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How extraordinary was it?: What development of an orphan drug meant for patients, their families, and their community

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Abstract

In various areas of science and technology, active involvement of non-scientists in their practices is increasingly considered valuable, and medicine is a notable example of such areas. Patients and their families used to be perceived as passive beneficiaries of medical advancement, but today they are encouraged to become active collaborators of medical professionals. Attempts have been made to characterize this trend, and sociological concepts like biological citizenship have been introduced. While increased attention to the new role of patients and their families in medical research may promote the trend, it can also trivialize the struggles that they - not only as individuals but also as members of their disease-based community - might have to face in trying to assume the role. This problem is particularly noticeable where a history of non-scientists' successful involvement in medicine is reduced to a heroic story focusing on a single individual. By examining the case of orphan drug development for a rare genetic disease called Pompe disease and presenting its complexity that is left out in its simplified accounts, I demonstrate that studies on contemporary history of science and technology can play an important role in documenting such complexity and counterbalancing the power of simplified accounts.

Keywords
Biological citizenship, Pompe disease, Enzyme replacement therapy, Patient Organization

Introduction

Among various areas of science and technology, medicine is one in which involvement of non-scientists in its practice is increasingly considered critical. Patients and their families, who used to be perceived as passive beneficiaries of its progress, in particular are encouraged today to become active collaborators of medical professionals, not only to shape how the discipline makes progress but also to re-define what it means to live with the diseases and conditions that they do. This corresponds to the argument that the questions of how their diseases and conditions are understood in medical terms and what kinds of technologies are assembled or developed to diagnose and treat them are at the frontline of the politics of life itself.[1] Since the mid-1990s sociological studies have attended to emergence of such active involvement of patients and their families in medical research,[2] and have made attempts to characterize how their lived experiences can influence both practices and outcomes of the production of new medical knowledge.[3]

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[1] Carlos Novas & Nikolas Rose, "Genetic risk and the birth of the somatic individual," *Economy and Society*, Vol. 29, No. 4 (2000): 485-513; Nikolas Rose, *The Politics of Life Itself: Biomedicine, Power, and Subjectivity in the Twenty-First Century* (Princeton, NJ: Princeton University Press, 2007).
[2] Steve Epstein, "The Construction of Lay Expertise: AIDS Activism and the Forging of Credibility in the Reform of Clinical Trials," *Science, Technology, & Human Values*, Vol. 20, No. 4 (1995): 408-437.
[3] Alan Stockdale & Sharon F. Terry, "Advocacy Groups and the New Genetics," in Joseph S. Alper *et al.* (eds.), *The Double-Edged Helix: Social Implications of Genetics in a Diverse Society* (Baltimore, MD: Johns Hopkins University Press, 2002): 80-101; Vololona Rabeharisoa, "The struggle against neuromuscular diseases in France and the emergence of the 'partnership model' of patient organization," *Social Science & Medicine*, Vol. 57, No. 11 (2003): 2127-2136.

Some such sociological attempts led to the concept of biological citizenship.[4] This concept was developed primarily in the context of medical genetics. The shift from biochemical approaches to molecular ones in the scientific field in the late twentieth century leading to so-called new genetics era turned our genetic make-up into the basis of our understanding of health and illness and even that of our identity. The idea of geneticization was proposed at that time to criticize the authoritative power of the professional knowledge of genetics in determining what counts as the normal body and the natural course of life as much as what counts as the deviation from them and hence the pathological.[5] Yet, observations of remarkable efforts by patients and their families to challenge their genetically-determined fate by engaging actively in the domains of both medical research and health policy also gave rise to this sociological concept indicating that rather different distribution of rights and responsibilities among those involved may be happening.[6]

The remarkable efforts of patients and their families have drawn attention not only of sociologists but also of mass media in some cases. Increased attention can have a positive impact, as knowing similar remarkable efforts are becoming prevalent would empower affected patients and families and encourage more of them to play a similarly active role in medical research and policymaking.[7] However, it is important to note that the ways in which such efforts are accounted tend to exhibit a considerable difference. As indicated by the concept of biological citizenship, their sociological accounts emphasize that advance in medical knowledge has resulted in formation of new communities with a shared genetic (or other biological) characteristic and that the efforts are responses of the patients and their families to being granted their membership often unexpectedly and unwillingly.[8] In contrast, their accounts in mass media are more likely to be simplified focusing on specific individuals.[9] What can be lost as a result of this narrowed focus is the complexity of individual cases, and in particular struggles of those who are not featured in such accounts but were equally determined to change their circumstance as members of the same community despite everyday implications of their diseases and conditions.

The case I examine in this article to demonstrate this point is that of a patient organization for a group of rare diseases called glycogen storage disorders (GSDs). This organization worked closely with scientists and biotechnology firms to develop a therapy for a particular type of GSDs from the mid-1990s to early 2000s. The story about development of this therapy later became well-known due to its coverage in mass media, which was then turned into a film. However, the organization's contribution that was critical for its success and the challenges that its members had to face at that time were not included in the account. It is not my intention to judge whether the popularized account in mass media is biased or even misrepresentative, but by offering a different account (a history rather than a moral fable), I argue that the story told in such a way has considerable implications for the practices of patient involvement and the care that ought to accompany its promotion.

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[4] Deborah Heath, Rayna Rapp & Karen-Sue Taussig, "Genetic Citizenship," in David Nugent & Joan Vincent (eds.), *A Companion to the Anthropology of Politics* (Malden, MA: Blackwell Publishing, 2004): 152-167; Nikolas Rose & Carlos Novas, "Biological Citizenship", in Aihwa Ong & Stephen J. Collier (eds.), *Global Assemblages: Technology, Politics, and Ethics as Anthropological Problems* (Malden, MA: Blackwell Publishing, 2005): 439-463.

[5] Abby Lippman, "Prenatal Genetic Testing and Screening: Constructing Needs and Reinforcing Inequities," *American Journal of Law & Medicine*, Vol. 17 Nos. 1 & 2 (1991): 15-50.

[6] Novas & Rose, "Genetic risk and the birth of somatic individual"; Anne Kerr, "Rights and responsibilities in the new genetics era," *Critical Social Policy*, Vol. 23 No. 2 (2003): 208-226; see also Koichi Mikami, "Citizens under the umbrella: citizenship projects and the development of genetic umbrella organizations in the USA and the UK," *New Genetics and Society*, Vol. 39, No. 2 (2020): 148-178.

[7] Aaron Panofsky, "Generating sociability to drive science: Patient advocacy organizations and genetics research," *Social Studies of Science*, Vol. 41, No. 1 (2011): 31-57.

[8] Rose & Novas, "Biological Citizenship".

[9] Carlos Novas, "Patients, profits and values: Myozyme as an exemplar of biosociality," in Sahra Gibbon & Carlos Novas (eds.) *Biosocialities, Genetics and the Social Sciences: Making Biologies and Identities* (Abingdon: Routledge, 2008): 136-156.

Here I also see an important role that studies of contemporary history of science and technology can play. Just as history of science and technology as a broader field of academic discipline has advanced with the conscious effort to avoid accounting history as a progress toward the present,[10] contemporary history of science and technology can demonstrate the complexity of individual cases that tends to be lost in their simplified and popularized accounts. And given that production of scientific knowledge and development of technology are becoming less centralized at universities and research institutes and more diffused within a broader societal context, without such historical studies there is considerable risk that the kind of information available to us today would be lost forever, potentially leaving such problematic accounts remain unquestioned. The information required to tell the history may not be available in the form of written documents but, just as the research that this article is based on did, interviews can be an effective methodological option for putting together experiences of the people involved. In some way, contemporary history of science and technology can and should, I argue, bear the responsibility of keeping the kind of historical records that is unlikely to be kept in formal institutional archives.

The Story of the Extraordinary Effort

Glycogen storage disorders (GSDs) are rare genetic diseases that affect the biochemical pathway of turning glucose into glycogen to store in the body and then back to glucose for use when it is needed as a source of energy. Depending on how this pathway is affected, their symptoms and severity vary, and for this reason the diseases are categorized into ten or so different types. One of the most severe is Type II, which is also known as Pompe disease, named after the Dutch pathologist Joannes Cassalanus Pompe, who characterized it in 1932.[11] Individuals affected with this disease cannot produce an enzyme called alpha-glucosidase, which breaks down glycogen, either in a required amount or in the proper chemical structure, and hence glycogen accumulates in their muscles and other tissues, eventually causing fatal cardio-respiratory problems. When Pompe first identified this disease, the mechanism was not known, and therefore he described it as a case of 'idiopathic hypertrophy of the heart.' The 'classic' form of Pompe disease occurs in infants typically before the age of 1, but there is also a milder form known to be 'late-onset,' indicating that the functional enzyme is produced just enough to slow down the speed of glycogen accumulation.

Pompe disease is still not curable but is now treatable with a medical approach to supply periodically the missing enzyme to the body. This approach is called an enzyme replacement therapy (ERT), and the history to be explored in this article is about the development of this therapeutic treatment.[12] The treatment involves a drug called alglucosidase alpha, which was put in the market first by an American biotechnology company Genzyme under the brand name of Myozyme in the mid-2000s. Myozyme was not the first ERT drug that this company produced. The company was founded in the early 1980s on a technique to produce alglucerase, which was developed as an ERT drug for another rare genetic disease called Gaucher disease. The drug was approved for marketing by the US Food and Drug Administration and marketed as Ceredase in the early 1990s, but was soon replaced by the company's newer recombinant version of the drug Cerezyme. While drugs for rare diseases, which are legally defined as 'orphan drugs' in the US, were considered non-profitable at that time, Cerezyme became one of the first commercially successful orphan drugs, inevitably causing a much controversy regarding the adequacy of the US Orphan Drug Act that provides advantageous conditions for companies developing such drugs.[13] And Myozyme was a new line of ERT drugs for the company.

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[10] Herbert Butterfield, *The Whig Interpretation of History* (London: W.W. Norton & Company, 1931 [1965]).
[11] John Fernandes, "The history of the glycogen storage diseases," *European Journal of Pediatrics*, Vol. 154, No. 6 (1995): 423-424.
[12] Kevin O'Donnell, who was a member of the patient organization, has written about this story from his perspective, 'Pompe Disease – The Real Story': http://pompestory.blogspot.com (last accessed on 15 June 2021).
[13] Koichi Mikami, "Orphans in the Market: The History of Orphan Drug Policy," *Social History of Medicine*, Vol. 32, No. 3 (2019): 609-630.

The story of Myozyme became known widely owing mostly to a Pulitzer Prize-winning journalist Geeta Anand's nonfiction book entitled *The Cure: How a Father Raised $100 Million – and Bucked the Medical Establishment – in a Quest to Save His Children*, which was published in 2006.[14] While she, being interested in the issues of expensive orphan drugs, had written about the story before,[15] the book was published after she received the Gerald Loeb Award for business reporting for a series of her articles examining the issues in the Wall Street Journal earlier in that year. Taking the central stage of her story is a father of two children with Pompe disease, John Crowley. Soon after his children were diagnosed, he started a patient organization to raise funds and support research on treatment for the disease, and then became a chief executive officer of a biotechnology company Novazyme to manage its line of research. When its early research showed promising results, the company was sold to Genzyme, which also had a research program to develop an ERT drug for Pompe disease. As part of the deal, Crowley joined Genzyme to oversee its entire research program. This story of the heroic father who was determined do everything possible to develop the therapy for the disease that affected his children was then turned into a film. This film, entitled *Extraordinary Measures*, was released in the United States in 2010.

Novas, in his sociological study on the roles of biotechnology firms and patient organizations in producing and capitalizing on future visions, characterizes this Crowley's story as "a human interest story," which presents how individuals should respond to their illness.[16] A model of patient involvement in the new genetics era has been provided by the experience of another heroic figure in genetics research, Sharon Terry. Terry too is a parent of two children who are affected with a rare genetic skin disorder, pseudoxanthoma elasticum (PXE). Like Crowley, soon after her children were diagnosed, she and her husband Patrick established a patient advocacy group. By managing access to their blood and tissue samples, which were critical for studying genetics of the disease, they tried to promote collaboration among scientists because they felt scientific competition was not helping the research to make progress. When their effort was paid off and the gene associated with PXE was identified in 2001, Terry was listed as one of the co-authors of the research articles reporting it.[17] In contrast, Crowley was, in addition to being a parent of the affected children and an active collaborator of scientists, an entrepreneur in the biotechnology industry, which was growing fast at that time. Although dedication and sense of urgency are common to both Crowley's and Terry's stories, therefore, Crowley's exhibits more explicitly the spirit of capitalism, or even that of bio-capitalism, highlighting a particular kind of work ethic associated with it.[18]

The ability of certain individuals to take on multiple and often equally demanding roles in the process of changing the fate of having a certain genetic make-up caught attention of some sociologists in the late 2000s and contributed to the discussion on biological citizenship.[19] And by featuring such an ability, mass media has also turned their experiences into modern tales with the moral message of how one should behave. As Novas points out, however, what the Crowley's popularized account has failed to talk about is the struggles experienced by those involved in the process, including "the sense of fear, worry, frustration, anxiety and distress."[20] Even when they are talked about, they are there to serve as rhetorical devices to accentuate the heroism of the remarkable

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[14] Geeta Anand, *The Cure: How a Father Raised $100 Million – and Bucked the Medical Establishment – in a Quest to Save His Children* (New York, NY, Harper Collins Publishers, 2006).
[15] Geeta Anand, "When Drug Research Is Personal – A Father Raises $27 Million and Comes Close to a Cure in Race to Save Children," *Wall Street Journal*, 30 July 2001; Geeta Anand, "Clinical Trials: For His Sick Kids, A Father Struggled to Develop a Cure; Mr. Crowley Built Biotech Firm, Ran Big Drug Program, but Still Faced Hurdles; 'What Color Is the Medicine?'," *Wall Street Journal*, 26 Aug 2003.
[16] Novas, "Patients, profits and values."
[17] Sharon F. Terry & Charles D. Boyd, "Researching the Biology of PXE: Partnering in the Process," *American Journal of Medical Genetics*, Vol. 106. No. 3 (2001): 177-184; Sharon. F. Terry, "Learning Genetics," *Health Affairs*, Vol. 22, No. 5 (2003): 166-171.
[18] Novas, "Patients, profits and values," 143.
[19] Carlos Novas, "The Political Economy of Hope: Patients' Organizations, Science and Biovalue," *BioSocieties*, Vol. 1, No. 3 (2006): 289-305; Rose & Novas, "Biological Citizenship"; Mikami, "Citizens under the umbrella."
[20] Novas, "Patients, profits and values," 142.

individual. Yet the struggles are not limited to the ones such heroic individuals faced. Because their extraordinary efforts are the most visible parts of the communal responses to their shared circumstances, the simplified accounts focusing on a heroic individual likely leave many struggles untold and unappreciated. The following section therefore examines what is left out in the popularized story of how the life-saving drug for Pompe disease was developed.

The History of Collaborations and Tensions

There were several patient organizations that took part in this history, and the one I examine here was founded in the UK before John Crowley's. In the 1980s, two local families started an informal network of patient families. Their babies were diagnosed of not Pompe disease but GSD Type I, which is also known as Von Gierke disease, about which they knew little beyond what their doctors had told them. Although the disease is not as fatal as Pompe disease, having found themselves suddenly in the challenging situation, both physically and emotionally, they were keen to know how other families affected by the same disease were coping with it. However, their doctors were not supportive about them getting in touch with each other, because it was commonly believed at that time that knowing about the situations of other families, which could be very different from their own, would do more harm than good.[21] The families learned about each other through a local support group for families with children with inherent metabolic disorders, and the mothers met up for the first time in 1984. They then realized that a patient organization dedicated for their disease already existed in the US, and decided to set up an equivalent in the UK by themselves in 1986.

Because the mothers like them were the main figures of the organization, its activities primarily centered around exchanging information about how to manage daily care, such as how to keep their children's blood sugar level sufficiently high over night, at school, or while they were on holiday, although some also made effort to understand the science of the disease.[22] Their doctors soon recognized the value of its activities particularly in making families of a newly-diagnosed infant understand the nature of the disease and the care it demands.[23] So they started offering support and referring such families to it.

As the organization grew, families with other types of GSDs joined – firstly GSD Type 3, or Cori disease, which manifests hepatic symptoms similar to those of Von Gierke, and then patients with GSD Type 5, or McArdle disease. The latter however was a source of surprise as much as that of confusion to its early members, because their doctors had told them that GSDs other than Types 1 and 3 were extremely rare, and also because the patients' concerns were quite different from those of the caring mothers as its diagnosis was often made in adulthood.[24] What the organization was able to do for them initially was simply offering them a space to converse with each other. That was the same for families with Pompe disease, but the nature of their conversation was more dispiriting. While their concerns were about their affected children, infant patients with its classic form tended to die before their first birthday. Therefore, the group stayed small and was also joined occasionally by parents who just lost their child to the devastating disease.

Kevin O'Donnell and his wife were such parents. In 1993, their son was diagnosed of Pompe disease before the baby turned one year old. Although their nurse told them about the organization, they did not have time to join it while their baby was alive, as he died within a couple of weeks after the diagnosis.[25] The organization still put them in touch with other families who had also lost their children to Pompe disease, and talking to them helped the couple to cope with the tragic event. Then O'Donnell came up with the idea of writing 'a laypersons' guide to Pompe disease.' He had a background in biology and it helped him to understand about the disease on his son's diagnosis, but

[21] Interview with AP a founding member of the organization on 8 March 2016.
[22] Interview with SD another founding member of the organization on 9 February 2016.
[23] Interview with a medical scientist JL on 26 November 2015.
[24] Interviews SD and AP.
[25] Interview with a member of the patient organization KO on 9 October 2015; O'Donnell, 'Pompe Disease.'

he sensed from his conversation with his wife as well as other families that its science could be difficult for those without that kind of background. By producing such a document, he thought, he could repay the kindness he and his wife received following the death of his baby. So he went to a local university library to collect as much information about the disease as possible. And there he found the work of a Dutch research group suggesting that development of an ERT for Pompe disease might be possible.[26] With the knowledge of this important work, O'Donnell began to play a key role in the patient organization.

In the next year, on his business trip to the Netherlands, O'Donnell contacted Arnold J. Reuser, the leader of the research group, and managed to meet him in person. Reuser decided to spare his time for the visitor because he was impressed by the layperson's guide that he had produced and considered him to be a scientist rather than just a parent who lost his son to Pompe disease, on which he had been working since his PhD.[27] At this meeting O'Donnell promised Reuser that he would find a way to help the research on an ERT for Pompe disease, and on his return to the UK, he proposed then board members of the patient organization to set up a research fund for such research. Some were hesitant initially because that was not the kind of activities that the organization had done previously, but they eventually decided to let him do so in his capacity as a representative of its Pompe group, partly because, again thanks to the layperson's guide, he had been known as one of a few scientists in the organization and partly because they were all sympathetic to the Pompe group, which tended to be the most dispirited within the organization.[28] Once this Pompe Fund was set up, many, both inside and outside the group, contributed to it.

The Fund was not quite enough for Reuser to advance his research project, but was used effectively to convince a local company to commit to it. His former PhD student Ans T. Van der Pioeg, who was the first author of the article on the ERT for Pompe disease that O'Donnell found, learned that a biotechnology company called Pharming, founded in the late 1980s, was interested in transgenic animals and looking for a new research program in this area. Having isolated the gene for the enzyme Reuser was working on Chinese Hamster Ovary (CHO) cells to produce it, just like Genzyme's method to produce Cerezyme, but still Van der Pioeg approached the company to see if there was any chance of collaboration. A bioreactor that Reuser made using the Pompe Fund indicated not only the possibility of scaling up the enzyme production but also the existence of an untapped market with the group of supportive patients who would potentially be participants in future clinical trials and also its long-time customers.[29] The latter was particularly important for the company because, unlike in the US, there was no legal arrangements to promote development of orphan drugs in Europe yet at that time.[30]

Their collaboration started in 1996 but with an interesting twist. There was a growing interest since the late 1980s in obtaining target proteins from the milk of transgenic livestock animals,[31] and some already had developed the techniques for certain animals and secured patents on them.[32] Pharming initially wanted to work on cattle but its speed of reproduction was found unsuitable for its project,[33] and it eventually decided to focus on rabbits, with a prospect of switching back to cattle in the

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[26] Ans T. Van der Pioeg *et al.*, "Intravenous Administration of Phsphorylated Acid α-Glucosidase Leads to Uptake of Enzyme in Heart and Skeletal Muscle of Mice," *Journal of Clinical Investigation*, Vol. 87 No. 2 (1991): 513-518.
[27] Interview with a scientist AR on 24 February 2016.
[28] Interview with SD.
[29] Interview with AR.
[30] The legal arrangement was also adopted in Europe in 1999. See The European Parliament, "Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products," *Official Journal of the European Communities* (2000): L18.
[31] Anthony J. Clark *et al.*, "Pharmaceuticals from transgenic livestock," *Trends in Biotechnology*, Vol. 5, No. 1 (1987): 20-24.
[32] For example, Grace Wright *et al.*, "High Level Expression of Active Human Alpha-1-Antitrypsin in the Milk of Transgenic Sheep," *Nature Biotechnology*, Vol. 9 (1991): 830-834.
[33] Alan Coleman, "Production of proteins in the milk of transgenic livestock: problems, solutions and successes," *American Journal of Clinical Nutrition*, Vol. 63 (1996): 639S-645S.

future. Pharming's transgenic rabbits project made swift progress, and the first clinical trials took place in 1998. To accelerate commercialization of its ERT product, the company also went into partnership with the American company Genzyme, which was already successful with its own ERT product Cerezyme.

By then, there were also a few other research groups in the US working on an ERT for Pompe disease, including that of Crowley's.[34] While the competition was getting intense, the Dutch team, that is, the collaboration between the Reuser's group and Pharming, was the first to report successful results of the clinical trials in 2000.[35] However, Genzyme soon made decision to buy up a line of research in the US to produce the same enzyme using CHO cells, the method it was more familiar with. Pharming's approach with transgenic rabbits was not as efficient as the company expected, and following Genzyme's decision the Dutch team had to switch to CHO cells, which was claimed to be more efficient,[36] despite that the original approach had already proven effective in humans while the new approach had not. For the company to undertake another round of clinical trials, it first had to build new production sites meeting regulatory standards, so the switch of the approach therefore meant significant delay in the commercialization. In 2001, Genzyme made another decision, and this time bought out Crowley's Novazyme, which claimed to have a more effective design of the enzyme. This was soon followed by the news that Pharming went into receivership, leaving its project entirely in the hands of Genzyme. Thus, by the end of 2001, the American company had all the potential lines of research existed at that time, having spent more than 150 million dollars in total. All these business actions caused anxieties to patient families and particularly those who participated in the earlier clinical trials and benefited from the enzyme they had been on since, while the company promised them of its supply until the transition to the newer version became possible.[37]

In 2006, Genzyme's ERT drug for Pompe disease was approved in Europe and began marketed under the brand name of Myozyme.[38] The final product is produced using the CHO cells approach but its chemical structure is different from the ones being developed by all the Dutch and American companies and costed more than 150 million dollars to Genzyme.[39] The most valuable that the company obtained through its business actions probably was the close connection with the patient community, as it assisted the company's application for the marketing authorization. It helped the company to set up sites for its clinical trials and to recruit infant participants. Furthermore, a compassionate scheme it offered to some adult patients in the community helped the company to demonstrate the drug's effectiveness for them as much as the existence of the unmet patients' need in the evaluation process resulting in approval of its use not only for the classic form but also for the late-onset one.[40] The annual meetings of the patient organization were main occasions where firstly Pharming and then Genzyme developed and maintained their close connection with the patient community in the UK since the mid-1990s. The Pompe group that used to be a small group gathering in a corner became the most active within the organization, and its size grew rapidly as its activities became heightened. Going through this remarkable period alongside, however, some early members of the organization felt the loss of organizational identity as the nature of the events has become totally different from how they were like before.[41]

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[34] These research groups in the US as well as the Dutch group benefited from support of the House family, which is another patient family closely involved in research on Pompe disease. See O'Donnell, 'Pompe Disease.'
[35] Hennerieke Van den Hout *et al.*, "Recombinant human α-glucosidase from rabbit milk in Pompe patients," *Lancet*, Vol. 356, No. 9227 (2000): 397-398.
[36] Andrea Amalfitano *et al.*, "Recombinant human acid α-glucosidase enzyme therapy for infantile glycogen storage disease type II: Results of a phase I/II clinical trial," *Genetics in Medicine*, Vol. 3, No. 2 (2001): 132-138.
[37] O'Donnell, 'Pompe Disease.'
[38] European Medicine Agency, 'European Public Assessment Report (EPAR): Myozyme': https://www.ema.europa.eu/en/medicines/human/EPAR/myozyme#overview-section (last accessed 15 June 2021)
[39] Anand, *The Cure*.
[40] An adult patient even attended the evaluation process of the European Medicines Agency and made a case for the extended approval. Interview with a patient MS on 25 February 2016.
[41] Interview with AP.

Concluding Remarks

It is not my intension to claim that the history I presented in this article is complete. Yet I hope it still presents a more complex picture of the development of the ERT drug for Pompe disease than the simplified story of John Crowley implicates. The father determined to do anything to help his affected children was undoubtedly a part of the history, but in it there were many other individuals and organizations involved and much more were happening too. Furthermore, not only that there was an independent and quite successful line of research on an ERT drug for Pompe disease in Europe but also that some patients and their families had already benefitted from its early product before Myozyme became available raise an important question of how essential Crowley was in the history. Had he not founded Novazyme, there was a good chance that an effective drug would still have been developed. The complexity of the history, therefore, help us to recognize the problem of reducing the historical achievement to the heroic act of the single individual.

The complexity of the history also allows us to see the act of certain individuals differently. Some actually suggest that Crowley's entrepreneurial endeavor, which is praised in the popularized story, caused confusion and incurred costs to many of those involved in the process including Genzyme, rather than speeded up its development of Myozyme.[42] So, were the amount of time and money that the company spent to acquire his line of research and conclude its ineffectiveness and also the anxiety that the series of its business acts caused to the patients and their families unnecessary? This alternative account may need be seen from multiple perspectives too. While his line of research did not lead to Genzyme's final product, with the money that he received from the company, he moved on to a next entrepreneurial project focusing on other rare diseases, such as Fabry disease and Batten disease.[43] This also reminds us that the history did not take place in isolation but was connected to other histories, some of which are yet to be told.

The similar ought to be said about the initiative of O'Donnell. As shown above, he played the important role in bringing the patient community, the scientists and the companies together. However, becoming the venue of their interactions, the patient organization changed considerably, leaving some of its non-Pompe group members troubled. Just as Epstein observed a "significant tension" or "divide" between the activists who became to speak and think like scientific experts and influenced the nature of AIDS research and others in the AIDS activism in early 1990s,[44] the expansion of the Pompe group since the late 1990s and its 'takeover' of the annual meetings caused considerable discomfort to some of its members. After O'Donnell's retirement from the organization, the legacy of the group also put his successor under pressure to keep its activity going while managing the relationship with other groups.[45] However, it should be noted that its activities encouraged other groups to be active too. For example, the organization's McArdle group began to work closely with local scientists since the early 2000s, and their collaboration resulted in a journal article.[46] Hence, the activities of the Pompe group served for others in the organization as an immediate model of patient involvement in medicine, even though it was not necessarily thinking about it in such a term then.

These observations suggest that simplified stories focusing on particular individuals also obscure the costs that other individuals and organizations than their main characters had to bear in the process. They may touch on some such struggles but only to the extent that they highlight what the heroic individuals had to overcome in achieving the success, and seldom include the ones that others in their communities had to face, no matter how persistent they might have been. However, as indicated by the discomfort that members of the patient organization felt as a result of the Pompe group's

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[42] Interview with KO.
[43] Amicus Therapeutics: https://www.amicusrx.com (last accessed 15 June 2021)
[44] Epstein, "The Construction of Lay Expertise," 429.
[45] Interview with a member of the patient organization AM on 10 February 2016.
[46] Alejandro Lucia *et al.*, "The 'McArdle paradox': exercise is a good advice for the exercise intolerant," *British Journal of Sports Medicine*, Vol. 47, No. 12 (2013): 728-729.

success in promoting research as well as the anxiety that patients and their families felt over Genzyme's post-clinical trial business decisions, the success to change their genetically-informed fate was associated with a series of communal challenges. The struggles or the costs to take on such challenges can be understood as 'clinical labor,' which Cooper and Waldby explain as the kind of labor that goes into the production of medical knowledge but remain unacknowledged in economic terms.[47] This important labor therefore tends to be left out in simplified stories because it is not necessarily of the individuals they feature and does not serve to justify the attention given to them.

Leaving such clinical labor unaccounted is a serious problem for simplified stories which deliver moral messages to society. They demonstrate not only that the change in the production of medical knowledge and the development of new biotechnologies would be desirable because medicine today is not as good as it should be to meet the needs of every patient but also that patients and their families can make it happen through their active involvement. However, what they present to the public is not a mere possibility but a promise of patient involvement, and the promise can become forceful.[48] By presenting the success achieved through someone's extraordinary effort, they encourage others to make comparable efforts but without necessarily informing them the kinds and extents of struggles they and fellow members of their community might have to face. Although not everyone is able to manage such struggles, their emphasis on both importance and prevalence of the extraordinary efforts can make those who are unable to do so with their limited resources feel incapable or even ineffectual. And it needs be noted that their messages tend to be more accessible than sociological accounts because they are often fused with the values of local culture, just as Crowley's popularized story highlighted contemporary American corporate culture and its working ethic.[49]

Although it may appear that the patient organization discussed in this article was unique in respect to its coverage of different disease types and hence to the diversity in its membership, it has been suggested that a disease is not a stable unit of classification, and that medical knowledge – and molecular genetics in particular – can promote sub-categorization as well as re-grouping of diseases.[50] In their effort to involve in medical research and policymaking, patient organizations therefore may well face the similar communal challenges with advances in medicine, no matter how united they might be at present. Knowledge about the complexity of patient involvement in the past would therefore help them prepare for taking on such challenges if they choose to do so and also institutionalize the kind of care that should be provided them with. And given that active involvements of patients and their families are usually beyond the scope of formal institutional archives, deliberate efforts, such as interviewing of not only those who led the activities but also those who experienced them closely, need be made to document them and keep such records available. While the issue of accessibility to the general public may remain a concern, studies on contemporary history of science and technology can serve a crucial role at least in documenting the complexity of the context in which their success was situated and counterbalancing the social pressure potentially caused by simplified and popularized accounts in mass media.

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[47] Melinda Cooper & Catherine Waldby, *Clinical Labor: Tissue Donors and Research Subjects in the Global Bioeconomy* (Durham, NC: Duke University Press, 2014).
[48] Harro van Lente, "Forceful Futures: From Promise to Requirement," in Nik Brown, Brian Rappart & Andrew Webster (eds.) *Contested Futures: A sociology of prospective techno-science* (Aldershot: Ashgate, 2000): 43-63, 59.
[49] Novas, "Patients, profits and values."
[50] Adam M. Hedgecoe, "Reinventing diabetes: Classification, division and the geneticization of disease," *New Genetics and Society*, Vol. 21, No.1 (2002): 7-27; Adam M. Hedgecoe, "Expansion and uncertainty: cystic fibrosis, classification and genetics," *Sociology of Health & Illness*, Vol. 25, No. 1 (2003): 50-70; Daniel Navon, "Genomic designation: How genetics can delineate new, phenotypically diffuse medical categories," *Social Studies of Science*, Vol. 41, No. 2 (2011): 203-226.

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