



2011

# Is Cystic Fibrosis Genetic Medicine's Canary?


Susan M. Lindee

*University of Pennsylvania*, [mllindee@sas.upenn.edu](mailto:mllindee@sas.upenn.edu)

Rebecca Mueller

*University of Pennsylvania*, [rebeccamontana@gmail.com](mailto:rebeccamontana@gmail.com)

Follow this and additional works at: [http://repository.upenn.edu/hss\\_papers](http://repository.upenn.edu/hss_papers)

 Part of the [Genetics and Genomics Commons](#), [History of Science, Technology, and Medicine Commons](#), and the [Medical Genetics Commons](#)

---

## Recommended Citation

Lindee, S. M., & Mueller, R. (2011). Is Cystic Fibrosis Genetic Medicine's Canary?. *Perspectives in Biology and Medicine*, 54 (3), 316-331. <http://dx.doi.org/10.1353/pbm.2011.0035>

This paper is posted at ScholarlyCommons. [http://repository.upenn.edu/hss\\_papers/15](http://repository.upenn.edu/hss_papers/15)  
For more information, please contact [repository@pobox.upenn.edu](mailto:repository@pobox.upenn.edu).

---

# Is Cystic Fibrosis Genetic Medicine's Canary?

## **Abstract**

In 1989 the gene that causes cystic fibrosis (CF) was identified in a search accompanied by intense anticipation that the gene, once discovered, would lead rapidly to gene therapy. Many hoped that the disease would effectively disappear. Those affected were going to inhale vectors packed with functioning genes, which would go immediately to work in the lungs. It was a bewitching image, repeatedly invoked in both scientific and popular texts. Gene therapy clinical trials were carried out with a range of strategies and occasionally success seemed close, but by 1996 the idea that gene therapy for CF would quickly provide a cure was being abandoned by the communities engaged with treatment and research. While conventional wisdom holds that the death of Jesse Gelsinger in an unrelated gene therapy trial in 1999 produced new skepticism about gene therapy for CF and suggests that CF may provide a particularly compelling case study of a failed genomic technology, perhaps even of a medical "canary." The story of CF might be a find of warning to us that genetic medicine may create as many problems as it solves, and that moving forward constructively with these techniques and practices requires many kinds of right information, not just about biology, but also about values, priorities, market forces, uncertainty, and consumer choice.

## **Disciplines**

Genetics and Genomics | History of Science, Technology, and Medicine | Medical Genetics

# IS CYSTIC FIBROSIS GENETIC MEDICINE'S CANARY?

---

SUSAN LINDEE\* AND REBECCA MUELLER†

**ABSTRACT** In 1989 the gene that causes cystic fibrosis (CF) was identified in a search accompanied by intense anticipation that the gene, once discovered, would lead rapidly to gene therapy. Many hoped that the disease would effectively disappear. Those affected were going to inhale vectors packed with functioning genes, which would go immediately to work in the lungs. It was a bewitching image, repeatedly invoked in both scientific and popular texts. Gene therapy clinical trials were carried out with a range of strategies and occasionally success seemed close, but by 1996 the idea that gene therapy for CF would quickly provide a cure was being abandoned by the communities engaged with treatment and research. While conventional wisdom holds that the death of Jesse Gelsinger in an unrelated gene therapy trial in 1999 produced new skepticism about gene therapy, the CF story suggests a different trajectory, and some different lessons. This article considers the rise and fall of gene therapy for CF and suggests that CF may provide a particularly compelling case study of a failed genomic technology, perhaps even of a medical “canary.” The story of CF might be a kind of warning to us that genetic medicine may create as many problems as it solves, and that moving forward constructively with these techniques and practices requires many kinds of right information, not just about biology, but also about values, priorities, market forces, uncertainty, and consumer choice.

---

\*Department of the History and Sociology of Science, University of Pennsylvania, Philadelphia.

†Department of Genetic Counseling, Arcadia University, Glenside, PA.

Correspondence: Susan Lindee, Department of the History and Sociology of Science, University of Pennsylvania, Suite 303, Cohen Hall, 249 S. 36th Street, Philadelphia, PA 19104.

E-mail: [mllindee@sas.upenn.edu](mailto:mllindee@sas.upenn.edu).

The authors are indebted to Barbara Bernhardt, Michael Mennuti, Reed Pyeritz, Ron Rubinstein, and other colleagues associated with the Center for the Integration of Genetic Healthcare Technologies at the University of Pennsylvania. This research was supported by CIGHT and dependent on the CF community at Penn and in the Philadelphia region.

*Perspectives in Biology and Medicine*, volume 54, number 3 (summer 2011):316–31

© 2011 by The Johns Hopkins University Press

POORLY UNDERSTOOD, linked in complex ways to ideas about race and European identity, and the focus today of an ethically vexed and rapidly expanding testing industry, cystic fibrosis is a relatively common life-threatening genetic disorder in the United States, the United Kingdom, and the European Union. Many genetic diseases are invisible to the general public, but CF is a high-profile genetic disease, often characterized as a “white” disease though it occurs in many populations. Over the last five years it has become the focus of genetic screening programs of many kinds, but especially for newborns, all over the world. CF is also a scientifically interesting genetic disease. By the simple if imperfect quantitative metric of citations in PubMed, CF has been the focus of more scientific papers than any other genetic disease. Currently at least a dozen biotechnology firms market various kinds of tests for CF, both to health care providers and in some cases directly to consumers online. A search for marketing and industry reports on CF testing brings up 24 printed since 2002, ranging in price from \$750 to \$7,995. Like many other genetic diseases, CF is expected to more readily generate profits through genetic testing and screening of large populations than through therapeutic interventions, though some interventions for CF have been profitable or at least promising. Most recently, in November 2010, an experimental drug was shown to improve lung function in 4 to 5% percent of CF patients who have a particular mutation, G551D-CFTR; this research finding could make genotype highly relevant to clinical intervention, as the drug, termed a “potentiator,” may increase the activity of defective cell-surface CFTR proteins, most commonly encoded by the G551D mutation (Accurso et al. 2010).

This kind of improvement, tied to a rare mutation and involving not an outright cure but a modest reduction in symptoms, bears little resemblance to the early promises generated when the gene was first identified and mapped in 1989. In the early 1990s, CF was supposed to be a disease that was about to disappear: it was widely expected to be the first genetic disease to be successfully treated with gene therapy, and the claims for gene therapy and its future efficacy in the early years were extravagant. But gene therapy did not succeed, CF did not disappear, and many questions about the disease and its treatment remain unresolved. Some research on CF gene therapy continues, but the idea of gene therapy as a simple solution that would eliminate the most problematic clinical manifestations of the disease, particularly long-term lung damage as a result of thickened mucus, ceased to be promoted within seven years of the discovery of the gene. While the death of Jesse Gelsinger in an unrelated gene therapy trial in the fall of 1999 at the University of Pennsylvania had a devastating impact on gene therapy everywhere, by that time the CF community had already left behind expectations that gene therapy would rapidly lead to a “cure” for CF (Stockdale 1999).

In this article, we consider the rise and fall of gene therapy for CF, placing these events in a context that suggests their possible relevance to contemporary

developments in genomic medicine, pharmacogenomics, and genetic testing generally. We bring to this project two perspectives, that of a historian of science and medicine who has worked on the history of genetic disease and human genetics generally (Lindee), and that of a genetic counselor in training, trained clinical research coordinator and CF patient activist who often helps clinicians understand the CF experience (Mueller). We suggest that the case illuminates the social process of hoping in genomic medicine, and that the disease itself might be understood as a medical “canary,” like those canaries that miners brought into coal mines because the birds could be expected to die rapidly if the mine contained methane or carbon monoxide. The story of CF might be a kind of warning to us that genetic medicine is taking us to forms of technical management that could create as many problems as they solve, and that moving forward constructively with these techniques and practices requires many kinds of right information, not just about biology, but also about values, priorities, uncertainty, and consumer choice.

#### THE COMPLEXITY OF CF

CF typically causes a build-up of thick mucus, which leads to chronic infection and can damage the lungs, as well as the failure of the pancreas to excrete digestive enzymes, which causes poor absorption of nutrients in the digestive tract and can lead to deficiencies and slow growth in children. It also causes salty sweat. Advice about excessively salty-tasting children, and their likelihood of dying young appears as early as the 16th century in German and other European medical texts. CF as a named clinical problem emerged after 1900, in a series of scientific studies that gradually linked its diverse manifestations to a single, though unknown, cause. The first publication on CF is usually attributed to the Swiss pediatrician Guido Fanconi and colleagues, who in 1936 described two children with “cystic pancreas fibromatosis and bronchiectasis” (Fanconi, Uehlinger, and Knauer 1936). In 1938, the American physician Dorothy Hansine Andersen correlated the characteristic cystic fibrosis of the pancreas with the lung and digestive disease prominent in CF. Most authors by this time also began to recognize a familial inheritance pattern, and Andersen and R. C. Hodges proposed an autosomal recessive pattern of inheritance in CF in 1946. In 1953, physician Paul di Sant’Agnese, who became a key figure in the creation of the Cystic Fibrosis Foundation in 1955, described abnormalities in sweat electrolytes, an insight which led to sweat testing, still a primary diagnostic test for CF.

Recognizing the disease, however, even in the age of genetic testing, remains complicated. CF has porous boundaries, and the diagnostic category has expanded (Kerr 2005). Technologies for detection can also be inconclusive. In 2008, the Cystic Fibrosis Foundation (CFF) Consensus Report noted that the diagnosis of CF remains uncertain, neither sweat chloride nor genetic testing always providing clear or prognostic results (Farell et al. 2008). By the 1980s,

major gains had been made in extending the lifespan of CF patients through clinical interventions in diet, physiotherapy, and pharmacology, making survival into mid-adulthood relatively common, but the disease remains difficult to understand. A 1987 paper called it “A Disease That Doesn’t Make Sense” (Beaudry 1987).

Early efforts to find the CF gene were directed by Francis Collins, then a new member of the faculty at the University of Michigan (and now, of course, the director of the NIH and a renowned gene hunter). In 1985 Collins’s group linked the CF gene to chromosome 7, and various labs worked to pinpoint the gene in a search that drew on new mapping methods. One article in 1988 called finding CF an “almost irresistible” intellectual challenge and “Nobel Prize material” (Roberts 1988, p. 141). Collins persuaded the CEO and the Scientific Director of the Cystic Fibrosis Foundation, Bob Dressing and Bob Beall, to support the search for the gene (Drumm 2001). Before the gene was identified, the Foundation also began to promote the possibility of gene therapy. In 1988 it brought together scientists on the NIH campus to examine gene therapy for CF, and six months before news of the gene’s discovery was reported, it announced a request for applications “to further stimulate interest in the field” of CF gene therapy (Beall 1999). By 1989, when Collins and his collaborators published a paper identifying cystic fibrosis transmembrane conductance regulator (CFTR) as the gene responsible for CF (Rommens et al. 1989), the CFF already had plenary and symposia focusing on gene therapy on the program of the Third Annual North American Cystic Fibrosis Conference. Meanwhile the foundation began supporting projects that ultimately set the stage for clinical trials of CF gene therapy, including the *in vitro* correction of CF cells via viral transduction (Beall 1999).

At the same time, the climate became increasingly favorable to gene therapy work in general. A year after the CF gene was discovered, W. French Anderson initiated the first trial of gene therapy for treatment of the rare immunologic condition adenosine deaminase deficiency, in a study that was widely perceived as a success. Anderson introduced a new journal, *Human Gene Therapy* (1990), and in an early issue Thomas Friedman (1990) explained how “The discovery of a new gene . . . is almost always accompanied by an implicit promise that a form of genetic therapy may eventually become possible. Certainly, the recent announcement of the isolation of the cystic fibrosis gene included such hopes” (p. 176). The CFF soon approached the U.S. Congress to ask for support of CF gene therapy research, and in 1992 Congress mandated that the NIH establish Gene Therapy Centers for Cystic Fibrosis, to be jointly funded by the NIH and the foundation. Together they infused more than \$50 million into CF gene therapy research (Beall 1999).

## CLINICAL TRIALS

Only three and half years after discovery of the CF gene, three proposals to initiate clinical trials were presented to the December 1992 NIH Recombinant DNA Advisory Committee. The three investigators had different professional profiles and proposed different research approaches. Michael Welsh of the University of Iowa, whose group had successfully corrected CFTR function in vitro, was a pulmonologist who had been investigating ion transport across epithelia in the years leading up to discovery of the CF gene; his scientific forays into gene therapy were limited to treatment of CF. James Wilson, who was in the process of moving from the University of Michigan to the University of Pennsylvania to head a new gene therapy institute, was considered the first professional gene therapist, and his commitments were to a form of intervention rather than a disease. Ronald Crystal, who was trained in pulmonology, had like Wilson worked in gene therapy. He was in the process of leaving the NIH for Cornell. Both Wilson and Crystal launched biotech ventures related to gene therapy. Welsh did not.

While each study involved a slightly different adenoviral vector, the main differences pertained to the sites and methods of administration, correlating roughly with the level of risk. Welsh proposed a pilot study involving administration of the CFTR cDNA with an adenoviral vector to the nasal epithelia of (only) three subjects with CF, noting that the nasal epithelia had traditionally been used for initial testing of therapies in CF because it was less invasive and was similar to airway epithelia. He felt that this “conservative approach” “provide[d] added assurance that if untoward effects occur, e.g. inflammatory response, the consequences will be less severe than effects that might occur in the lung.” Selection of the nasal administration was also based on the idea that it would provide more valuable efficacy data, since “the investigators will have more direct access to the transduced tissue,” which could be easily sampled and directly assessed for changes in transepithelial voltage across the nasal epithelium (RAC 1992). Welsh would measure success with the “nasal potential difference” test, a test of transepithelial voltage that can be used to resolve borderline cases of CF that are difficult to diagnose by other means. The test is, however, notoriously difficult to perform and interpret. It requires that electrodes connected to a voltmeter be placed in the nasal mucosa and the forearm skin to measure electrical conductance in nasal passages at baseline and then again after perfusion with several different solutions. Since the CFTR gene encodes a chloride ion transport channel that regulates the salt content in the fluid that covers the surface of the nose and lungs, electrical conductance at baseline and in response to perfusion by different salt solutions differs in individuals with CF. However, these measurements do not correlate with clinical parameters like lung function. Since gene therapy was one of the first treatments expected to influence the underlying pathophysiology rather than the immediate clinical symptoms of disease, it was not clear how to see it working. The nasal potential difference test thus emerged as a practical but problem-

atic endpoint, and the methods for measuring nasal potential were repeatedly questioned and modified as the decade progressed. The selection of this ambiguous test with unknown relevance to clinical outcomes to track the results of gene therapy is suggestive. The changes expected in these clinical trials were relatively subtle, and not necessarily directly relevant to a cure.

Crystal's planned study was significantly more invasive and aggressive than Welsh's. He proposed a dose-escalation study in 10 subjects, each of whom would receive nasal administration of the adenoviral vector followed 24 to 48 hours later by administration of 20ml of vector solution to the main bronchus of the lung—a more risky plan. While his study endpoints paralleled Welsh's, rather than limit biopsies to the nasal epithelium, his plan included nine to 11 bronchoscopies for each research subject (RAC 1992). This seemed high-risk to the RAC reviewers, especially in comparison to Wilson's proposal of four bronchoscopies per subject, and to Welsh's, which excluded lung administration altogether. Wilson's study plan was similar to Crystal's, but it lacked the preliminary nasal administration of the vector (which served as a safety check of sorts) and involved occlusion of an airway for 10 minutes to "achieve excellent gene transfer" via administration of vector solution (RAC 1992).

Approaches to gene therapy for CF thus seemed to be shaped by the individual investigator's primary interests in the technique or the disease. The RAC review involved questions about everything from public health and the risk of viral shedding by subjects, to the proportion of cells that needed to be transduced for clinical efficacy. The committee members also worried about journalists: investigators were asked to protect their research subjects from the news media (RAC 1992). The most important problem noted with all three proposals was that they did not have an identified, and justifiable, target cell type. While adenoviral vectors were primarily thought to target airway epithelial cells, a variety of lung cells express the CFTR protein. Therefore, even if transduction of the airway epithelial cells was successful, it was not known whether this would result in clinical benefit. Despite these gaps and uncertainties, all three protocols were approved with minor changes.

In April 1993, Crystal administered the first dose of CFTR vector. The *New York Times* reported: "fulfilling hopes that had gathered locomotive force in the past several months, a 23-year-old man this weekend became the first patient to receive human gene therapy against cystic fibrosis" (Angier 1993). Crystal commented on the exciting first, saying that initiation of the study "helps unfurl a new era of medicine." He saved the syringe used to administer the vector, as a historical artifact. CFF Scientific Director Beall offered a slightly more modulated assessment, explaining that "we have yet to save a life," but that the potential therapy was the first to get "to the cause of the disease rather than just treating the symptoms." With less fanfare, Michael Welsh's team at the University of Iowa completed their small study of CF gene therapy and published in the jour-



nal *Cell*. Welsh's study demonstrated safety of the nasal administration and apparent correction of the chloride transport defect as measured by nasal potential difference, but the team did not find mRNA transcripts or CFTR protein product (Zabner et al. 1993).

Thus two major gene therapy trials had been completed without a consensus about what would eventually constitute evidence of success, or about how to measure the results. The next year, after an additional eight unsuccessful trials, a paper in *Nature Genetics* describing an adverse event provoked a discouraging editorial. Crystal's team had reported a patient who experienced a "transient systemic and pulmonary syndrome" in response to the trial. While Crystal proposed that despite this event his study demonstrated "feasibility" of "adenoviral vector transfer" (Crystal et al. 1994, p. 42), U.K. researchers Eric Alton and Duncan Geddes (1994) were more critical, proposing that the cumulative results presented "a mixed message for cystic fibrosis gene therapy": "although the appropriate cells to target [with gene therapy] are not known, this ignorance is well matched by an inability to target a particular cell type with existing gene transfer technology." They questioned the efficacy of gene therapy, the means of measuring it, and the endpoints chosen, stating that "it would be a mistake to enter into large-scale clinical trials until these questions are resolved" (pp. 8–9).

At this point, many in the CF community were still promoting the idea that gene therapy promised a rapid cure for CF. At the 1994 North American Cystic Fibrosis conference, Wilson spoke of the "tremendous progress" being made toward "successful application of gene therapy for the treatment of CF," proposing that "the next year will be exciting as the existing gene therapy techniques are further tested in the clinic and as novel approaches are developed in the laboratory" (NACF 1994, p. 71).

Meanwhile, CF patients had their own perspectives on gene therapy and its potential. In Cystic-L, an email list server begun in 1994 and now archived, they debated possibilities for a cure and discussed their perceptions of the scientific promise of gene therapy research. With 600 subscribers, most of whom were American adults with CF and parents of children with the disease, the Cystic-L archives provide some insight into experiences on what one participant called the "bleeding edge" of biomedical research (Cystic-L 1995).

The CF community posting to Cystic-L was acutely aware of the capital being invested in gene therapy research, as Alan Stockdale's (1999) study has demonstrated. Stockdale analyzed interviews and Cystic-L list server correspondence from the mid- to late-1990s and explored how the participants expressed frustrations with the CFF and its focus on gene therapy research. Many seemed to feel that the day-to-day needs of the community were being ignored, and even those favoring significant research funding questioned the emphasis on gene therapy and wondered why support was not more evenly distributed to other potential therapies. One participant repeatedly noted that "in the gene therapy rush," the possibility of "a viable pharmacological approach" had been

ignored (Cystic-L 1994–1996). Another explained that even as “the vast majority of research funds are being sunk into the glamorous gene therapy approach, there are a few hardy souls (steeled against continual rejections from grant giving bodies) who are working on a pharmacological approach” (Cystic-L 1995). While some felt CF gene therapy research detracted from other projects, others said any research would have collateral benefits and ultimately help all individuals with the disease. Another proposed that all CF researchers “reap benefits from the gene therapy hype,” which had “generated a lot of general scientific interest in CF” (Cystic-L 1994).

In an impassioned defense of gene therapy, one participant showed considerable insight into the uncertainties and deep levels of social trust involved in his or her own decision:

I'm doing gene therapy and signed papers that said this COULD cause lung cancer (where is the lesser of two evils?) and they really don't know all the side effects (there haven't been any short-term). I also realize I have to do something to help myself and the rest of us with CF and that I'm using my educated opinion and that of others a whole lot smarter than me to make a decision to participate and put my faith in researchers. I'm trusting animal studies—have you ever heard a mouse cough?—and I'm also trusting that some intern at Targeted Genetics didn't just have a final exam he was up for 34 hours studying for and didn't just break up with his girlfriend and had a parent die the night he made up my “batch” of genes. And I'm trusting what's being put into my body is the corrected CF gene on the adeno-associated virus [sic] (AAV) and not the Ebola virus!! (Cystic-L 1996)

For this patient, the profound trust required to participate in gene therapy was visible and the points at which the system could break down were not just technical: a romantic disappointment or a mixed-up virus were both possibly implicated in the medical outcome.

#### GENES IN A JAR

All three of the CF trials approved by the RAC in 1992 had support from biotech firms (Genetic Therapy Inc, Genzyme, and potentially GenVec; Culotta 1993). Biotechnology publications started to “segment” the gene therapy market, and CF was widely reported to be a \$600 million gene therapy market, expected to open in the early 2000s (Carey 1993). The 1983 passage of the Orphan Drug Act made treating such a niche market potentially profitable with tax breaks and extended exclusive patents. Genzyme, a biotechnology company that had focused on developing enzyme and carbohydrate expertise (which resulted in a lucrative therapy for another rare genetic condition), became involved in CF research as early as 1990; Alan Smith, a Genzyme scientist, coauthored Welsh's seminal paper on *in vitro* transduction of CF cells (Alster 1991). In addition, Genentech (with help from Ronald Crystal) was developing a recombinant

DNA-based non-gene therapy medication for CF, Pulmozyme, that entered the market in 1994. Pulmozyme was termed a “star drug” that netted \$22.4 million in first-quarter sales and perhaps indicated to both companies and investors that CF presented market opportunities (Fisher 1994; Hamilton 1993).

While the relatively large size of the CF market made it a desirable target for commercial efforts at gene therapy, the fact that it would be amenable to so-called in vivo forms of gene therapy also made it appealing to biotechnology companies. Initial gene therapy studies were ex vivo, involving the removal, treatment, and reintroduction of cells to patients which made gene therapy “more of a service business than a traditional pharmaceutical business.” The idea of “genes in a jar or syringe” was commercially more appealing (Pollack 1992), and with CF, gene therapy could (in theory) be aerosolized for a group of patients who were already accustomed to doing multiple nebulizers daily.

By 1995, nine publicly traded companies were involved in gene therapy programs, three of which were targeting CF, namely Genzyme, Targeted Genetics, and Vical (Fisher 1995). By 1998, seven firms (both American and European) were supporting CF gene therapy studies, suggesting that commercial interest in CF gene therapy was greater than for any other monogenic disorder (Martin and Thomas 1998). Industry investments almost certainly surpassed the \$50 million that the CFF and NIH invested in the early phases of CF gene therapy research, with Genzyme reportedly spending in excess of \$24 million annually on gene therapy research and development, and Genentech investing \$17 million in GenVec’s CF gene therapy research (Beall 1999; Martin and Thomas 1998).

In June 1995, a workshop on gene therapy was held at the University of Pennsylvania, where researchers, economists, and journalists gathered to discuss the socioeconomic and ethical issues pertinent to gene therapy. Among the attendees were Penn bioethicist Arthur Caplan and gene therapist James Wilson—later, of course, key figures in the Gelsinger case. In an overview published in *Human Gene Therapy*, one report described a consensus that the field of gene therapy was “not ready for a market-driven approach. As a result, gene therapy research should remain in the academic sector for a longer time than has been the case with traditional drug therapies” (Hillman et al. 1996, p. 1139). Wilson said that the involvement of the biotechnology industry in gene therapy was premature and “counterproductive,” because “the need for short-term return on venture capital-financed biotechnology is at odds with the early development of the field and the need for more fundamental research in core gene transfer technologies” (p. 1140). Another researcher present suggested that gene therapy might never fit into a corporate model, because if it could truly bring about cures, it would render many lucrative drugs obsolete, thereby threatening “the economic structure of the traditional pharmaceutical industry” (p. 1141).

When Ronald Crystal published still another promotion of gene therapy in 1995, his paper on “The Gene as the Drug” provoked a letter to the editor that explicitly, and cogently, contradicted the many claims for gene therapy that were

appearing in major scientific journals. J. A. Dodge (1995) of Queen's University of Belfast noted the contrast between the "cautious tone" of some gene therapy researchers and the "exaggerated prospects for gene therapy claimed" by Crystal. Dodge reminded readers that CF is a multi-system disease that likely causes entirely irreversible damage to multiple tissues, including the lungs. As such, he stated that "gene therapy will not cure cystic fibrosis" and insomuch as it might allay pulmonary symptoms in undamaged lungs, he reminded readers that: "We simply do not know what to expect in terms of the duration of effect or the frequency with which inhalation may need to be repeated, and there is considerable uncertainty about the exact respiratory epithelial cells which should be targeted" (p. 182). Dodge went on to suggest that germ-line CF gene therapy might some day cure CF, but that in the meantime "we should explore other promising avenues and build on the understanding of CFTR function which has been developing even more rapidly than attempts at gene therapy." Lastly, he lamented the overly optimistic media coverage of gene therapy for CF and asked readers to counteract such accounts by taking "a balanced and responsible view of the prospects for control of cystic fibrosis."

The same year an NIH committee echoed his concerns: "In the enthusiasm to proceed to clinical trials, basic studies of disease pathophysiology, which are likely to be critical to eventual success of gene therapy, have not been given adequate attention" (Orkin and Motulsky 1995, p. 1). The panel also concluded that "results had been oversold by investigators and sponsors," leading to the "mistaken and widespread perception that gene therapy is further developed and more successful than it actually is" (p. 2). Increasingly, standards for the assessment of gene therapy were rising, and expectations of quick success were falling. A 1995 editorial by J. M. Leiden in the *New England Journal of Medicine* concluded that "despite remarkable progress in establishing the conceptual basis of somatic gene therapy, the practical reality is more sobering. To date, there is little or no published evidence of the clinical efficacy of gene therapy" (p. 871). Leiden proposed that enthusiasm for gene therapy should not be altogether abandoned, but that perhaps gene therapy researchers had simply chosen the wrong diseases as the initial targets. Like many others, he called scientific and lay claims about gene therapy misleading, and he asked scientists (and the press) to present and publish results in "a balanced way and temper our enthusiasm with practical reality" (p. 872).

The year 1995 therefore marked a turning point. In 1996, Collins noted that "cystic fibrosis, with its complex effects on cell membranes, involvement of multiple organ systems, and potential for unpredictable clinical behavior, has proven to be a challenging target for the forces of modern molecular medicine" (NACF 1996, p. 74). By this time even the Foundation was deemphasizing gene therapy studies (Couzin-Frankel 2009, p. 1506). At the 1999 NACF conference, held a few weeks after the death of Jesse Gelsinger at Penn, only a single workshop and two roundtable discussions were devoted to gene therapy. The topic was notably absent from the plenary summaries and symposia. In 2005, attendance at the annual

meeting of the American Society of Gene Therapy (ASGT) fell to 1,900, after a peak of 2,845 in 2002. At a stakeholders' meeting in Arlington, Virginia, that year, gene therapists discussed whether it was possible to revive the field (Hoag 2005). By that time, two children in a clinical trial for the treatment of X-linked severe combined immunodeficiency (X-SCID), led by Alain Fischer at the Necker Hospital in Paris, had developed leukemia after the retroviral vector integrated itself into or near an oncogene. In response, clinical trials were shut down and restarted repeatedly in the United States and Europe as adverse events were disclosed and as regulatory bodies determined if and how such trials should proceed.

Targeted Genetics finally abandoned its gene therapy clinical trial for cystic fibrosis in 2005, and the same year Avigen announced that it would cut short its adeno-associated virus gene therapy trials for hemophilia B, after 13 years of work. Avigen had long provided funding support for clinical trials to Katherine High, president of the ASGT, and to Mark Kay, director of the program in human gene therapy at Stanford School of Medicine and a founder of the ASGT. In 2008, the ASGT renamed itself the American Society of Gene and Cell Therapy, because "the concept of gene therapy includes gene-modified cell therapy, and an inclusive name will empower the Society to expand its membership base and help foster further collaborative research to advance the use of genes and cells as medicine to treat disease" (Woo 2008). In other words, they were expanding their focus and modulating the emphasis on gene therapy, partly in order to appeal to a broader membership base.

A September 2009 report in *Scientific American* proposed that "Ten years ago this month the promise of using normal genes to cure hereditary defects crashed and burned, as Jesse Gelsinger, an 18-year-old from Tucson, Ariz., succumbed to multiorgan failure during a gene therapy trial at the University of Pennsylvania" (Wenner 2009, p. 14). This is certainly reflective of the common wisdom about gene therapy, but the CF story suggests that Gelsinger's death was less a precipitating event than a crucial blow to a research field that was already staggering.

### **THE SOCIAL PROCESS OF HOPING**

What can the CF gene therapy story suggest for our understanding of contemporary genomic medicine? In retrospect, the CF community seems to have seized on the general enthusiasm for gene therapy to promote interest in the disease and to encourage federal research funding to be devoted to it. For the CFF, the gene therapy program was productive even if gene therapy itself was not successful: it called attention to the disease and generated increased public funding for CF related research. This suggests that therapeutic interventions can have some qualities of fashion, and that "hope" may be an empirical matter. Perhaps fashion and hope could become part of the planning and assessment process for new medical interventions, in ways that build in the right level of caution, calibrated to balance the social enthusiasms that shape biomedical research.

The CF case also suggests the potential paradoxes involved in research programs focused on success in whatever form it takes: CF was known to be an extremely complex disease (though many diseases are complex), and trials began despite considerable confusion and uncertainty about which cells would be affected by gene therapy, how many cells would need to be exposed to the vectors, and even what needed to be measured in order to show an effect. These criticisms of course came from within the scientific community. Those engaged in developing gene therapy for CF recognized that they were moving forward without a real consensus about what endpoint would count as a cure, or what measurements would be definitive signs of success. They sometimes resorted to “correction of the phenotype” as a shorthand description of an uncertain outcome—but did not always agree about what that correction would look like in practice. The hope that gene therapy would succeed—indeed, the expectation that it would succeed rapidly and completely—may have contributed to a sense that no definitive endpoint or measurement was necessary. If gene therapy was going to make the disease disappear, it was apparently going to happen so quickly that figuring out the proper cells to target (and how to target them) was less important than getting the trials going. Caution, in such a climate of intense expectation, could look like a mistake.

Finally, it is clear from the CF case that actors with different stakes saw the risks and plans differently. As a rough approximation, researchers with a primary stake in CF tended to be more conservative in their research plans; those with a primary stake and perhaps faith in gene therapy, more aggressive. Patients, who have the highest stakes in any cure, were among the more trenchant observers of the entire enterprise—alternately enthusiastic and skeptical, worried about industry interests, and aware of the uncertainties of scientific knowledge. Communications research spanning the last 30 years has demonstrated that the supposed “female” ability to rapidly read behavior and body language can be better understood as a learned response to powerlessness, and that in any interaction, the less powerful person, of necessity and because the stakes are higher, may be able to see more, or at least to see things that others situated in more empowered locations do not see (Henley 1977). Biomedical research has a similar dynamic, and high stakeholders are also potential sources of truths that are not necessarily technical, but that matter nonetheless to technical and natural truth and to the application of scientific advances to clinical care.

While hope was generally a productive resource—a form of social capital—for the professional and fundraising networks around gene therapy research, for CF patients and their families hope involved both a promise and a threat: a cure “just around the corner” raised the stakes on preserving lung function, making daily decisions about disease management that much more highly charged. One parent who we consulted who did not want to be named in this paper shared a diary entry from mid-December 1991:

How much worse it would be to miss the benefits of a new treatment by a matter of months because of a serious setback than to simply decline along an inevitable course that one cannot hope to change. . . . Falling behind now could mean Rachel would just miss the chance for a full life. It is like running for a finish line that is somewhere up ahead, rather than walking along a path that leads to certain loss. . . . Hope puts more responsibility—yet no more power—back on us.

The repeated invocation of the value of individual choice around genetic technologies often overlooks this powerless responsibility and its social meanings for those who are presumably expected to benefit the most.

It is perhaps worth noting that CF is the first genetic disease for which a relationship between adult carrier screening and reduced incidence in newborns has been tentatively tracked. Newborn screening for CF began in the 1990s and is now almost universal. Carrier screening of reproductive age couples began systematically in the United States around 2002. After only one year of reproductive screening in California, the incidence of CF in newborns was found to have been reduced by 50% (Witt et al. 2003). Similar effects were documented in Massachusetts and in Italy (Castellani et al. 2009; Hale et al. 2008). While it is not clear exactly how and why these effects occurred, the cases suggest that genetic information provided to people who are screened has consequences for reproduction and public health, and serious effects in both the intimate world of individual decision making and the public world of clinical care and accounting for health-care costs. As adult carrier screening for many more genetic diseases—perhaps for dozens more—could conceivably become a routine part of the clinical management of prospective parenthood, it seems important to reflect on the CF case and its practical consequences.

When profound uncertainties and ambiguities are threaded through every level of a technical system, the notion that individual patient choice in an open market provides a solution to these uncertainties is a cruel and dangerous fiction. And it is a fiction increasingly promoted in the networks invested in increased genomic testing across populations. With this in mind, we have sometimes called cystic fibrosis an informative train wreck, or a canary suggesting where genomic medicine is taking us: the rise of screening at every life stage, almost simultaneously (carrier, fetal, newborn); a condition with a vexed phenotype-genotype correlation and at least 1,500 mutations, none of which is decisive or completely predictable in its individual bodily consequences; a costly clinical regime for those affected; enough patients to be of significant commercial interest; and the dream of comprehensive gene therapy left reluctantly behind. There are echoes of many genetic conditions in these complexities.

Today the term “gene therapy” refers to a wide range of possible interventions and differing technologies that focus on genetic processes and information. Research continues on the potential of gene therapy to treat many conditions, including HIV, but there are no gene therapy drugs, injections, inhalants, or proce-



dures available on a non-experimental basis to patients in the United States, and gene therapy has proven to be one of the most disappointing biomedical technologies of the last 20 years. A prominent recent story in the *New York Times* called attention to the very limited clinical payoff from the Human Genome Project (Wade 2010), and a 2010 report in the *Journal of the American Medical Association* found that taking a family history was a better way to predict heart disease than tracking the 101 genetic variants that have been statistically linked to heart disease in various genome-scanning studies (Paytner 2010). The variants could not, the *JAMA* paper reported, reliably forecast disease in 19,000 women followed for 12 years, while the family history could. As we rapidly seem to approach the “thousand-dollar genome” scan, a price point widely seen as the threshold for mass use, the CF gene therapy case begins to look like an early warning about technological hopes and the complexity of biological interventions.

#### REFERENCES

- Accurso, F. J. et al. 2010. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med* 363(21):1991–2003.
- Alster, N. 1991. Henri Termier's orphan drug strategy. *Forbes*, May 27.
- Alton, E., and D. Geddes. 1994. A mixed message for cystic fibrosis gene therapy. *Nat Genet* 8(1):8–9.
- Andersen, D. H. 1938. Cystic fibrosis of the pancreas and its relation to celiac disease. *Am J Dis Child* 56:344.
- Andersen, D. H., and R. C. Hodges. 1946. Genetics of cystic fibrosis of the pancreas with a consideration of etiology. *Am J Dis Child* 72:62–80.
- Anderson, W. F. 1990. Why start a new journal on human gene therapy? *Hum Gene Ther* 1(1):1–2.
- Angier, N. 1993. Gene therapy begins for fatal lung disease. *NY Times*, April 20.
- Beall, R. J. 1999. The Cystic Fibrosis Foundation. In *Cystic fibrosis in adults*, ed. J. R. Yankaskas and M. R. Knowles, 477–83. Philadelphia: Lippincott-Raven.
- Beaudry, P. H. 1987. Cystic fibrosis: Clinical viewpoint—A disease that doesn't make sense. *Prog Clin Biol Res* 254:1–5.
- Carey, J. 1993. The \$600 million horse race. *Bus Week*, Aug. 23.
- Castellani, C., et al. 2009. Association between carrier screening and incidence of cystic fibrosis. *JAMA* 302(2):2573–79.
- Couzin-Frankel, J. 2009. The promise of a cure: 20 years and counting. *Science* 324 (5934):1504–7.
- Crystal, R. G. 1995. The gene as the drug. *Nat Med* 1:15–17.
- Crystal, R. G., et al. 1994. Administration of an adenovirus containing the human CFTR cDNA to the respiratory tract of individuals with cystic fibrosis. *Nat Genet* 8(1):42–51.
- Culotta, E. 1993. New start-ups move in as gene therapy goes commercial. *Science* 260 (5110):914–15.
- Cystic-L. 1994–1996. <http://community.lsoft.com/scripts/wa-lsoftdonations.exe?a0=cystic-l>.
- Di Sant'Agnes, P. A., et al. 1953. Abnormal electrolytic composition of sweat in cystic



- fibrosis of the pancreas: Clinical significance and relationship to disease. *Pediatrics* 12(5):549.
- Dodge, J. A. 1995. Gene therapy for cystic fibrosis. *Nat Med* 1(3):182.
- Drumm, M. 2001. The race to find the cystic fibrosis gene: A trainee's inside view. In *Cystic fibrosis in the 20th century*, ed. C. F. Doershuk, 79–89. Cleveland: AM Publishing.
- Fanconi, G., E. Uehlinger, and C. Knauer. 1936. Das Coeliakiesyndrom bei angeborener zystischer Pankreasfibromatose und Bronchiectasien. *Wein Med Wchnschr* 86:753.
- Farell, P. M., et al. 2008. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr* 153(2):S4–S14.
- Fisher, L. 1994. Genentech says profit surged. *NY Times*, April 16.
- Fisher, L. 1995. Bottling the stuff of dreams. *NY Times*, June 1.
- Friedman, T. 1990. The evolving concept of gene therapy. *Hum Gene Ther* 1(2):175–81.
- Gross, S. J., B. A. Pletcher, and K. G. Monaghan. 2008. Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med* 10(1):54–56.
- Hale, J. E., R. B. Parad, and A. M. Comeau. 2008. Newborn screening showing decreasing incidence of cystic fibrosis. *N Engl J Med* 358:973–74.
- Hamilton, J. 1993. A star drug is born. *Bus Week*, Aug. 23.
- Henley, N. 1977. *Body politics: Power, sex, and non-verbal Communication*. Englewood Cliffs, NJ: Prentice-Hall.
- Hillman, A. L., et al. 1996. Special feature. Gene therapy: Socioeconomic and ethical issues—A roundtable discussion. *Hum Gene Ther* 7(9):1139–44.
- Hoag, H. 2005. Careers and recruitment: Gene therapy rising? *Nature* 435:530–31.
- Kerr, A. 2005. Understanding genetic disease in a sociohistorical context: A case study of cystic fibrosis. *Sociol Health Illn* 27(7):873–96.
- Leiden, J. M. 1995. Gene therapy—promise, pitfalls, and progress. *N Engl J Med* 333(13): 871–73.
- Martin, P. A., and S. M. Thomas. 1998. Special feature. The commercial development of gene therapy in Europe and the USA (Chapters 5 and 6 of the STEEP Special Report #5, Science Policy Research Unit, University of Sussex, Brighton, United Kingdom). *Hum Gene Ther* 9(1):87–114.
- North American Cystic Fibrosis Conference (NACF). 1994–1999. Conference programs.
- Orkin, S. H., and A. G. Motulsky. 1995. Report and recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, Dec. 7. <http://oba.od.nih.gov/oba/rac/panelrep.pdf>.
- Paytner, N. P., et al. 2010. Association between a literature-based genetic risk score and cardiovascular events in women. *JAMA* 303(7):631–37.
- Pollack, A. 1992. Commercial test of gene therapy. *NY Times*, Feb. 14.
- Recombinant DNA Advisory Committee (RAC). 1992. U.S. Department of Health and Human Services. National Institutes of Health. Minutes of the Recombinant DNA Advisory Committee. [http://oba.od.nih.gov/rdna\\_rac/rac\\_past\\_meetings\\_1990.html#RAC1992](http://oba.od.nih.gov/rdna_rac/rac_past_meetings_1990.html#RAC1992).
- Roberts, L. 1988. The race for the cystic fibrosis gene. *Science* 240:141–44.
- Rommens, J., et al. 1989. Identification of the cystic fibrosis gene chromosome walking and jumping. *Science* 245:1059–65.
- Stockdale, A. 1999. Waiting for the cure: Mapping the social relations of human gene therapy research. *Sociol Health Illn* 21(5):579–96.

- Wade, N. 2010. A decade later, genetic map yields few new cures. *NYTimes*, June.
- Wenner, M. 2009. Tribulations of a trial. *Sci Am* 301(3):909–14.
- Witt, D. et al. 2003. Cystic fibrosis prenatal screening of over 50,000 members in a large HMO: Program update with an emphasis on the outcomes of high-risk pregnancies, reduction in the incidence of CF, and clinical utility. Abstract, Annual Meeting of the American Society of Human Genetics.
- Woo, S. L. C. 2008. From “gene therapy” to “gene and cell therapy”: Why? *Mol Ther* 16(12):1899–1900.
- Zabner, J., et al. 1993. Adenovirus-mediated gene transfer transiently corrects the chloride transport defect in nasal epithelia of patients with cystic fibrosis. *Cell* 75(2):207–16.