

# Genetic Research as Therapy: Implications of “Gene Therapy” for Informed Consent

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In March 1996, the General Accounting Office (GAO) issued the report *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*. It stated that “an inherent conflict of interest exists when physician-researchers include their patients in research protocols. If the physicians do not clearly distinguish between research and treatment in their attempt to inform subjects, the possible benefits of a study can be overemphasized and the risks minimized.”<sup>1</sup> The report also acknowledged that “the line between research and treatment is not always clear to clinicians. Controversy exists regarding whether certain medical procedures should be categorized as research.”<sup>2</sup>

This problem currently plagues gene transfer research. A few months prior to the GAO report, an ad hoc committee appointed by National Institutes of Health (NIH) Director Harold Varmus expressed similar concerns in its assessment of NIH investment in research on gene therapy. The committee’s report stated:

Expectations of current gene therapy have been oversold. Overzealous representation of clinical gene therapy has obscured the exploratory nature of the initial studies, colored the manner in which findings are portrayed to the scientific press and public, and led to the widely held, but mistaken, perception that clinical gene therapy is already highly successful.<sup>3</sup>

In mid 1996, the Recombinant DNA Advisory Committee’s (RAC) five-year status report of gene therapy described the situation this way:

It is clearly too early ... to assess the therapeutic effi-

cacy of gene therapy or even to predict its promise. Numerous studies have reported the ability to express recombinant DNA *in vivo*, but few have reported clinical efficacy... The few “dramatic” successes claimed are not dissimilar to those that were reported with a variety of other therapeutic techniques for which enthusiasm ultimately dampened over time.<sup>4</sup>

Yet despite this cautionary report, and despite the fact that no therapeutic benefit has been clearly demonstrated for the more than 2,100 subjects enrolled in gene transfer research worldwide,<sup>5</sup> enthusiasm for gene therapy persists unabated.

What accounts for this enthusiasm and the consequent problem of the overselling of gene therapy? Some of the enthusiasm stems from the general optimism surrounding the Human Genome Project (HGP) and other ventures to understand the genetic basis of disease.<sup>6</sup> The explicit purpose of the HGP is to map the entire human genome, yet the project’s practical import lies in the expectation that many diseases might be cured by employing the information contained in such genomic maps. The hope that the HGP will help precipitate a therapeutic revolution has translated into widespread promotion of human gene transfer research as therapy.

This discrepancy between reality and aspiration is not confined to the HGP and genetic research; it is also symptomatic of a persistent failure to distinguish clearly between research and therapy in medical science. As the Advisory Committee on Human Radiation Experiments (ACHRE) reported, this failure has been particularly prominent when research subjects are also patients, that is, when research takes place within the social and moral setting of clinical care.<sup>7</sup> The federal systems of regulation and oversight set up to monitor medicine and the burgeoning enterprise of

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medical research have only been partially successful in dispelling the confusion between research and therapy in clinical settings.

When read together, the GAO and Varmus reports indicate that conducting gene transfer research in the context of patient care has exacerbated this long-standing confusion. Our initial aim is to trace this confusion through an examination of *The Belmont Report* in order to argue that a vital aspect of *Belmont's* distinction between research and therapy has been neglected. This neglect has serious implications for informed consent. We also argue that the proper objectives of informed consent have been outlined by Alexander Capron, but that these objectives are jeopardized by the current routinization of consent, at precisely the time they are most needed: when assessments of gene therapy research are oversold and inflated to patient-subjects, professionals, media, policy-makers, and public alike. In the conclusion, we list five recommendations necessary to correct the confusion and to improve the consent process in gene transfer research.

### The legacy of *Belmont*: a pattern of growing exceptions and confusions

Informed consent in the United States has been largely shaped by a distinction between those interventions that are “research” and those that are “therapy.” This distinction has governed the application of federal regulatory policy to scientific and medical interventions since the 1960s and 1970s, when rising concern about the protection of human subjects in research led to the requirement that the research subject’s consent should be both voluntary and informed.<sup>8</sup> Although research was viewed during this period as a risky, potentially dangerous activity for its human subjects, therapy largely retained its wholesome connotations. Therapy remained grounded in trust rather than consent, and was, therefore, somewhat resistant to the increased supervision applied to research with human subjects. Even when the doctrine of informed consent was applied in the courts to the physician-patient relationship during this period, law and policy maintained a distinction, in a variety of ways, between those medical interventions done for scientific advancement and the procurement of knowledge and interventions done for the therapeutic benefit of individual patients.<sup>9</sup>

Despite its conceptual appeal, the distinction between research and therapy has often proven elusive in the clinical setting. In fact, many medical interventions being used in the setting of patient care involve elements of both research and therapy, sometimes in ambiguous combinations. The Declaration of Helsinki recognized that some medical research is conducted in conjunction with clinical care, presenting special ethical hazards—for example, that patients’ dependency on their physicians may unduly influ-

ence their decisions to consent to an untested form of treatment.<sup>10</sup> Yet in keeping with the traditions of a trust-based relationship between physician and patient, the 1964 version of the Declaration permitted the physician-researcher to forgo obtaining informed consent in the hybrid category of “therapeutic research,” if doing so was believed to be “consistent with patient psychology.” Subsequent versions of the Declaration deleted this terminology and exclusion, and the concept of *therapeutic research* is now disfavored as *prima facie* self-contradictory.<sup>11</sup> Nonetheless, the current version of the Declaration still provides a means of conducting research in the clinical setting without informed consent.

Federal research guidelines have also encountered difficulties with situations that involve elements of both research and therapy. Current federal regulations governing research with human subjects find their theoretical underpinnings in *The Belmont Report*.<sup>12</sup> In separating “research” from “the practice of accepted therapy,” *Belmont* stated that “research” denoted “an activity designed to test a hypothesis ... and contribute to generalizable knowledge” and that “the practice of accepted therapy” denoted “interventions that are designed solely to enhance the well-being of an individual patient ... and that have a reasonable expectation of success.”<sup>13</sup> This research/therapy distinction separated those activities requiring regulation from those that did not. *Belmont* also reiterated the importance of an informed and voluntary consent to research by human subjects.

Following *Belmont*, current federal research regulations governing informed consent require that considerable information be given to potential subjects, whether they are healthy or sick. This disclosure of information to the research subject is often more detailed than that routinely provided to a patient in standard clinical care. For example, informed consent requirements for clinical care vary from state to state, and typically contain more exceptions and qualifications, most notably the patient waiver exception, where the patient may decline information, and the therapeutic privilege provision, where the physician may withhold information. Despite regulatory attempts to retain the clarity of *Belmont's* distinction between research and therapy, that clarity tends to dissolve when proposed interventions are thought to involve aspects of both research and therapy. Thus, for many clinicians and researchers, confusion sometimes persists as to how to talk about interventions that resist categorization as purely research or purely therapy. Confusion about the potential therapeutic value of research increases when it is conducted on sick subjects because such research routinely takes place in a clinical setting, where the atmosphere is more conducive to a focus on the patient’s trust of the physician and sometimes less attentive to the subject’s right to a full disclosure of information.

Recently, there have been calls from professionals and

the public to relax the regulatory requirements for research. We have entered an era in the United States in which exclusion from participation in medical research is often viewed as a discriminatory denial of beneficial treatment. Many patients and practitioners have come to regard research not as a potentially hazardous undertaking from which citizens should be protected, but as a beneficial practice that citizens are sometimes denied.<sup>14</sup> This phenomenon is related to, but separate from, the concern that certain groups of people, such as women or children, have been categorically excluded from research protocols and therefore cannot obtain the future benefits that come from research. The alleged discrimination we point to here is grounded, rather, in the assumption that participation in clinical research is itself a mode of access to beneficial medical care.

It is easy to see why such thinking seems appropriate. For example, placebo-controlled randomized drug trials in the 1980s raised such agonizing ethical questions in the midst of the AIDS epidemic that many physicians and researchers began welcoming activists' proposals to open up research to more individuals seeking access to new treatment.<sup>15</sup> As Steven Epstein has noted, physicians and researchers "reacted with sympathy" to "easing the tension between the roles of 'patient' and 'subject'" because doing so "might serve the ends of both science and ethics."<sup>16</sup> This practice also accords with a long-standing tradition in medical practice that allows physicians to offer experimental interventions to desperately ill patients.<sup>17</sup> Although many of these innovative practices are not strictly speaking research, the tradition of experimenting in desperate situations has shaped clinicians' and patients' views about the therapeutic value of research. Medical researchers have often used patients as subjects when these patients were thought by their physicians to have no better treatment option than an unproven intervention currently being studied.

Regulators have responded to these professional and public calls to relax federal requirements for research—including but not limited to informed consent requirements—by modeling them on the therapeutic alliance between physician and patient, rather than on the scientific alliance between researcher and subject. In some instances, regulatory bodies themselves have employed the language of "discrimination" in the sense noted above.<sup>18</sup> More broadly, the trend toward relaxing research requirements includes a variety of Food and Drug Administration (FDA) regulations that create exceptions and alternatives to the rigorous control of unapproved drugs, devices, and biologicals. Such regulations permit investigational drugs to be used for treatment (sometimes loosely and incorrectly called "compassionate use"),<sup>19</sup> even without prior institutional review board (IRB) approval in an emergency,<sup>20</sup> and without informed consent if the "emergency use" is thought necessary "to preserve ... life."<sup>21</sup> Other regulations expand

access to unapproved therapies and accelerate the approval process for promising treatments of life-threatening illness.<sup>22</sup> Gene transfer research even has its own "desperate use" guidelines, modeled after the "emergency use" exceptions.<sup>23</sup> These regulations all shift unproven interventions from the category of "research" to "therapy" in certain limited circumstances. Finally, new emergency research regulations allow IRBs to waive informed consent from subjects entirely when subjects are unable to give consent, time is short, and there is potential for the intervention to provide "direct benefit to the individual subjects."<sup>24</sup>

Through all of these modifications, research has become identified with an "intent to benefit," and thus has acquired connotations of therapy. Such language imparts beneficent motives to clinical research and may lead patients mistakenly to believe that their participation in research is simply another form of therapy. Moreover, as we have seen, demonstrations of an "intent to benefit" or "compassionate intent" have become sufficient, absent "a reasonable expectation of success," to qualify research participation in the clinical setting as therapeutic. The practical effect of this growing pattern of associations is that *The Belmont Report's* original two-part definition of *therapy*—an intervention that is intended to benefit the patient and that has a reasonable chance of success—has been reduced to only one part: "the intent to benefit" or "compassionate intent."

Of course, the loosening of protective rules is both compassionate and appropriate when a patient with an otherwise untreatable disease desires an experimental intervention in the clinical setting, fully understands the effects of such intervention—including the improbability of success—and voluntarily assumes any risks involved. Yet when compassion is seen as the chief justification for eliciting enrollment in a research protocol, the information giving and candid conversations about a "reasonable chance of success" are likely to take a secondary role. This likelihood that compassion will preempt information giving and conversation between researcher and subject is compounded by the fact that research interventions often occur in a moral and social context otherwise devoted to standard clinical care. The invocation of "compassionate intent," in other words, runs the hazard of short-circuiting conversation about the exact nature of the intervention as research, and thereby compromises the autonomy of the subject and the consent process itself. The presumptive categorization of research as therapeutic obscures not only consideration of any evidence for benefit but also other objectives that a robust consent process should achieve.

These other objectives have been nicely summarized and discussed by Capron. In 1974, just as heady optimism about heart transplants in the pre-cyclosporine era was giving way to more realistic assessments of such experiments,<sup>25</sup> Capron enumerated six goals that were, by then, widely

accepted as the aims of informed consent: (1) to promote individual autonomy; (2) to protect the patient-subject's status as a human being worthy of respect; (3) to avoid fraud and duress; (4) to encourage self-scrutiny by the physician-researcher; (5) to promote rational decision making; and (6) to involve the public in important questions about health care policy and research.<sup>26</sup> By framing this list alongside Denton Cooley's precipitous and unsuccessful implantation of an artificial heart into Haskell Karp in 1969, Capron pointed to a gap between the goals of informed consent and the flawed informed consent process. Capron's perspective remains useful two decades later, when optimism about the benefits of gene therapy abounds and when the material resources and social interests driving biomedical research are even more potent than they were in the late 1960s. Above all, Capron's list indicates that beneficent intentions and compassion are no substitute for candid conversation, self-scrutiny, rational decision making, and careful weighing of the evidence for potential benefit. Genuine beneficence always grounds an intent to benefit with some reasonable evidence that such intent is a well-founded and reasonable expectation.

One of Capron's major claims was that the use of experimental treatments for catastrophic diseases is best undertaken "when all the participants can behave as collaborators, each with a vital interest and an independent voice in the steps to be followed."<sup>27</sup> When research is promoted as therapy, however, that independence of voice is quite fragile. It is clear from recent studies, for example, that subject participation is heavily influenced by discussion of possible benefits, and that the long-range promise that the results of research hold for future patients is often understood by subjects as an offer of personal therapy. The Subject Interview Study done in conjunction with the ACHRE investigation and report stated that patients "did not readily make distinctions between research and medical treatment" and that, particularly for patients with serious diagnoses, "research was often viewed as one of the treatment options."<sup>28</sup> Not only did ACHRE investigators identify that patient-subjects are often confused about the difference between research and treatment, but they also wondered what accounted for this "therapeutic misconception." Even though the ACHRE committee did not investigate this question formally, at least one of its members and one prominent commentator believe that the therapeutic misconception endures because it reinforces the needs of both patient-subjects and clinical researchers.<sup>29</sup>

The degree to which subjects misunderstand the nature of their participation in research can be exacerbated by how the potential benefits of research are presented to them, for example, in the statement: "This protocol is your best treatment option." We do not dispute that, in some limited circumstances, this statement may be true, nor do we doubt that it is motivated in good conscience by com-

passion for the suffering individual. Yet compassionate motivations can obscure the nature of an intervention and can compromise full consideration by physicians and researchers, as well as by patients and subjects, of whether there is a "reasonable chance of success" or any evidence that benefit will occur.<sup>30</sup> Moreover, compassion-based recommendations further obscure the profound differences between the scientific alliance between researcher and subject and the therapeutic alliance between doctor and patient. The distinct roles of each party to these relationships become indistinguishable when physicians offer research participation as therapy.

The desire, in the present climate, to open research to more sick people in the name of compassion is very strong, and this fact is reflected in the therapeutic idioms used to describe the principal actors in clinical research. Not only are persons who are solely research subjects routinely referred to as "patients,"<sup>31</sup> but research subjects also routinely think of themselves as "patients."<sup>32</sup> If the intent of calling research subjects patients is to signal a special class of vulnerable subjects—as distinguished from normal, healthy subjects—this is best done through the use of the term *patient-subjects*, denoting their dual status. Calling research subjects simply patients obscures rather than clarifies their special vulnerability. In a similar fashion, the widespread use of the term *gene therapy* is confusing in the clinical research context. Although it describes the long-range aspirations of researchers, it obscures the extent to which the interventions studied in clinical trials fall short of being accepted therapies.

There are, to be sure, legitimate uses of the language of individual beneficence in research settings, that is, situations in which beneficent intent is grounded in reasonable evidence for a potential benefit to research subjects. If properly designed, interventions offered in many Phase III studies, and perhaps a few Phase II studies, would qualify for some measure of a beneficence by satisfying both parts of the *Belmont* criteria for therapy. Yet it is clear that many would not, and that the increasing tendency to describe research as therapy and to see patient-subjects simply as patients contributes to a widespread confusion that has a powerful dampening effect on informed consent practices, with profound implications for what is currently called gene therapy.

In brief, as measured according to either the objectives of informed consent summarized by Capron or a proper understanding of *Belmont's* two-part definitions of research and therapy, it is evident that informed consent today tends to break down precisely when it is most needed. In the hardest cases, where research participation is offered in the clinical setting, the intent of helping tends to overshadow full consideration of "a reasonable chance of success." The balanced discussion and deliberation necessary for genuinely informed consent to research in the clinical setting is

jeopardized by the current atmosphere of beneficent intent, therapeutic misconception, and escalating scientific aspirations. Many aspects of Capron's model of informed consent have been neglected, and the current, truncated use of *The Belmont Report* no longer serves us well.

### The routinization of consent and the inflation of gene therapy

At present, gene transfer research amplifies the already existing confusions between research and therapy and intensifies extant problems of informed consent. To elucidate this thesis further, we examine how informed consent has become a routine medical and social practice and how gene therapy, as an idea, has been embraced with inflated expectations by physicians, researchers, patients, and public alike.

In their comprehensive treatise on informed consent, Ruth Faden, Tom Beauchamp, and Nancy King argue that the primary justification for informed consent, as it evolved historically and ethically, was to enable autonomous choice by the recipients of medical treatment and the subjects of research.<sup>33</sup> Widespread discussion about informed consent in research emerged in the United States during the 1960s and 1970s out of a deep concern for the protection of human subjects and from a strong affirmation of self-determination for both research subjects and patients. Along with the civil rights movement, well-publicized cases like Krugman's Willowbrook hepatitis study and the U.S. Public Health Service's Tuskegee syphilis study heightened public concerns about ensuring individual autonomy in medical research. In the 1970s, federal regulation of human subjects research, including informed consent requirements, coalesced with American society's growing commitment to individual autonomy,<sup>34</sup> emerging at this time, as David Rothman has observed, as consumer protection laws designed to redress the power imbalance between researchers and subjects.<sup>35</sup> Yet to the extent that research with very ill patients is currently interpreted as treatment and justified on therapeutic grounds, the function of consent to ensure the autonomy of human subjects is compromised.

Jay Katz has argued persuasively that, in the clinical setting, informed consent has never been embraced by physicians as a means of achieving patient autonomy, but has only been tolerated by them as a necessary legal obligation or, at times, as a form of protective beneficence. In Katz's vivid terms, the medical profession has demonstrated a strong preference, deeply rooted in custom and tradition, for "custody" over "liberty" in patient care decision making.<sup>36</sup> The result is too often a form of Mirandizing, in which consent for routine patient care is seen as a legal encumbrance, introduced with words such as, "We have to consent you now." This routinization of consent is inappropriate in the ordinary clinical setting, but it becomes

even more problematic when it is transferred into the domain of research. When informed consent for research is administered in a way that parallels its typical routinized use in ordinary patient care, the potential for confusion escalates, and the autonomy of the subject is at great risk of being supplanted by the physician's traditional preference for "custody."<sup>37</sup>

Of course, consent forms for research with human subjects are scrutinized by IRBs, and in some cases by government agencies, and their content, readability, and comprehension level, as well as estimates of risk and benefit, are carefully reviewed. Yet these reviews are part of an oversight process that takes place apart from the conversations between investigators and subjects. IRBs review forms and reports, not the details of the human interaction. Furthermore, IRBs can do little or nothing about the prevailing atmosphere of beneficence and assumptions of trust that both researchers and subjects bring to studies in the clinical care setting. The function of the consent process to promote critical reflection for decision making and to empower the voices of subjects is thereby weakened. Instead of the robust exchange characterized by Capron and toward which the federal regulations aim, informed consent can become captive to the therapeutic environment with its traditional customs and priorities.

At the same time that informed consent has been woven into the routine work of medical institutions and culture, the medical research enterprise has grown in size and importance. In the increasingly competitive research world, breakthroughs are sought by every scientific team because continued funding hinges on demonstrated progress. The pressures to sustain expectations and exaggerate claims are high, both for individual researchers and research projects and for entire avenues of research. As a result, the public is sometimes subjected to inflationary rhetoric about the therapeutic promise of new interventions.

Consider, for instance, the following excerpt from the minutes of 1991 meetings of RAC and its Human Gene Therapy Subcommittee. In the subcommittee's 1991 review of a protocol for gene therapy for familial hypercholesterolemia, not only is the research described by some discussants as treatment, but some subcommittee members also considered it "discriminatory" to "treat" adults before children were entered in the protocol.<sup>38</sup> This is not an isolated example of the conflation of research and therapy. Indeed, the basis of this ambiguity is built into the ethical guidelines that RAC uses to review protocols for gene transfer research. The most recent version of RAC's "Points to Consider" document refers to research participants as "patients" in some places and "subjects" in others, and sometimes refers to clinical studies as "treatments."<sup>39</sup> This oscillation in language cannot be helpful for the process of informed consent.

The tendency of policy-makers to see entry into gene

transfer research protocols as a viable avenue of treatment further diminishes the possibility for a robust exercise of informed consent in the research context. Such thinking indicates to the potential research subject that clear therapeutic benefits can be obtained in gene transfer research, when the actual likelihood of individual benefit for the subject is often minimal or nonexistent. Properly understood, research has the search for new knowledge as its primary aim. It is precisely for this reason that research with human subjects is more extensively regulated than is ordinary clinical practice, and that research ethics are appropriately modeled on different values and priorities from those that govern clinical care. Policy-makers have sometimes failed to understand the full significance of this difference. From this vantage point, the call of activists, patients, researchers, and regulators for greater access to research protocols emerges as a symptom of the overselling of medical research as therapy.

We have emphasized many difficulties associated with informed consent in settings where research is conducted in conjunction with clinical care. The habitual tendency in clinical research settings to conflate research and therapy is especially evident in the current usage of the term gene therapy. At least two understandings of this term inform the categorization of gene transfer research as a therapeutic modality. One of these understandings of gene therapy signifies revolutionary, almost miraculous, insight into the workings of the human body; the other connotes routine therapeutic practice. It is the former, revolutionary interpretation that gives gene therapy its unique cultural appeal, and it is the latter, conventional interpretation that allows this experimental intervention to be rushed to clinical application as just another therapeutic modality.

First, the idea of gene therapy is culturally and clinically enticing because it promises to transform chronic, debilitating, and often fatal diseases into ones that can be cured, rather than merely managed. No other therapeutic modality, with the exception of vaccines, has carried this promise of a permanent and lasting cure. Despite the cautionary tone and disclaimers of the Varmus committee report, both the scientific community and the public generally seem to share the sense that research with genes constitutes research into the human essence that will readily translate into future cures. In fact, the concept of gene therapy carries the implications of a lasting fix precisely because it focuses therapy at the fundamental locus of an individual's disorder. When this concept was articulated in the late 1960s and 1970s, the idea was that, in the case of genetic-based disease, a "normal" gene could be transferred to the defective cells and integrated into those cells, thereby erasing the defect permanently. The promise that healthy genes can act as curative drugs is so appealing today that a variety of diseases, which a decade ago would have been considered primarily metabolic, environmental, behavioral,

or social—including many cancers, alcoholism, and Alzheimer's disease—are now being redefined as genetic.

Yet although gene therapy is conceived as revolutionary, its administration is viewed as routine. For example, many advocates describe gene therapy as merely "a novel form of drug delivery,"<sup>40</sup> where this description does not refer to the practice of manufacturing traditional drugs with recombinant DNA techniques, but to gene transfer. Almost everyone agrees that germ-line intervention—affecting future generations and involving a host of unknowable consequences—presents major new ethical issues, but the accepted wisdom is that somatic cell gene transfer is simply a part of the therapeutic continuum, presenting no novel ethical dilemmas.<sup>41</sup> For instance, in the inaugural issue of the journal *Human Gene Therapy* published in January 1990, Henry Miller, while serving as FDA's representative on RAC, wrote an editorial advancing this interpretation. That editorial went so far as to say:

There remains a long way to go, and we will not get there unless ... [we understand] that gene therapy and its attendant ethical considerations are not really "uncharted." What we need is not more committees evaluating gene therapy and creating more regulatory hoops; rather, we must get therapies more quickly to the patient, and more of the correct perspective on new techniques to the public.<sup>42</sup>

Miller's editorial links the idea that gene therapy is neither technically nor ethically remarkable to his own desire, as a scientist, for less institutional oversight of the research process. By 1995, this former member of RAC was recommending the elimination of this regulatory committee at NIH, arguing that such a move would be a "win-win proposition" in that it would entail the "reduction of unnecessary federal and researchers' spending on regulation; more resources available for the actual research; and with diminished regulatory disincentives, greater interest in gene therapy from industry."<sup>43</sup> Miller's rhetoric stimulates inflationary uses of gene therapy in the research setting, making it likely that the ethical issues of informed consent will be underestimated in the effort to promote therapy for patients through increased access to gene transfer research.

The revolutionary rhetoric about addressing the essence of disease in scientific research is fueled, of course, by the agendas of those with major social and economic investments in the gene therapy enterprise.<sup>44</sup> Physicians and researchers working on gene transfer techniques have substantial interests in promoting this nascent field of medical science. Biotechnology companies, moreover, have an interest in turning out numerous products related to the so-called genetic revolution—for example, diagnostic tests and DNA-based medicines. The cluster of scientific, economic,

and cultural hopes swirling around our genes seems to intensify and sustain the future promise of gene therapy at the same time that it frames this revolutionary concept in traditional garb—as merely the next wave of therapeutic options. The failure to discuss these factors candidly leads regulators, professionals, and the public to perpetuate confusion, misrepresentation, and disappointment in the sometimes appropriate, and occasionally misguided, pursuit of medical advancement.

As a final illustration of inflated and misleading rhetoric about gene therapy, it is instructive to review what has been commonly cited as the first big success in this field, that is, the celebrated case of Ashanti DeSilva.<sup>45</sup> DeSilva was enrolled in what French Anderson described as an “ADA gene therapy protocol” in 1990.<sup>46</sup> She was born with an extremely rare inability to produce the enzyme adenosine deaminase (ADA), which leads to a form of severe combined immune deficiency (SCID) and results in life-threatening infections. There are fewer than 100 persons worldwide who are known to be afflicted with ADA deficiency.<sup>47</sup> For the previous two years, DeSilva had been treated with PEG-ADA, a recently approved synthetic form of the adenosine deaminase enzyme designed to replace the enzyme missing in ADA-SCID patients, but one that is prohibitively expensive and was only partially successful with her. The “ADA gene therapy protocol” was designed, according to Anderson, to test two objectives.<sup>48</sup> The scientific objective was to determine whether DeSilva’s gene-corrected T lymphocytes could survive and would express ADA after intravenous injections. The clinical objective was to “evaluate the possible therapeutic efficacy” of these corrected T cells for the patient’s immune system. To protect this young patient-subject, the PEG-ADA treatment was continued, as it has been for all patient-subjects subsequently enrolled in this protocol. Improved immune function studies at the end of the trial allowed the investigators to call this study a success, but not without several troubling qualifications.

One seldom discussed qualification is that the second patient-subject enrolled in this ADA gene therapy protocol did not fare nearly as well as DeSilva on the scientific objective. Blood tests indicated that over 50 percent of DeSilva’s circulating T cells contained the new, corrected gene after three years, compared to only 0.1 to 1 percent in the second patient-subject.<sup>49</sup> Yet clinical signs have improved for both patient-subjects, and this points to a second qualification on the success of this study. Because the gene therapy was superimposed, for appropriate reasons of safety, on the new but standard PEG-ADA treatment, it has been very difficult to determine precisely how much of either the scientific or the clinical success was due to PEG-ADA, the gene-corrected cells, or to some combination of the two. As Eliot Marshall put it in *Science*, the “jury [is] still out.”<sup>50</sup>

Our point, however, is that, in terms of the public re-

ception, the jury is definitely in. In September 1994, the chair of the Science Committee of the U.S. House of Representatives announced that DeSilva was “living proof that a miracle has occurred.”<sup>51</sup> The media and other public officials have expressed similar enthusiasm.<sup>52</sup> In fact, the overall problem of overselling that was identified in 1995 by the Varmus committee report has been virtually ignored. Panelists Stuart Orkin and Arno Motulsky argued then that the overselling of gene therapy “goes beyond PR,” neglects “basic questions about stem cell function, gene regulation, and disease pathophysiology,” and gives patients potentially “the wrong idea about what is currently feasible.”<sup>53</sup> Even though most investigators have since refocused their attention on the basic scientific matters, they have also failed to discuss, or even recognize, the morally substantive issues of how overselling might affect patient-subject autonomy or their own capacity for professional self-scrutiny.

The concerns we raise here are not about the propriety of enrolling Ashanti DeSilva or others in the ADA gene transfer trial; still less would we want to question the motives of those involved. Rather, our concern is with the language in which this endeavor is embedded. When one places a clinical objective side-by-side with scientific aims and characterizes the whole effort as a successful therapy, one is basically inviting premature conclusions and encouraging unwarranted optimism, from patient-subjects, medical professionals, policy-makers, and public alike. Most important, such language promotes an uncritical acceptance of the wholesale combination of scientific and therapeutic aims by current and future gene transfer investigators. These individuals clearly have a great deal at stake in how such protocols are perceived and how quickly they are approved, but they also have the ethical charge of ensuring that informed consent meets standards of subject autonomy and professional self-scrutiny as their research advances toward clinical trials. In other words, these researchers should recognize that their linguistic behavior can feed the therapeutic misconception wherever their language inflates the expectations of anyone who may have a stake in the gene therapy enterprise. Our concern, therefore, is to help promote a thoroughly informed consent process, as outlined in *Belmont* and described by Capron, by prompting a discussion of how the overselling of gene therapy might enable therapeutic misconceptions among those involved in current clinical studies of gene transfer.

## Conclusion

Informed consent is fundamentally about language, about how doctors and patients, researchers, and subjects communicate. As a practice, informed consent is intended to foster genuinely collaborative decision making in both the research and patient care settings. But in the current milieu

of therapeutic enthusiasm for research, informed consent has become a way of not talking, or more precisely, a way of not talking with sufficient candor. By failing to dispel confusion about the therapeutic intentions of gene transfer research, the consent process often perpetuates a false promise to subjects. To promote conversation, researchers must earn the trust of their subjects through communication that avoids the false appeal of a beneficence warranted only by compassionate intent and devoid of evidence of benefit. In promoting an ethically sound genetic research enterprise involving human subjects, policy-makers should craft institutional opportunities for meaningful informed consent discussions in which the nuances can be sorted out.

To achieve these goals, the minimum requirement is conceptual clarity. We argue that rectifying the language of the regulatory bodies is essential for restoring informed consent for research to its original role as a collaboration-oriented process that promotes appropriate access and yet fully informs and protects subjects from inflated promises of benefit.

Specifically, with regard to gene therapy, we suggest the following.

First, RAC, FDA, and the Office for Protection from Research Risks should delete the terms *gene therapy* and *gene therapy research* and any language that would imply that a gene therapy already exists from the informed consent process and committee deliberation. This conceptual clarity is essential in those oversight institutions that set the tone for researcher-subject discussions. The term *gene transfer research* more accurately conveys the experimental practice that is currently at issue.

Second, RAC should rewrite its "Points to Consider" to differentiate clearly patients from subjects and research from treatment where those references are misleading.<sup>54</sup> In this regard, the recent diminution of RAC's oversight role is troubling. Over the past few years, RAC has received an abundance of criticism, including charges that it has exceeded its authority, delayed approval of protocols, and functioned in a "purely cosmetic" way.<sup>55</sup> Members of RAC have seen their role differently, recognizing that they are charged with reviewing a "new form of medical experimentation."<sup>56</sup> In many cases, RAC has changed the language of consent forms to delete terms like *therapy* and often challenged what it has perceived as overestimates of potential benefit from participation in gene transfer protocols, similar to the concerns we have discussed here. If the confusions about gene therapy are to be dispelled, we believe a more robust role for RAC is required, rather than a diminished one.

Third, all institutions (and investigators) charged with responsibility for protecting human subjects and ensuring their informed participation in research should critically rethink the ethical norms that currently shape the language of informed consent in areas like human gene transfer re-

search. The meaning of the principle of beneficence as direct benefit to the patient-subject should be clearly distinguished from beneficence as a possible benefit to future patients. The use of beneficence to refer to motivations of compassionate intent or desperate use in research contexts is misleading, especially to patient-subjects, and should be eliminated. The appropriate place for beneficence in genetic research is almost always as a long-range, aggregate good stemming from research results, and not as an immediate benefit resulting directly from research participation. The goal of genetic research is generalizable knowledge to benefit future patients, not current subjects. This is especially relevant to the Phase I and II protocols for gene transfer now extant. Subjects are treated ethically only when a robust exercise of consent is combined with a commitment to eliminate or reduce harms. Beneficence is too often translated into false promises of therapy for subjects, and this compromises the consent process.

Fourth, consent forms should state clearly and explicitly that there is no expected benefit to the individual patient who becomes a subject in current gene transfer research. Moreover, researchers should work to minimize the unwarranted therapeutic assumptions that inevitably result when research is conducted in the physical environment and moral context of ongoing patient care. One way to achieve this would be for each protocol and informed consent document to provide a separate section entitled "Evidence of Benefit," thereby calling attention to whatever evidence for individual benefit exists and laying it open to critical scrutiny by federal oversight bodies, IRBs, investigators, and subjects.<sup>57</sup>

Finally, the NIH training program in research ethics should make a significant investment in educating investigators to view informed consent as conversation, in the service of subject autonomy and professional self-scrutiny, and aimed ultimately at an improved, collaborative decision-making process in research.

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