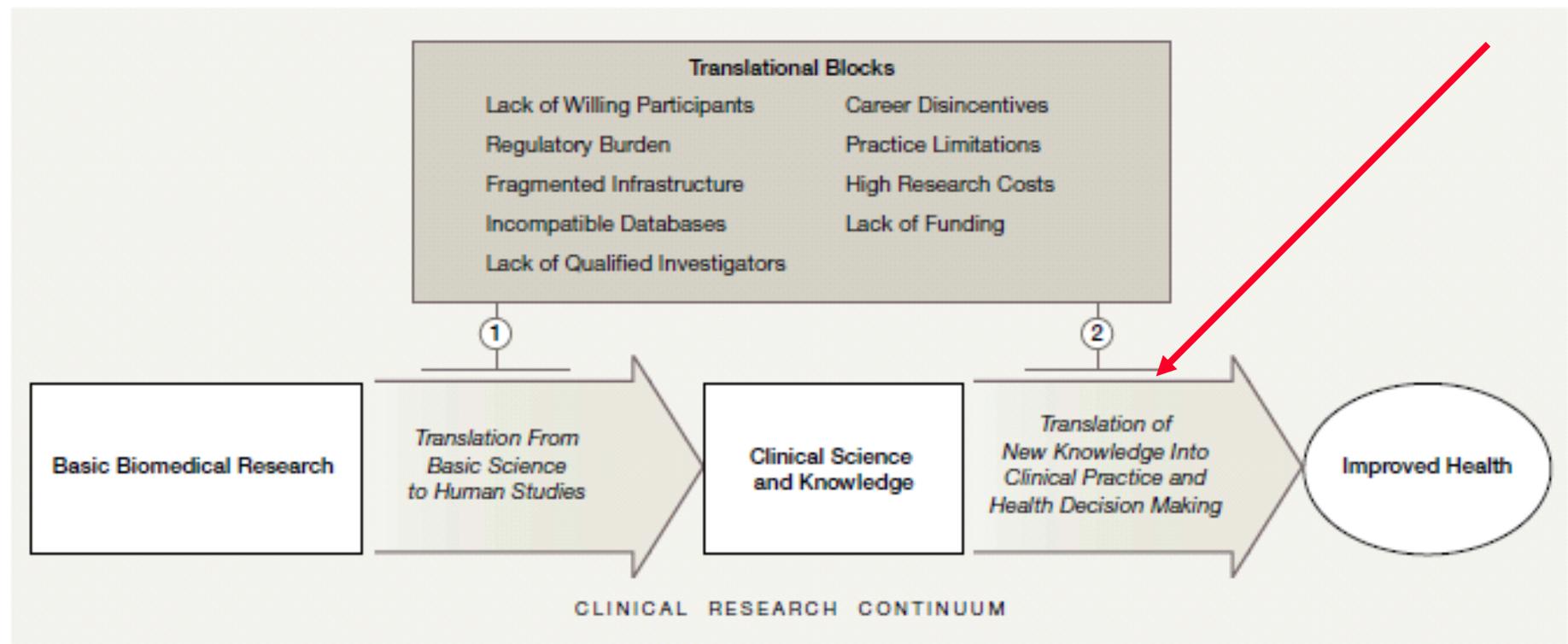
- The principal investigator held \$13 million in equity in Genovo, the biotechnology firm supplying the viral vector used in the trial.
- The host institution also had a substantial financial interest in the research.
- Both Wilson and Penn denied that this influenced how they proceeded with the research.
- ...not to be cynical, but the size of the conflict may matter!

Denouement

- September 2000, Jesse's father sued the research team, U Penn, the Children's Hospital of Philadelphia and bioethicist Arthur Caplan
- Settled out-of court in 6 weeks for an undisclosed amount.

Translation of New Knowledge into Clinical Practice and Health Care Decision Making

Figure 1. The 2 Translational Blocks in the Clinical Research Continuum



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JAMA. 2003; 289 (10): 1278-1287

T-2: Translation of New Knowledge into Clinical Practice and Health Decision Making

- Step 1: Need to show the new therapy or diagnostic tool is effective, replicable, and generalizable to a more diverse population (repeat Phase 3 Clinical Trials)
- Step 2: Need to study the safety and efficacy in a more diverse population (Phase 4 Clinical Trials)
- Step 3: Need to disseminate into community practice and into practice guidelines

Studies in new populations

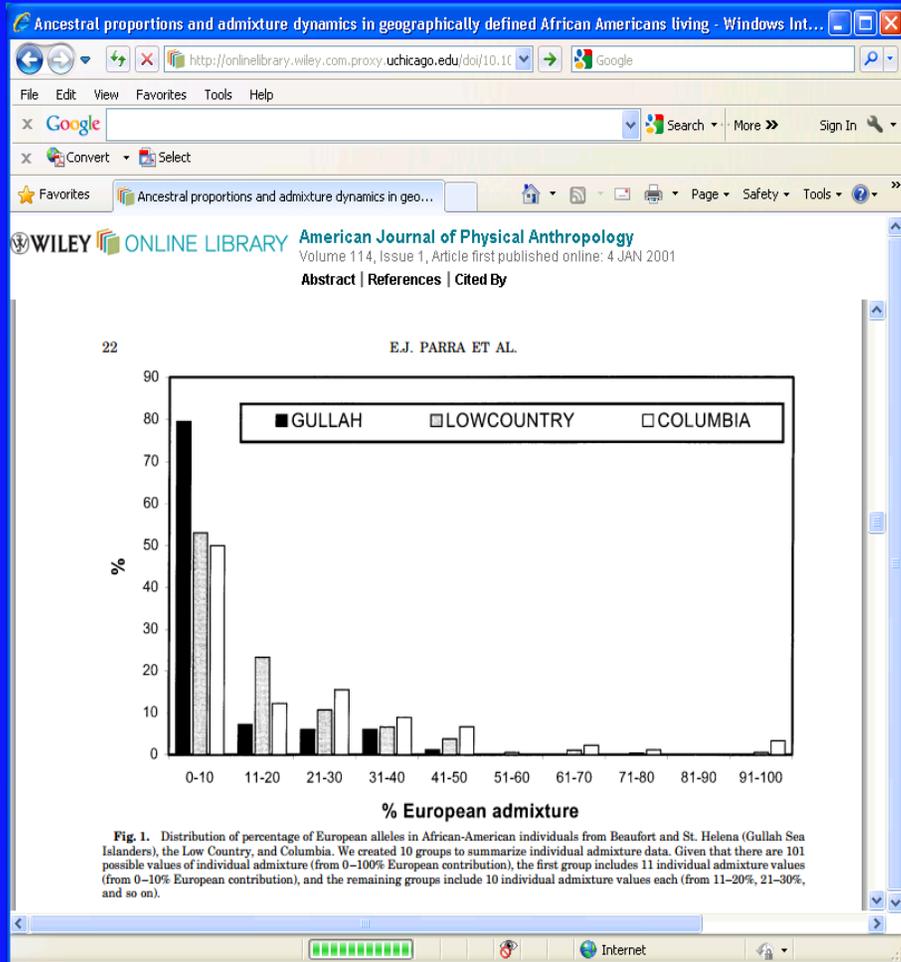
Heart Failure Therapy

- BiDil: combination of 20mg of isosorbide dinitrate and 37.5mg of hydralazine hydrochloride.
- The components have "been used for years to treat high blood pressure and angina (chest pain)"
- Veterans' Administration Cooperative Vasodilator Heart Failure Trials: V-HeFT-I and II:
 - V-HeFT-I, the combination of hydralazine and isosorbide dinitrate provided a beneficial effect on prognosis in heart failure.
 - V-HeFT-II demonstrated that enalapril had a more favorable effect on 2-year survival than a combination of hydralazine plus isosorbide dinitrate.
- Post-hoc subgroup analyses of the 2 earlier trials found that the combination might be better in Blacks than Whites.
 - Problem (like all post hoc analyses, potential for covariate imbalances (N.B. V-HeFT trials did not report disaggregated data on baseline characteristics).
- New study done that only enrolled African Americans
- A-HeFT
 - Taylor AL et al. for the African-American Heart Failure Trial Investigators*
"Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure"
N Engl J Med 2004;351:2049-57.

A-HeFT Study Design

- **Inclusion and exclusion criteria:** “Patients 18 years of age or older, self-identified as black (defined as of African descent), who had had NYHA class III or IV heart failure for at least three months were eligible for screening.” at p. 2050
- **What does it mean to be Black?**
 - Historical US policy of the “one drop rule”
 - More recent genetic admixture studies

What does it mean to self-identify as Black?



Am. J. Hum. Genet. 74:1001–1013, 2004

Table 2
Characteristics of Samples

SAMPLE EXAMINED	n	POPULATION CONTRIBUTION ASSESSED BY STRUCTURE ^a (%)			
		European	African	Asian	Amerindian
European American:					
Chicago ^b	39	98.4	.4	.7	.5
Baltimore ^b	39	97.5	.4	.9	1.3
African American:					
Chicago ^{b,c}	18	18.4	80.6	.7	.3
Pittsburgh ^{b,c}	23	18.3	80.6	.6	.5
Baltimore ^d	45	15.9	83.2	.5	.5
North Carolina ^c	23	18.8	79.6	.5	1.1
African:					
Senegal ^e	46	2.8	95	1.6	.6
Ghana ^f	33	.1	99.8	.1	.1
Cameroon ^g	20	.1	99.8	.1	.1
Botswana ^h	21	1.2	98.4	.3	.1
Chinese:					
Cantonese ⁱ	40	.2	.1	98.9	.8
Amerindian:					
Mexican Zapotec ⁱ	29	4.3	.3	.5	94.8

^a The STRUCTURE analysis (Falush et al. 2003) was based on the 2,034 SNPs from the reduced 2,154-marker map that were genotyped in the samples above. The relative log likelihoods for the two-, three-, four-, five-, and six-population models in STRUCTURE (Falush et al. 2003) were -25055 , -6612 , 0 , -756 , and -667 , respectively. We used a four-population model because it is most probable given the data.

^b From the Multicenter AIDS Cohort Study (Kaslow et al. 1987).

^c From the Multicenter Hemophilia Cohort Study (Goedert et al. 2002).

^d From the AIDS Link to Intravenous Experiences study (Vlahov et al. 1998).

Results/Discussion

- RESULTS:

- A-HeFT: BiDil provides some benefits to African Americans in heart failure

- DISCUSSION:

- “Our trial represents a departure from the recent approach to the design of cardiovascular trials. Rather than studying a large heterogeneous population, we examined a specific population in whom efficacy was more likely to be established. A heterogeneous population may have substantial variations in genetic and environmental factors that influence disease progression and the response to therapy. Since subgroups of the trial cohort are rarely large enough for statistical analyses of the heterogeneity of an effect, the standard thinking is that the overall response to therapy should be accepted as a mandate for the use of that therapy in all subgroups in the trial.” at p. 2055
- Again, what does it mean to be “black”?

Commentaries

- Why did the company want to show that BiDil was effective in African Americans?
- The patent was going to expire, but this would allow the company to extend their patent for many years
- Jeffrey Kahn, in the *Social Studies of Science* 2008; 38(5):737-58 writes: “In fact, however, BiDil is not about personalizing medicine: it is about exploiting race to obtain cheaper, quicker FDA approval for a drug.”
- George Ellison and Colleagues writing in the *Journal of Law, Medicine, and Ethics*, 2008; 36(3):449-57 write: The FDA’s encouragement of A-HeFT and its subsequent approval of BiDil appears to “dismiss the serious ethical concerns that arise when the development of group-specific therapies invoke race as a discrete marker of innate difference, and are subject to commercial incentives rather than scientific evidence or therapeutic imperatives.”

Patient Care

- Of note, efficacy of BiDil was proven in a study designed to compare BiDil with placebo
- BiDil has never been compared to ACE inhibitors (the standard of care) in congestive heart failure
- What medication would I recommend to a patient with congestive heart failure...
- ...If the patient were white?
 - ACE inhibitor would be first line therapy
- ...If the patient were black?
 - ACE inhibitor would be first line therapy

Pediatric Research Policies

Regulations for Children in Medical Research 1970s-80s

- National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, “Report and Recommendations: Research Involving Children”, 1977.
- Federal Regulations, 1983, revised 1991. “Additional Protections for Children Involved as Research Subjects.”
- The focus of the Regulations was protection, particularly for vulnerable populations like children.

In contrast, the focus of the policies of the last 2 decades have been on access

- Food and Drug Administration, 1994 Rule (59 FR 64240): manufacturers of marketed drugs had to survey existing data and determine whether those data were sufficient to support additional pediatric use.
- 1998 NIH policy to require inclusion of children or explain why not
- Food and Drug Administration Modernization Act of 1997. (Public Law 105-115):
 - Economic incentives for conducting pediatric studies on drugs by extending exclusivity or patent protection on drugs for which FDA had requested Pediatric studies.
- Re-authorized in 2002 as Best Pharmaceuticals for Children Act (BPCA) for another 5 years
 - Continues to be re-authorized.
- Congress passed Pediatric Rule, November 2003.
 - Whereas BPCA is the carrot, Pediatric Rule is the stick.

BPCA and labeling in pediatric drugs: The Case of Asthma Revisited*

- FDA written request to GlaxoSmithKline 06-25-99, amended 10-25-01 for pediatric studies of the fluticasone propionate [FP] moiety (an inhaled corticosteroid).
- BPCA Clinical Summary of NDA 20-548, SE8-018, reviewed 06-04-03.
 - Reviewed 2 clinical trials, a pharmacokinetic trial [PK], and an in vitro study report.

*Thanks to Robert M Nelson, MD, PhD for pointing out this case.

GlaxoSmithKline Clinical Trials

- The two clinical trials were placebo-controlled clinical trials (PCTs)
- Entry criteria for both PCTs:
 - Required that the children were on maintenance asthma medication other than systemic corticosteroids on a regular basis for preceding 6 weeks; or
 - Required that the children received short-acting beta-agonist for relief of respiratory symptoms at least twice per week over preceding 3 weeks.
- Both PCTs were 12 weeks in duration
 - Children 6-23 months (n=211; 54 centers)
 - Children 24-47 months (n=332, 77 centers)

GlaxoSmithKline Data Quality

- “Plasma samples from all subjects were measured for FP prior to unblinding. 13 samples in the placebo group of 107 subjects had measurable FP concentrations.”
 - These 13 patients had no record of receiving FP during the study and were not exposed to FP on the day of PK testing.
- Many patients on active treatment did not have detectable FP levels...suggesting that the problem may have been larger than stated.

Study Results: Efficacy and Safety

- The FDA concluded that a meaningful interpretation of the efficacy results could not be made because of detectable plasma levels of fluticasone seen in placebo treated patients.
- The FDA concluded that the safety data were uninterpretable as to the true extent of the safety risk... because it was impossible to evaluate the actual patient exposure in the two clinical studies submitted.

FDA Action?

- Exclusivity was granted to GlaxoSmithKline under Best Pharmaceuticals for Children Act.
(<http://www.fda.gov/cder/foi/esum/2003/20548se8-018BPCArev2.pdf>)
 - Exclusivity granted 02-25-2003
- Flovent sales (2000)
 - \$1,307,000,000
 - Added protection: \$653,500,000

DIFFUSION and DISSEMINATION

A Case Study of Diffusion: Beta-blockers post-myocardial infarction

- 1982: Beta-Blocker Heart Attack Trial (BHAT) published: found beta-blockers reduce mortality.
- 2007, National Committee for Quality Control (NCQA) removed the measure from quality of care reporting...because >90% receive Rx.

Eulogy for a Quality Measure

New England Journal of Medicine; 2007;357: 1175-7.

Thomas H. Lee, M.D.

On May 8, 2007, one of the best-known quality measures in health care was put to rest. The percentage of patients with acute myocardial infarction who receive a prescription for beta-blockers within 7 days of hospital discharge has been used to evaluate U.S. managed care plans since 1996. This measure will no longer be reported by the National Committee for Quality Assurance (NCQA) because it is simply no longer needed — a development that offers encouragement and important lessons.

The data in the graph show

why the NCQA Committee on Performance Measurement voted unanimously to retire the beta-blocker measure. A decade ago, only two thirds of U.S. patients who survived acute myocardial infarction received beta-blockers; today, nearly all do. As the curve representing the 10th percentile crept above 90%, the NCQA found little variation among health plans. At least when it comes to this intervention, the U.S. health care system has become reliable.

This story is hardly one of overnight success: the NCQA's action came 25 years and 6 weeks after

the publication of the Beta-Blocker Heart Attack Trial (BHAT).¹ This randomized trial sponsored by the National Heart, Lung, and Blood Institute was stopped 9 months early because, after a 2-year follow-up period, mortality in the group of patients receiving propranolol was 7.2%, as compared with 9.8% in the placebo group. Subsequent data suggest that the relative reduction in mortality might be as high as 40% and that these benefits apply even to patients with relative contraindications to treatment with beta-blockers, such as chronic ob-

Conclusion

- Good science requires good ethics
- Translational research has great potential benefits, but raises ethical issues at all stages of the translational enterprise.
- CTSA infrastructure should provide resources for ethics (and regulatory) services.