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## HEALTH LAW, ETHICS, AND HUMAN RIGHTS

## Cancer and the Constitution — Choice at Life's End

George J. Annas, J.D., M.P.H.

J.M. Coetzee's violent, anti-apartheid *Age of Iron*, a novel the *Wall Street Journal* termed "a fierce pageant of modern South Africa," is written as a letter by a retired classics professor, Mrs. Curren, to her daughter, who lives in the United States. Mrs. Curren is dying of cancer, and her daughter advises her to come to the United States for treatment. She replies, "I can't afford to die in America. . . . No one can, except Americans."<sup>1</sup> Dying of cancer has been considered a "hard death" for at least a century, unproven and even quack remedies have been common, and price has been a secondary consideration. Efforts sponsored by the federal government to find cures for cancer date from the establishment of the National Cancer Institute (NCI) in 1937. Cancer research was intensified after President Richard Nixon's declaration of a "war on cancer" and passage of the National Cancer Act of 1971.<sup>2</sup> Most recently, calls for more cancer research have followed the announcement by Elizabeth Edwards, wife of presidential candidate John Edwards, that her cancer is no longer considered curable.

Frustration with the methods and slow progress of mainstream medical research has helped fuel a resistance movement that distrusts both conventional medicine and government and that has called for the recognition of a right for terminally ill patients with cancer to have access to any drugs they want to take. Prominent examples include the popularity of Krebiozen in the 1950s and of laetrile in the 1970s. As an NCI spokesperson put it more than 20 years ago, when thousands of people were calling the NCI hotline pleading for access to interleukin-2, "What the callers are saying is, 'Our mother, our brother, our sister is dying at this very moment. We have nothing to lose.'"<sup>2</sup> Today, families search the Internet for clinical trials, and even untested chemicals such as dichloroacetate, that seem to offer them some hope. In addition, basing advocacy on their personal experiences with cancer, many

families have focused their frustrations on the Food and Drug Administration (FDA), which they see as a government agency denying them access to treatments they need.

In May 2006 these families won an apparent major victory when the Court of Appeals for the District of Columbia, in the case of *Abigail Alliance v. Von Eschenbach* (hereafter referred to as *Abigail Alliance*),<sup>3</sup> agreed with their argument that patients with cancer have a constitutional right of access to investigational cancer drugs. In reaction, the FDA began the process of rewriting its own regulations to make it easier for terminally ill patients not enrolled in clinical trials to have access to investigational drugs.<sup>4</sup> In November 2006, the full bench of the Court of Appeals vacated the May 2006 opinion, and the case was reheard in March 2007.<sup>5</sup> The decision of the full bench, expected by the fall, will hinge on the answer to a central question: Do terminally ill adult patients with cancer for whom there are no effective treatments have a constitutional right of access to investigational drugs their physicians think might be beneficial?

## THE CONSTITUTIONAL CONTROVERSY

The Abigail Alliance for Better Access to Developmental Drugs (hereafter called the Abigail Alliance) sued the FDA to prevent it from enforcing its policy of prohibiting the sale of drugs that had not been proved safe and effective to competent adult patients who are terminally ill and have no alternative treatment options. The Abigail Alliance is named after Abigail Burroughs, whose squamous-cell carcinoma of the head and neck was diagnosed when she was only 19 years old. Two years later, in 2001, she died. Before her death she had tried unsuccessfully to obtain investigational drugs on a compassionate use basis from ImClone and AstraZeneca and was accepted for a clinical trial only shortly before her death.

Her father founded the Abigail Alliance in her memory.<sup>6</sup>

The district court dismissed the Abigail Alliance lawsuit. The appeals court, in a two-to-one opinion written by Judge Judith Rogers, who was joined by Judge Douglas Ginsburg, reversed the decision. It concluded that competent, terminally ill adult patients have a constitutional “right to access to potentially life-saving post-Phase I investigational new drugs, upon a doctor’s advice, even where that medicine carries risks for the patient,” and remanded the case to the district court to determine whether the FDA’s current policy violated that right.<sup>3</sup>

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#### THE RIGHT TO LIFE

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The appeals court found that the relevant constitutional right was determined by the due-process clause of the Fifth Amendment: “no person shall be . . . deprived of life, liberty, or property without due process of law.” In the court’s words, the narrow question presented by *Abigail Alliance* is whether the due-process clause “protects the right of terminally ill patients to make an informed decision that may prolong life, specifically by use of potentially life-saving new drugs that the FDA has yet to approve for commercial marketing but that the FDA has determined, after Phase I clinical human trials, are safe enough for further testing on a substantial number of human beings.”<sup>3</sup>

The court answered yes, finding that this right has deep legal roots in the right to self-defense, and that “Barring a terminally ill patient from the use of a potentially life-saving treatment impinges on this right of self-preservation.”<sup>3</sup> In a footnote, the court restated this proposition: “The fundamental right to take action, even risky action, free from government interference, in order to save one’s own life undergirds the court’s decision.”<sup>3</sup> The court relied primarily on the *Cruzan* case,<sup>7</sup> in which the Supreme Court recognized the right of a competent adult to refuse life-sustaining treatment, including a feeding tube:

The logical corollary is that an individual must also be free to decide for herself whether to assume any known or unknown risks of taking a medication that might prolong her life. Like the right claimed in *Cruzan*, the right claimed by the [Abigail] Alliance to be free of FDA imposition does not in-

volve treatment by the government or a government subsidy. Rather, much as the guardians of the comatose [sic] patient in *Cruzan* did, the Alliance seeks to have the government step aside by changing its policy so the individual right of self-determination is not violated.<sup>3</sup>

The appeals court concluded that the Supreme Court’s 1979 unanimous decision on laetrile,<sup>8</sup> in which the Court concluded that Congress had made no exceptions in the FDA law for terminally ill cancer patients, was not relevant because laetrile had never been studied in a phase 1 trial and because the Court did not address the question of whether terminally ill cancer patients have a constitutional right to take whatever drugs their physicians prescribe.

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#### THE DISSENT

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Judge Thomas Griffith, the dissenting judge, argued that the suggested constitutional right simply does not exist. He noted, for example, that the self-defense cases relied on are examples of “abstract concepts of personal autonomy,” and cannot be used to craft new rights. As to the nation’s history and traditions, he concluded that the FDA’s drug-regulatory efforts have been reasonable responses “to new risks as they are presented.”<sup>3</sup> Accepting his argument leaves the majority resting squarely on *Cruzan* and the laetrile case. As to *Cruzan*, the dissent argued that “A tradition of protecting individual *freedom* from life-saving, but forced, medical treatment does not evidence a constitutional tradition of providing affirmative *access* to a potentially harmful, even fatal, commercial good.”<sup>3</sup> As to the laetrile case, the judge noted simply that the Court had agreed with the FDA that, “For the terminally ill, as for anyone else, a drug is unsafe if its potential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit.”<sup>3,8</sup>

Finally, the dissenting judge argued that if the new constitutional right were accepted, it was too vague to be applied only to terminally ill patients seeking drugs that had been tested in phase 1 trials. Specifically, the judge asked, must the right also apply to patients with “serious medical conditions,” to patients who “cannot afford potentially life-saving treatment,” or to patients whose physicians believe “marijuana for medicinal pur-

poses . . . is potentially life saving?”<sup>3</sup> In other words, there is no principled reason to restrict the constitutional right the majority created to either terminally ill patients or to post-phase 1 drugs.

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#### DISCUSSION

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The facts as illustrated by stories of patients dying of cancer while trying unsuccessfully to enroll in clinical trials are compelling, and our current system of ad hoc exceptions is deeply flawed. The central constitutional issue, however, rests primarily on determining whether this case is or is not like the right-to-refuse-treatment case of Nancy Cruzan, a woman in a permanent vegetative state whose family wanted tube feeding discontinued because they believed that discontinuation was what she would have wanted. I do not think *Abigail Alliance* is like *Cruzan*. Rather, it is substantially identical to cases involving physician-assisted suicide, in which a terminally ill patient claims a constitutional right of access to physician-prescribed drugs to commit suicide.

The Supreme Court has decided, unanimously, that no right to physician-prescribed drugs for suicide exists.<sup>9,10</sup> There is no historical tradition of support for this right. And although the right seems to be narrowly defined, it is unclear to whom it should apply — why only to terminally ill patients? Don't patients in chronic pain have even a stronger interest in suicide? Why is the physician necessary, and why are physician-prescribed drugs the only acceptable method of suicide? None of these questions can be answered by examining the Constitution.<sup>11</sup>

Similarly, in *Abigail Alliance*, the new constitutional right proposed has no tradition in the United States, and it cannot be narrowly applied. For example, why should a constitutional right apply only to people who have a particular medical status? And why should a physician be involved at all? If patients have a right to autonomy, why isn't the requirement of a government-licensed physician's recommendation at least as burdensome as the requirement of the FDA's approval of the investigational drug? And why would the Constitution apply only to investigational drugs for which phase 1 trials have been completed? Why not include access to investigational medical devices, like the artificial heart, or even to Sched-

ule I controlled substances, like marijuana or lysergic acid diethylamide (LSD)? If it is a constitutional right, these should be available too, at least unless the state can demonstrate a “compelling interest” in regulating them.

My prediction is that after rehearing this case en banc, the full Circuit Court will reject the position of the Abigail Alliance for the same reasons that the Supreme Court rejected the “right” of terminally ill patients to have access to physician-prescribed drugs they could use to end their lives.<sup>9-11</sup> To decide otherwise would entirely undermine the legitimacy of the FDA. Patients in the United States have always had a right to refuse any medical treatment, but we have never had a right to demand mistreatment, inappropriate treatment, or even investigational or experimental interventions. This will not, however, be the end of the matter. After the physician-assisted-suicide cases, the fight appropriately shifted to the states, although so far only one, Oregon, has provided its physicians with immunity for prescribing life-ending drugs to their competent, terminally ill patients.<sup>12</sup> In the *Abigail Alliance* case, the debate will continue in the forum in which it began — the FDA — and in Congress.

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#### CONGRESS

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Congressional action also had its birth with the story of one patient with cancer and was also heavily influenced by another individual patient involved in a controversy over removal of a feeding tube. “Terri's Law” was enacted in Florida in 2003 to try to prevent the removal of a feeding tube from Terri Schiavo; the case was substantially similar to *Cruzan*. Terri's case gained national attention 2 years later.<sup>13</sup> In the midst of it, in March 2005, the *Wall Street Journal* asserted, in an editorial titled “How About a ‘Kianna's Law?’,” “If Terri Schiavo deserves emergency federal intervention to save her life, people like Kianna Karnes deserve it even more.”<sup>14</sup> At the time, Kianna Karnes was a 44-year-old mother of four who was dying of kidney cancer. Her only hope of survival, according to the editorial, was to gain access to one of two experimental drugs in clinical trials, but neither of the two companies running the trials (Bayer and Pfizer) would make the drugs available to her on a compassionate-use basis. This was because, according to the *Wall Street Journal*,

the FDA “makes it all but impossible” for the manufacturers “to provide [drugs] to terminal patients on a ‘compassionate use’ basis.”<sup>14</sup>

Almost immediately after the editorial was published, both drug manufacturers contacted Kianna’s physicians to discuss releasing the drugs to her. But within 2 days after publication, she was dead. The *Wall Street Journal* editorialized, “Isn’t it a national scandal that cancer sufferers should have to be written about in the *Wall Street Journal* to be offered legal access to emerging therapies once they’ve run out of other options?”<sup>15</sup> It noted that Mrs. Karnes’ father, John Rowe — himself a survivor of leukemia — was working with the Abigail Alliance on a “Kianna’s Law.” That law, formally titled the “Access, Compassion, Care, and Ethics for Seriously Ill Patients Act” or the “ACCESS Act,” was introduced in November 2005 and is an attempt to make it much easier for seriously ill patients to gain access to experimental drugs.<sup>16,17</sup>

The act begins with a series of congressional findings, including that “Seriously ill patients have a right to access available investigational drugs, biological products, and devices.” The act permits the sponsor to apply for approval to make an investigational drug, biologic product, or device available on the basis of data from a completed phase 1 trial, “preliminary evidence that the product may be effective against a serious or life-threatening condition or disease,” and an assurance that the clinical trial will continue.<sup>17</sup> The patient, who must have exhausted all approved treatments, must provide written informed consent and must also sign “a written waiver of the right to sue the manufacturer or sponsor of the drug, biological product, or device, or the physicians who prescribed the product or the institution where it was administered, for an adverse event caused by the product, which shall be binding in every State and Federal court.”<sup>17</sup>

Although Congress is the proper forum to address this issue, this initial attempt has some of the same problems as the *Abigail Alliance* decision: the patients to whom it applies are ambiguously classified, and clinical research seems to be equated with clinical care. Also troubling is that the patients (and would-be subjects) are asked to assume all of the risks of the uncontrolled experiments, and current rules of research — which protect subjects by prohibiting mandatory waiv-

ers of rights — are jettisoned, with the requirement of such waivers becoming the price of obtaining the investigational agent from an otherwise reluctant drug company.

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#### FDA PROPOSAL

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In direct response to *Abigail Alliance*, the FDA proposed amending its rules to encourage more drug companies to offer their investigational drugs through compassionate-use programs.<sup>4</sup> These programs first came into prominence during the early days of infection with the human immunodeficiency virus (HIV) and AIDS, when there were no effective treatments and AIDS activists insisted that they have early access to investigational drugs because, in the words of their inaccurate slogan, “A Research Trial Is Treatment Too.”<sup>18</sup> Because the FDA could not stand the political pressure generated by the activists, the compassionate-use program was developed as a kind of political safety valve to provide enough exceptions to save their basic research rules. In early December 2006, the FDA continued this political-safety-valve approach by issuing new proposed regulations with a title that could have been taken directly from the AIDS Coalition to Unleash Power (ACT-UP): “Expanded Access to Investigational Drugs for Treatment Use.”<sup>19</sup>

The FDA’s expanded-access proposal applies to “seriously ill patients when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient’s disease or condition.”<sup>4</sup> Manufacturers are required to file an “expanded access submission,” and the product must be administered or dispensed by a licensed physician who will be considered an “investigator,” with all the reporting requirements that role entails.<sup>3</sup>

Whether or not the proposal is adopted, it will do little to increase access, since the major bottleneck in the compassionate-use program has never been the FDA. The manufacturers have no incentives to make their investigational products available outside clinical trials. This is because direct access to investigational drugs by individuals may make it more difficult to recruit research subjects, and thus to conduct the clinical trials necessary for drug approval, and could also subject the drug manufacturer to liability for serious adverse reactions. Even without a lawsuit, a seri-

ous reaction to a drug outside a trial could adversely affect the trial itself.<sup>4,16,20</sup> The drug companies are right to worry that the approaches of the judiciary, Congress, and the FDA will probably make clinical trials more difficult to conduct, because few seriously ill patients who have exhausted conventional treatments would rather be randomly assigned to an investigational drug than have a guarantee that they will receive the investigational drug their physician recommends for them. This could result in significant delays in the approval and overall availability of drugs that demonstrate effectiveness — a result no one favors. Even if patients with cancer are willing buyers, drug manufacturers are not willing sellers.

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#### PHYSICIANS AND PATIENTS

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The cover story for all the proposed changes is patients' choice. But without scientific evidence of the risks and benefits of a drug, choice cannot be informed, and for seriously ill patients, fear of death will predictably overcome fear of unknown risks. This is understandable. As psychiatrist Jay Katz, the leading scholar on informed consent, has noted, when medical science seems impotent to fight nature, "all kinds of senseless interventions are tried in an unconscious effort to cure the incurable magically through a 'wonder drug,' a novel surgical procedure, or a penetrating psychological interpretation."<sup>21</sup> Another *Wall Street Journal* article, entitled "Saying No to Penelope,"<sup>22</sup> illustrates the impossibility of limiting access to unproven cancer drugs to competent adults. The article tells the story of 4-year-old Penelope, who is dying from neuroblastoma that has proved resistant to all conventional treatments. Her parents seek "anything [that] has a prayer of saving her." In her father's words, "The chance of anything bringing her back from the abyss now is very low. But the only thing I know for sure is if we don't treat her, she will die." With Penelope hospitalized and in pain, her parents continue "searching Penelope's big brown eyes for clues as to how long she wants to continue to battle for life."

It is suggested that the requirement of a physician's recommendation can safeguard against "magical thinking" and help make informed consent real.<sup>23</sup> But as Katz has noted, although physicians (and, he could have added, drug companies) often justify such last-ditch interventions as

simply being responsive to patient needs, the interventions "may turn out to be a projection of their own needs onto patients."<sup>21</sup>

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#### GOVERNMENT AND THE MARKET

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Another recurrent theme is the belief that government regulation is evil, a central tenet of the laetrile litigation of the 1970s. The court hearing *Abigail Alliance* was correct to note that laetrile never underwent a phase 1 trial, but every indication was that the drug, also known as vitamin B<sub>17</sub>, was harmless, albeit also ineffective against cancer. Laetrile became a legal cause celebre in 1972, when California physician John A. Richardson was prosecuted for promoting laetrile. Richardson was a member of the John Birch Society, which quickly formed the Committee for Freedom of Choice in Cancer Therapy, with more than 100 committees nationwide.<sup>24</sup> It took another 7 years before the FDA prevailed in its case against laetrile before the Supreme Court.<sup>8</sup> The basic arguments against FDA regulation remain the same today: the FDA follows a "paternalistic public policy that prevents individuals from exercising their own judgment about risks and benefits. If the FDA must err, it should be on the side of patients' freedom to choose."<sup>25</sup>

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#### PUBLIC POLICY

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The FDA will prevail again today, not only because there is no constitutional right of access to unapproved drugs but also because even if there were, the state has the same compelling interest in approving drugs as it has in licensing physicians. From a public policy view, the *Abigail Alliance* court, the Congress, and the FDA all seem to be suffering from the "therapeutic illusion" in which research, designed to test a hypothesis for society, is confused with treatment, administered in the best interests of individual patients.<sup>21,26,27</sup> Of course there is a continuum, and it is perfectly understandable that many patients with cancer, told that there is nothing conventional medicine can do for them, will want access to whatever is available in or outside the context of clinical trials. But this is a problem for patients, physicians, the FDA, and drug manufacturers. First, because terminally ill patients can be harmed and exploited, there are better and worse ways to die.<sup>21,26</sup> Second, it is only through research, not "treat-

ment,” that cancer may become a chronic illness that is treated with a complex array of drugs, given either together or in a progression.<sup>28,29</sup> The right to choose in medicine is a central right of patients, but the choices can and should be limited to reasonable medical alternatives, which themselves are based on evidence.

This is, I believe, good public policy. But it is also much easier said than done.<sup>30</sup> Death is feared and even dreaded in our culture, and few Americans are able to die at home, at peace, with our loved ones in attendance, without seeking the “latest new treatment.” There always seems to be something new to try, and there is almost always anecdotal evidence that it could help. This is one reason that even extremely high prices do not affect demand for cancer drugs, even ones that add little or no survival time.<sup>31,32</sup> When does caring for the patient demand primary attention to palliation rather than to long-shot, high-risk, investigational interventions? Coetzee’s Mrs. Curren, who rejected new medical treatment for her cancer and insisted on dying at home, told her physician, whom she saw as “withdrawing” from her after giving her a terminal prognosis — “His allegiance to the living, not the dying” — “I have no illusions about my condition, doctor. It is not [experimental] care I need, just help with the pain.”<sup>31</sup>

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