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Strand, Dixi Louise; Holen, Mari

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Patient-led Research and Displacements of Biomedical Knowledge Production, Distribution, and Consumption

Abstract

Patient and Public Involvement in Research (PPIR) has become an increasingly prevalent and integral part of biomedical research. In this paper, we focus on patient-led research, taking as our case the construction of new biomedical knowledge regarding the rare disease ADNP syndrome. Specifically, we seek to understand how concepts of experiential knowledge and lay expertise become integral to rather than separate from scientific expertise. In the case of ADNP, the parent-led research "mimes" biomedical knowledge practices in a way that, on the one hand, enhances the legitimacy of science and scientific expertise, and on the other displaces and transforms science by the fact that other knowledge agents (patients, next-of-kin) enter these practices.

Keywords

Patient and public involvement, health activism, lay-scientist interactions, citizen science, patient advocacy, patient activism, knowledge production, biomedicine

Introduction

Patient and Public Involvement in Research (PPIR) has become an increasingly prevalent and integral part of biomedical research. In the United Kingdom PPIR has been promoted by the National Institute of Health Research and most research funders[i]. Likewise, the National Institute of Health and the Center for Advancing Translational Sciences in the United States advocate patient and community engagement throughout the research process[ii]. In Denmark, where the authors of this paper are located, PPIR is also becoming an indispensable component of translational health research agendas. Guidelines, principles, and recommendations on how to involve patients and publics in research are voluminous, including approaches to assess and denote the degree of involvement and the added value achieved (Nielsen et al., 2018). Criticism also plays a role in the policy debates on PPIR. Criticisms(Barnes and Cotterell, 2011; Beresford, 2021) highlight tokenism, inequity in terms of not including marginalized patients and their agendas, and a mismatch between public interest in health as a much broader "quality of life" versus a biomedical focus on specific and delimited diseases and treatments. In PPIR, many policy models rely on an underlying conception of the patient as a passive subject (Arnstein, 1969) that should be activated in research production (Schroegel and Kolleck, 2019).

In contrast to the 'patient as a passive subject,' a somewhat overlooked aspect of these debates is the phenomenon of patient-led research; patients and citizens initiating and leading biomedical research, where patients and citizens take authoritative responsibility for research priorities, research design, and research implementation (Rabeharisoa, Moreira, et al., 2014). This is unsurprising given that user-led, community-based, and participatory forms of research have been somewhat disregarded by mainstream funding agencies and institutions. For example, indigenous and feminist research, also within health research, has a long history of operating in deeply participatory and community-led ways, and in many cases, has been conducted to disrupt the very power dynamics within biomedicine that this paper similarly is investigating. See for example (Israel, 2013; Morris and Spivak, 2010; Smith, 2021). In this paper, we focus on patient-led research, taking as our case the construction of new biomedical knowledge regarding the rare disease ADNP syndrome, also known as Helsmoortel-van der Aa syndrome.

We investigate patient-led research as an upcoming movement, that seems to be gaining influence. Such movements lead us down new paths for discussing the role of patients and citizens in science. This is a role that differs from and can extend existing ways of framing PPIR in terms of research impact and democratic ideals. We question the basic premise often taken in PPIR, that lay expertise and experience-based knowledge of patients and citizens exist "outside" of a scientific realm and is either "invited in" as in PPIR or "pushed through" as in patient activism[iii]. Instead, we suggest thinking about the practices of patient-led research as a case of biomedical scientific knowledge production in its own right – as science in the making. With this inversion of biomedical science agency, we seek to shed new light on PPIR debates and assumptions.

Building on Science and Technology Studies, we focus on issues of expertise and scientific authority in relation to patient-led research, and in this particular case parent-led research. Our investigations have explored the following two questions related to patient-led research as it is presented and performed online: *How do patients' and citizens' lay expertise and experience-based knowledge come to have influence upon biomedical science? How can patient/citizen claims to knowledge and expertise be made and mobilized?* We seek to highlight and discuss mixed forms of knowledge that cross over and blur the distinction between experience-based knowledge and scientific knowledge. This attentiveness to an evidence-based ideology in relation to alternative forms of knowledge is inspired by previous critiques of

biomedicine's epistemic underpinnings (Holmes et al., 2006). In closing, we link our interest in forms of knowledge to debates about expertise and scientific authority in relation to PPIR.

Methodology

Our empirical case here is the development of diagnosis and treatment for the rare disease ADNP syndrome. The syndrome ADNP was first described in 2014 as a genetic mutation linked to a complex range of clinical characteristics found in children. As of 2022, 300 children had been diagnosed worldwide through genetic testing. Parents are connected in an open-access online community that shares experiences and struggles with the disease while also working towards increased awareness, advocacy, and research funding. Parents have also developed scientific expertise and have taken part in constructing new knowledge related to the syndrome. One parent led an effort to systematically collect patient-based evidence leading to the development of a new biomarker in 2017(Gozes et al., 2015, 2017). Another parent applied an artificial intelligence (AI) tool to search medical literature for possible new treatment ideas or drugs that could be repurposed, leading to a clinical trial initiated in 2020 testing a new treatment drug on 12 children recruited through the community(Kolevzon et al., 2022). We introduce the stories of these parents as examples of a re-thinking of possible citizen-scientist relations and agencies[iv]. The analysis is inspired by previous work of Rabeharisoa and colleagues and recent work of Epstein (Callon and Rabeharisoa, 2003; Epstein, 2021, 2022; Rabeharisoa, Callon, et al., 2014; Rabeharisoa and Callon, 2004), by focusing on knowledge claims and strategies used by the parents. As detailed below, we specifically build on the three concepts of experiential knowledge, lay expertise, and evidence-based activism discussed in this literature.

We used public online material to explore the different mechanisms through which claims to knowledge and expertise in relation to ADNP syndrome were made and mobilized by parents of children diagnosed with ADNP[v]. An iterative mapping methodology and our analytical focus on knowledge "shifts" (see further below) led us to the selection of three parent stories that could portray some of the elements, arenas, and positions mapped. The stories also served to convey three shifts: undone research, collecting empirical data, and finding a cure. These three shifts have subsequently structured the presentation and sequence of the stories and the analysis in this paper. In this way, our study seeks to highlight different mechanisms through which a patient and public perspective is claimed and mobilized.

Our first parent story illustrates how parents and a parent community have produced *experiential knowledge* on their children's illness. As one parent notes "we know more than the doctors" due both to their everyday experiences with their children and their role as *the* continuous factor in a chaotic process of moving from one medical specialist to the next in search of answers and a diagnosis. Online platforms join these parents and their experiences together. Together they highlight unanswered questions, raise awareness of lacking science, and point out a knowledge gap that urgently needs to be filled, all based on their present experience. The second parent story illustrates the building of *lay expertise*, showing how a parent started searching for and collecting relevant biomedical research in the face of a lack of knowledgeable professionals and a lack of credentialed expertise. This parent also embarked on systematically collecting *patient-based evidence* throughout the community, thus building a knowledge repository concerning the illness. Along with other parents, she established a patient organization and started to form alliances with relevant established research groups. In the third and final example in this paper, we see how parent's use an AI tool to conduct research and thereafter define and pitch a new idea for a new clinical trial to test a repurposed drug on children with ADNP syndrome. Here, evidence and authority are claimed by the parents through their alliance to AI.

These stories contribute to our understanding of PPIR and the ways in which patients and publics can achieve influential engagement in science in uninvited and unexpected ways. The stories selected and explored here, also indicate ways in which patients, citizens, and researchers can work together across a science-public divide to build a new arena of knowledge on ADNP. Our analysis suggests that such practices are in no way alleviated of the constraints of existing academic or economic research agendas but work with and find ways to negotiate these circumstances to meet specific ends. In the discussion section of this paper, we discuss the implications of the analysis in relation to PPIR as a possible shift or displacement of contemporary biomedical knowledge production, distribution, and consumption. Through parent-led research, we find that biomedical knowledge is simultaneously destabilized *and* strengthened in that experience-based knowledge becomes an integral part of scientific knowledge production. The aim of this article is thus primarily to illustrate an example of how biomedical knowledge is produced when patients and next-of-kin are the initiators and drivers of new research.

The paper is structured as follows. We begin by briefly presenting key ideas from the field of Science and Technology Studies that are relevant and of interest in relation to PPIR: scientific knowledge production as situated, the science-society relationship, experiential knowledge, lay expertise, and evidence-based activism. Next, we present ADNP syndrome, our data, and methods. Hereafter, the three parent stories of Peter, Laura, and Jonas are analyzed applying the concepts of experiential knowledge, lay expertise, and evidence-based activism[vi]. In closing we discuss these stories in relation to PPIR and their implications for our understanding and practices of PPIR.

Scientific knowledge production as situated

As mentioned above, patient-led research offers an opportunity for thinking in new ways about biomedical research and innovation, about where it starts, what constitutes its agencies, and its sites of production. These questions link to studies in the field of Science and Technology Studies working towards "opening the black box" of science and making scientific practices more transparent. STS studies have, for example, explored how scientific knowledge is practiced and accomplished by studying the specific social, institutional, historical, and material settings of science (Fujimura, 1996; Knorr Cetina, 1999; Latour and Woolgar, 2018).These historical and empirical analyses of scientific knowledge production have enabled awareness as to how scientific knowledge and facts are products of negotiations, complex decisions, for example regarding what counts as scientific reliability and evidence[vii]. This STS approach to understanding scientific practice can be of use to PPIR.

Biomedical knowledge can be viewed as, on the one hand, aligning with a scientific ideal of objectivity and a clear separation between researcher and subject in order to secure safety and reliability in its application. On the other hand, biomedical knowledge is also continually made public and contested as it is a form of knowledge production that concerns and affects citizens in very material and bodily ways (Clarke, 2010; Lupton, 2012). This characteristic of being both a safe and a public matter is also stressed in PPIR and the calls for involvement and engagement of patients and publics in knowledge production and innovation. Involvement of patients and publics in knowledge production is deemed as indispensable in order to create public relevance, acceptance and impact.

We will briefly zoom in on three concepts from the field of STS: experiential knowledge, lay expertise, and evidence-based activism. We chose these concepts during the iterative process of analysis because they were appropriate to the stories we started working with and enhanced our focus on knowledge forms and knowledge shifts.

With reference to PPIR, Pols explores *experiential knowledge* and how we better can articulate and render useful the knowledge that patients develop, how the particular and practical patient experience and patient knowledge can be translated into and be of use in medical science. Pols discusses how patients are experts of experience, experts on their own daily lives and illness. As such they constitute an important source of knowledge for biomedicine. Pols's discusses two forms of patient knowledge; episteme and techniques. Episteme is experiential knowledge consisting of both home-grown knowhow, that evolves through daily practice and living with a disease and is linked to practice and experience. Techniques are more established objects of knowledge that can be collected as guidelines, tricks, and case stories. Following Pols, it is important to note that biomedical scientific and clinical knowledge form an integral part of patient knowledge (Pols, 2014).

The next concept of *lay expertise*, we borrow from Wynne's study of ways in which Cumbrian sheep farmers act as lay experts and engage with scientists by contributing with valuable knowledge about local conditions, knowledge that otherwise was unattainable by the scientific experts (Wynne, 1998). Epstein later developed the term lay experts to describe patients that acquire scientific and medical knowledge related to their own condition, and he has, using the case of HIV research, analyzed ways in which communities of lay experts developed and interfered with biomedical research, its protocols and designs. In this way, specific publics and those affected by science and policy participate as experts in knowledge production (Epstein, 1995) .

The last concept *evidence-based activism* refers to activism in relation to biomedical knowledge production, where patients and next-of-kin establish biomedical expertise and enter into networks and partnerships with existing, credentialed scientific networks and medical industry (Rabeharisoa, Moreira, et al., 2014). Examples here include systematic collection of patient-based knowledge on specific illnesses, where the scientific evidence and foundations of new knowledge production are created by the patients and next-of-kin themselves. Scientific protocols and standards are used in activism to align with and join up to existing academic and economic agendas of biomedicine, while forwarding specific areas of research.

Data collection and analysis

ADNP syndrome is a rare disease in children about which quite little is known at the time of the study. There is no cure, there are no medical standards, and prognoses for the children diagnosed with ADNP syndrome are uncertain. The syndrome was first described in an article from 2014 (Helsmoortel et al., 2014) as a genetic disorder in one of a small group of genes related to characteristic facial features, growth issues, feeding difficulties, developmental and cognitive delays, speech disorders, autism – and other medical problems of heart, stomach and brain. The disorder is thought to be caused by a mutation or partial deletion of the gene designated Activity Dependent Neuroprotective Protein (ADNP), the child therefore not receiving sufficient ADNP protein for development of the brain. There are about 300 people known to have the condition in 2022. Scientific research on the syndrome is scarce, and that which exists is mainly linked to a handful of researchers in genetics and molecular neuroscience and their research networks – *and* to a network of parents, which is the focus of this paper.

Inspired by Lupton's suggestions for conducting fieldwork during a pandemic, we have worked with content already generated and available on the internet as a source of research materials (Lupton, 2021). During November 2020 - April 2021 the first author collected publicly available online data from ADNP websites, open Facebook groups[viii] including organizational charters of the ADNP foundation, scientific publications on ADNP, press releases about clinical trials, and online open access materials from workshops and conferences related to ADNP. As in Hine's work on virtual ethnography, the Internet and its online

materials are approached as a site for studying actions, interactions, and meaningful connections (Hine, 2015) – here of the parents involved in research on ADNP. The online material was transferred and analyzed thematically in NVivo. Clarke's extended version of grounded theory has been used as resource for the analysis (Clarke et al., 2017). The NVivo software was used to tag patterns and themes in the data and for open iterative coding. Parallel to working with themes and codes, the authors used the "messy mapping" approach as a flexible and exploratory way of working with and discussing the material. Four messy mappings were produced on paper and these led to the selection of parent stories that thematically could portray some of the elements, arenas, and positions mapped out. In the next stage of analysis of these three examples, we focused in particular on shifts or moves in the knowledge interests proposed by the parents. We identified three shifts: undone research, collecting empirical data, and finding a cure. These three shifts have subsequently structured the further analysis and presentation of the stories and the analysis in this paper.

The three examples do not aim at providing a complete picture of the complexities involved in research on ADNP and the role of parents. They were however reoccurring and foregrounded in the online presentations and discussions collected, and thus are assumed to be important and central for this parent community. It is notable that these parents themselves have built their expertise and knowledge networks online. A virtual ethnographic approach is therefore a highly relevant starting point for planning further study because these forms of expertise and the research networks in question have also originated and manifested themselves online (Kozinets, 2015).

Following Mackenzie et. al. (2007) and Mol (2002) we also approach these online materials and inscriptions as being performative and taking part in generating practices and creating the world they describe. In this sense, we approached the collected online materials and the three parent stories as important and interesting initial clues for embarking on a new research project on how parents/patients/citizens develop scientific expertise and participate in constructing new scientific knowledge related to health and illness in new and shifting ways (Holen and Strand, 2022).

Ethical considerations

The authors have used Ethical Guidelines 3.0 from the Association of Internet Researchers, Danish Data Protection Agency and the Danish Code of Conduct for Research Integrity. According to Danish research guidelines, qualitative studies require no further approval process for this type of health-related study. Ethically, we worked with a process- and context-oriented approach that includes reflection on own research practices and associated risks against the data collection, analysis and selection of cases (Franzke et al., 2020). The research has therefore worked with continual ethical judgements, as advocated by AoIR. Our ethical "judgement-calls" in relation to the specific cases were the following: The data collection and analysis did not include an informed consent process, due to the fact that the materials collected were public and online, as well as the timing of the study that was carried out during lock-down in what Lupton calls an "affective atmosphere" (Lupton 2021). This was a time of uncertainty and worry in particular for parents of vulnerable children. The individuals' emails and contact details were therefore not collected and no communication was initiated during the empirical phase of the study[ix].

An ethical choice was made to only collect material publicly available online. This choice did thus not require access to private parent forums or direct interactions with the creators of the materials during the pandemic. All data was accessed through manually search engines and snowballing links on the websites. The three stories selected were reported on various public forums; formal websites, published articles, news sites, and open groups with no membership required. The study does not include, collect, or store

private and potentially sensitive data without informed consent. Names have been changed although we are aware that this is a pseudo-anonymity and does not ensure complete anonymity for the parents involved. The first author sent a late draft to the parents of the three stories to make them aware of the forthcoming publication and allow for their comments and corrections to be incorporated. Through such ongoing considerations and "judgement calls", the study has sought to avoid ethically significant risks and harm (Markham and Baym, 2008).

The impact of experiential knowledge in the face of no available scientific expertise: Peter's story

Peter's story and "road to diagnosis" was presented at a EUROPLAN workshop in 2017[x]. EUROPLAN is an initiative under the European Rare Diseases Organization (EURORDIS), an umbrella organization embracing many different European rare disease patient advocacy groups. This patient organization works to increase public awareness of rare diseases and to promote scientific and clinical research on behalf of different disease-specific patient organizations and their communities. EURORDIS is linked into a set of alliances in research, policy, and industry, and EUROPLAN is a specific initiative to ensure and encourage the implementation of national plans and strategies for rare diseases in specific countries, such as Denmark.

Peter, father of Thomas, relates the chain of events and "a long journey through a land of diagnosing" that finally led to the diagnosis ADNP-syndrome. After an unremarkable pregnancy, Thomas was born into what Peter describes as a situation of chaos in which close to 15 different medical experts were called into the delivery room. The day after, the boy was baptized quickly, moved to intensive care at another hospital, and received his first diagnosis, Tetralogy of Fallot, a rare condition caused by a combination of heart defects present at birth. In the following months other diagnoses are added to Thomas' medical journal: Torticollis (abnormal neck tilt and rotation), Plagiocephaly (flattened skull), together with frequent visits to departments of cardiology, physical therapy, and pediatrics at the hospital. Other disorders emerge such as early teething, abnormal facial features, and later on seizures – some of which are written off as unrelated and dismissed by specialists. Through his day care institution, Thomas is also referred to child psychiatry due to possible autism. As a closed case in pediatrics, further examinations of Thomas are moved into the field of psychiatrics, and he receives diagnoses of atypical autism, intellectual disability, and non-organic insomnia. Adding to the list of symptoms and diagnoses are diarrhea and digestive issues that lead to a referral on to specialists in gastroenterology and yet another diagnosis, Crohn's disease. Throughout this period various medications were prescribed with varying effect. Thomas also underwent operations on several occasions. Meanwhile a cardiologist following Thomas' development also referred him to genetic testing for various syndromes that might explain the combination of symptoms. Tests for a variety of symptoms come out negative until further tests for the genetic mutations lead to the diagnoses ADNP syndrome.

Peter's story resonates a collection of similar stories of ADNP parents' long and strenuous journeys, extensive investigations and examinations, being sent from one department and specialist to the next, and the lack of links and coordination between these various specialists. As an extremely rare and complex syndrome, obtaining a diagnosis is difficult and fraught with frustrations (Rabeharisoa, Moreira, et al., 2014)). With their son now two years old, Peter and his wife are notified that they are the first child in Denmark with this diagnosis and one of 24 worldwide. "Luckily the others had already created a Facebook group we could join", he adds. In this group and associated webpages, they found a lot of useful information as well as emotional support, all of which helped them to "hold on to the many loose ends" when dealing with the many departments and with the amount of information presented related to the various symptoms and the uncertain medicine and treatment options. Over time, European ADNP parent

communities and networks also emerge in for example Italy, Germany, France, and Belgium that Peter also engages in.

Peter's story expresses the importance of finding an online community of parents with similar experiences, struggles and frustrations. Through this community he gains access to both patient-produced and patient-collected information about the illness. These sites and the community become places for Peter to share stories and experiences, tricks and therapies, practical and emotional support and as such it contributes to what Conrad has coined as moving illness from a private experience to a public experience (Conrad et al., 2016) both across ADNP, but also connecting with other rare diseases.

Peter and his wife have at this point, in his own words, become "the experts" since they, as Thomas' parents, become the continuous and connecting factor throughout his trail of symptoms and diagnosing. Due to the rareness of this illness, they now know more than the physicians and experts they can find in Denmark. Together with the other parents in the online community they have become not only experts, but the only experts on an illness that in the established system is still a "medical mystery".[xi]

This expertise can be characterized as both episteme and technique as described by Pols: practical, experience-based knowledge and the experience of living with the illness (of their child) and technical, sharing of tricks, techniques, and what they have learned from online platforms. The ADNP platforms comprise a multitude of accounts of medical issues, surgeries, and experiences as well as treatment and training experiences. The parents share the skill development of their children and new milestones such as the child's first steps, first bicycle ride, potty training, milestones related with both detailed stories and videos. Experience with assistive technologies and devices are also discussed and shared, for example devices for communication with children who are unable to speak. In Peter's story a claim to knowledge and expertise is built though experiential, practical knowledge. His knowledge, along with the community's collected and shared experiential knowledge, forms a knowledge repository that has credibility and authority as being *the* only knowledge source available. Experience becomes expertise in a situation where expertise has not yet been established as part of the formal medical system. The biomedical science of ADNP is as yet non-existing. Credentialed experts are lacking[xii]. The availability of online platforms, the Facebook tool in particular, as well as the actors' proficiency to form a community by way of these platforms, is an important aspect of mobilizing collective experiential knowledge.

Developing lay expertise, new knowledge networks, and improved diagnostic tools: Laura's story

Laura's formal education consists of a high school GED, yet since her son's diagnosis she has become a leading expert on ADNP syndrome. She forms part of various research networks, has co-authored articles with genetic researchers and neuroscientists, and her accounts of everyday life with her son are coupled with technical presentations and explanations of neuroprotective proteins, DNA characteristics, scientific methodologies, and translational study techniques. Laura started the Facebook group and the growing parent community that Peter found and joined. She has worked towards collecting evidence and building new research networks that have led to the development of a new biomarker of ADNP syndrome.

We will look at Laura' story from the time her son is diagnosed. She cannot locate any experts nationally or internationally and can only find one medical publication about this genetic mutation. She recounts how no doctors knew about the disease. There were no medical protocols, support groups, available treatments, or even a website about the condition, and after struggling to receive a diagnosis, yet another journey begins. Upon receiving the news of an ultra-rare genetic mutation, she was, as she puts it, sent "on my merry way". She describes this as the beginning of an even bigger struggle "because our children are diagnosed with something that the normal medical world doesn't know about. There are so many issues because this is a

new and relatively unknown syndrome. It is insane that we have had to fight for years to find out what was wrong with our children, and now, we have to fight because what they have is so unknown".

Laura embarks on an internet search for information, publications, and researchers who might know more. Through her searches she finds a cognitive genetics researcher in the Belgium who had identified the first ADNP patient and written a publication linking the ADNP gene to autism in 10 children. She contacts this researcher hoping to be able to learn more and get into contact with these families, and he agrees to give her contact information to the family physicians that pass it on to the parents and share a link to a Facebook group Laura has just set up. Within a few weeks Laura is connected to the parents of the Dutch children. Over time, through the Facebook page, she gets into contact with more parents from different countries.

Through contact with this growing number of parents, Laura starts collecting information about the children, very systematically in a spreadsheet, plotting their characteristics, features, diagnoses, and treatments, thus producing a collection of evidence mapping the characteristics associated with the genetic mutation. Laura was struck by how the children shared similar physical features as well as many of the same medical experiences. Noting similarities in these stories, she found that most of the children had a full set of teeth, including molars, by the age of one. Laura read up on medical literature to find that this was actually quite a remarkable and unique trait, since children otherwise rarely have more than incisor teeth at this age. She also conducted further searches on the topic to confirm that no other disease was at that point associated with this kind of very early tooth eruption. Laura collected the shed teeth of both her son diagnosed with ADNP and his twin brother with no diagnosis as a control measurement. She systematically arranged the teeth chronologically as they fell out. A line up of the two sets of teeth worked as patient-based scientific evidence of ADNP related toothing. Laura was able to document differences between the two sets, that the ADNP teeth were smaller and more jagged in comparison to the control. This led to a later CT scan of these teeth to determine that a child diagnosed with ADNP also had less enamel thickness due to being underdeveloped and erupting early.

Laura and another parent contacted a clinical biochemistry researcher in Israel, one of the very few that had written about the ADNP gene. Together, Laura and other parents, along with research teams from Belgium and Israel prepared a formal study, with a questionnaire about teething on the parent website to collect additional data confirming what Laura had noted in her original spreadsheet. The findings were also used in an Israeli laboratory in a study on mice, where this link could be replicated showing that ADNP deficient mice also had dysregulated teething. In this way, Laura and parents worked to both produce and bring together various forms of knowledge; patient-based evidence, laboratory evidence, and clinical evidence.

These collaborations lead to the formal establishment of a unique biomarker to provide a simpler and earlier way of diagnosing the ADNP syndrome, and consequently paving the way for early interventions and treatment plans that were not previously possible. As such, the biomarker might alleviate some of the parent frustrations in the stories above about searching for a diagnosis. The evidence Laura compiled in the original spreadsheet, her collection of teeth, and the collaborations she sought out also sparked further studies of interactions been the ADNP gene and tooth and bone development currently explored in further studies and in relation to new treatment possibilities.

In Laura's story, she starts out by conducting her own online searches, educating, and training herself in relation to research that might be related to ADNP. This is done by "night stocking the internet" on her own and later participating in drug development conferences, rare disease entrepreneurship boot camps

organized by rare disease patient organizations and finding opportunities to learn and discuss ideas with credentialed, formal researchers and experts. Knowledge of research methodologies and linking to existing networks, enable Laura to gather patient/parent experiences data in systematic, methodological ways – producing patient-based data and rendering experience-based knowledge legitimate and valuable within a scientific realm. Her story is thus both one of producing new evidence, but also of building the very networks and infrastructures through which this evidence can establish a new scientific breakthrough – a new biomarker for early detection and diagnosis of ADNP syndrome[xiii]. This story is thus about successfully establishing lay expertise and building patient-based evidence, as well as about recruiting established researchers to apply their time, expertise, and credibility in research defined by the parents.

Finding the cure for our children: Jonas' story

Our last story is that of Jonas, also a parent of a child with ADNP syndrome. In contrast to the other two, Jonas has formal, credentialed expertise in neuroscience. His story is one of playing a major part in developing a possible new treatment of ADNP syndrome. His son was diagnosed with ADNP about the same time as Peter and Laura's children, and he met them and other parents online as well as personally in a Rare Disease Summit.

Jonas worked with the father of a child with another rare disease, who was developing an artificial intelligence tool for reading large bodies of medical literature, registries, and databases in search of potential drug candidates for his son's rare disease. This parent helped Jonas to use this tool to search for drugs somehow associated with the ADNP gene in the literature. With this tool Jonas together with Laura found several animal studies indicating that low doses of the drug ketamine might affect the production of ADNP in the brains of mice. Ketamine is an already approved drug for treatment of other illnesses. The repurposing of an existing and approved drug is much faster and less costly than developing a new drug. This is advocated by rare disease patient organizations as a viable and affordable way to find new treatments for rare diseases with small patient populations where developing a new drug would be too costly for pharmaceutical companies in relation to the few potential consumers of the new drug (Hernberg-Ståhl and Reljanović, 2013). Using a drug already on the market, several steps of drug testing can be skipped, since, for example, its safety has already been established in previous studies and approved by regulatory authorities.

Together Jonas and Laura combed the multitude of studies and literature found using the AI search. They also studied the process of drug development, with scientific and regulatory ways of testing an existing drug for new purposes. They suggested the set-up and outcome measures for a potential study. The parents also prepared a pitch for a pharmaceutical company or a research institute that might be willing to conduct a clinical trial to test the drug. As part of this process, Jonas and Laura hired an attorney and filed a patent protection document for the particular use of ketamine to treat ADNP syndrome, thus protecting intellectual property rights of the findings and file patent.

In 2019, Jonas and Laura contacted researchers at a non-profit research institution proposing that they conduct a small-scale clinical trial to test the use of ketamine on children diagnosed with ADNP syndrome. The proposal was based on their own search through medical literature, their findings and hypothesis. Researchers at this institute work across genetics research and clinical research and have a focus on genes that have mutated in children diagnosed with autism. In collaboration, they applied to the FDA to carry out the study. Through the parent community they also managed to raise $150,000 to fund the study. Patient recruitment for the clinical trials is rapid, as they entered their own children into the study. 10 children

were recruited to test the drug in a phase 2a drug trial, and updates on the trial were thereafter continually posted on the foundation's website and on the Facebook page.

Through Jonas' story we find patient/citizen claims to knowledge and expertise are made and mobilized through an alliance with the AI tool. This tool offers the parent group fast and inexpensive search capabilities and provides them with results that otherwise would not be possible. With the results found and developed through their further detailed reading and discussions of the literature, an authoritative hypothesis could be claimed. Backed by the community's funding and a convincing pitch to a group at the autism research center, a clinical trial and testing of a new drug on children was initiated within the established medical research system.

If we look at the list of members of the ADNP foundation's scientific and medical committee, we find that all the names of the various parents and researchers of the stories above are joined together[xiv]. What is striking here, is that Laura and the other parents are actively involved in initiating and furthering the foundation, driving new diagnoses and treatment research. This is done by not only linking up to and furthering their own interests and agendas into existing scientific networks – but by building a new network that joins together researchers from different areas of expertise and geographic locations, furthermore, also linking these to a community of parents and patients.

The stories above are thus also stories of building of new research infrastructure that previously did not exist. This infrastructure cuts across patient community, clinical research, genetics research, biochemical research and more. In these stories, the digital possibilities play an important role - both in the sense that a new community was established through online platforms, patient evidence was collected through these platforms, and in the sense that the exploration of the existing more formal and established knowledge base took place through online searching and AI. Digital possibilities of Facebook communities, Internet searches of existing science and scientific networks, as well as a particular AI-tool seem to be crucial for the building of experience-based knowledge, lay expertise and evidence-based activism.

Discussion

This study has been guided by asking how patients and citizens can come to have an influence on biomedical research and how involvement is made possible. We have explored this question using what can be characterized as an unknown illness, where the disease itself, the diagnoses, and possible cures are in the making and have been driven by the public or next-of-kin. The three parent accounts are stories about medical science as initiated, constructed, and funded by a parent community. The parents have taken part in pinpointing the disease and have contributed with a way of diagnosing it. They also manage to assemble a group of experts across geographic divides, across neuroscience, genetics, psychiatry, and clinical practice, and this process has grown into what we can think of as a new biomedical infrastructure, including themselves and their lay expertise, and it is in part driven by them. This can be characterized as a uninvited involvement, as public-science practices taking place "in the wild" (Callon and Rabeharisoa, 2003).

We suggest that these stories can open a new path for thinking about PPIR. The stories are grounded in affect, emotions, frustrations with the medical system, as well as in very strong hopes for and expectations of future science. In classical evidence hierarchies, what might be categorized as bias and partiality is here what motivates public engagement and the creation of new diagnostics and treatments (Holmes et al., 2006). In addition, we find the perseverance and pioneering creativity of these parents as important part of the story, in particular their use of digital resources such as Facebook, public research databases and researcher profiles, as well as an AI-tool.

PPIR has during ~~the~~ recent years gained influence as a concept and set of practices that can democratize biomedical knowledge production. PPIR has gained a strong influence in the social services field and in psychiatry but has more difficulty finding a footing in biomedical research in the light of biomedical scientific standards of neutrality and objectivity. Therefore, it is particularly interesting to explore a case such as that of ADNP and the shifts where PPIR constitutes a new loci of production of knowledge. Here, the relevant patients and publics do not pre-exist waiting to be activated, involved, and engaged through various methods and involvement set-ups. Through the case of ADNP, we illustrate in contrast how parents can act as knowledge agents and activists on their own initiative and premises. They are the initiators rather than the involved. This constitutes a shift from "Patient and Public *Involvement* in Research" to "Patient and Public *Initiation* of Research".

These parents are as such not skeptical towards biomedical knowledge nor positioned critically in relation hereto. They believe that biomedical knowledge can help their children significantly, as long as a search for new evidence continues. Furthermore, they are at the outset not as bound by the restrictive, regulatory system of medical science as credentialed experts and formal professionals. Rather, we find that these parents by way of knowledge sharing and networking, act as knowledge agents, who can claim to "know more" than educated medical experts through their specific combination of experiential knowledge and lay expertise. They initiate contact to and tie together a cross disciplinary and transnational research networks. We find that knowledge of a new illness - its diagnostics, etiology, pathogenesis, as well a possible treatment is created. The increasing "hyper specialization" of biomedicine seems to lead to a situation where it becomes impossible for medical experts to stay updated and knowledgeable on all diagnoses and treatment possibilities, where it is impossible to find the right solutions to all medical conditions. This development is (mis)matched by growing expectations from the public in relation to the hopes and promises of biomedicine, where COVID-19 also serves as an example of the potentials of biomedicine for developing breakthrough and applicable knowledge in a relatively short time span. This mismatch, between medical hyper specialization and public expectations for cures, creates a gap or a kind of crack in biomedical knowledge production. Our cases illustrate such a crack where new forms of citizen-led networks and knowledge formations grow to in order to ensure that biomedicine related to ADNP is prioritized and updated. As such, the stories illustrate a user-led, community-based, and deeply participatory form of research.

These cases parallel what Epstein has explored as a more pervasive contemporary shift in which those affected by biomedical science participate in its production (Epstein, 2022) This is therefore also a shift in the infrastructures that construct biomedical knowledge. In the making is not only the disease, diagnosis, and new treatments, but also new citizen scientists, new forms of collaborative research opportunities for credentialed scientists. In the case of ADNP, the parent-led research mimes biomedical knowledge practices in a way that, on the one hand, enhances the legitimacy of science and scientific expertise, and on the other displaces and transforms science by the fact that other knowledge agents (patients, next-of-kin) become part of these practices. Their experiential knowledge and lay expertise become integral to rather than separate from scientific expertise. Shifts in biomedical knowledge production, distribution, and consumption invoke new questions and ways in which we might think about scientific bias, objectivity and informed consent in regard to patient participation in medical trials. Parents enrolling their own children in medical trials, trials also initiated by themselves, can be seen as ethically biased. The concepts of bias and consent form a very fundamental basis of conducting medical research on human subjects. The stories presented here provoke and challenge this very basis of evidence-based health science. We hope this paper can encourage further debate and perhaps new conceptions of ethics, bias, and objectivity in biomedical research "gone wild".

Conclusion

In this article, we have analyzed how a group of parents function as self-appointed biomedical knowledge agents on an unsolved medical challenge. Several components are important for them to succeed in their mission. First, they are parents of children who are seriously ill. In other words, there is no doubt that the problems the children struggle with are biomedical and at the same time unsolved. Second, these parents have acquired the competencies to collect and systematize experiential knowledge. Their ability to transform this lay knowledge into biomedical signs/symptoms are so compelling that established biomedical researchers find interest in being part of their network. Thirdly, the parents themselves create results through the innovative use of tools that can further highly specialized biomedical hypotheses that likewise gain recognition by biomedical professionals. They are also able to create a setup including research financing, where their hypotheses can be tested.

Overall, we see that the parents convincingly mimic biomedical scientific processes, which means that they gain credibility as agents of knowledge, even though they are lay persons. In addition, they cannot be said to be neutral and independent, something that is often emphasized in biomedical research and fundamental requirements of non-bias and objectivity. Parent-led research mimes biomedical knowledge practices, thereby enhancing the legitimacy of science and scientific expertise, while also displacing and transforming science by the fact that other knowledge agents (patients, next-of-kin) become an integral part of scientific practices.

Academic and political discussions on PPIR often revolve around participation by invitation and issues of representation. Our analysis points to PPIR activities taking place in non-invited arenas shifting the way we think about representation in PPIR. This calls for an increased attention towards the relation between democracy and knowledge and how this relation comes into play in such publicly led initiatives and activities. Also, it becomes necessary to focus on inequity since not all patients, next-of-kin and groups have access to the necessary resources and conditions for conducting or influencing science. Our case also points to new kinds of relations between publics and the medical industry. The public is often not recognized as knowledge agents and experts per say and therefore may not have the same opportunities for lobbying activities. Likewise, they are not at the outset part of an infrastructure where they can be contacted by lobby. We call for further study of such relations between publics, lobby, and the medical industry.

Our analysis of the ADNP case indicates a possible shift in the way we think about and delineate experiential knowledge, lay expertise and evidence-based activism as these practices and their consequences are changing in some arenas. This raises questions on how resources best can be prioritized in relation to rare diseases verses broader public health challenges. Biomedical knowledge is continuously entangled with public, funding, and political considerations. Entry points to knowledge production are multiple and perhaps increasing, and as such, types and characters of knowledge production are shifting and changing. In this paper, we conclude that the forms of parent-led knowledge activities analyzed here both invigorates production of new biomedical knowledge as well as challenging its foundation of scientific objectivity.

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[i] See https://www.nihr.ac.uk/documents/ppi-patient-and-public-involvement-resources-for-applicants-to-nihr-research-programmes/23437 for UK and NIHR research standards, guidelines, evaluation and reporting on PPIR

[ii] See NIH requirements for community involvement and collaboration here https://ncats.nih.gov/engagement

[iii] The terms used here references framework where 'scientists' are professionally educated, part of formal scientific institutions and conducting research within the framework of science organizations. In parallel, this has been discussed as a mode-1 form of science science: pure mono-disciplinary science independent of outside influence, for example patients and publics (Nowotny et al., 2003).

[iv] There is an important body of literature that critique cure-ing above care-ing apporaches to disablity, and childhood disability in particular. Clare (2017) for example discusses the consequences of turning cure to an ideology. We do not intend to take part in this specific discussion by elevating stories of parents aiming to "cure" their children. Rather we use the case to analyze the relationship between experience-based knowledge and biomedical science.

[v] https://www.facebook.com/ADNPkids, https://www.facebook.com/ADNPFoundation, https://sjaeldnediagnoser.dk/wp-content/uploads/2017/12/Diagnostik-Jesper-Kokkendoff.pdf, https://www.statnews.com/2021/08/05/artificial-intelligence-rare-disease-andp-medikanren/, newsletters, links and research articles available through http://www.adnpfoundation.org/

[vi] Names have been changed as courtesy to these individuals.

[vii] Another strand of STS has been engaged in exploring ways in which scientific knowledge, including knowledge produced within STS, might be shared with consumers and citizens. Irwin, for example, has contributed to developing the concept of citizen science to address how non-scientists or lay people might also be given a say and more active role in discussions of "good" science, research priorities and choices involving how to deal with inherent uncertainties of science (Irwin, 2001; Irwin et al., 2013). Here, STS intersects to the PPIR debates noted above where discussions relating to public engagement in science, citizen science, and open science have increased during recent years. This entails a shift in the authority and position of science and scientists as unique or privileged, which has also been brought up in discussions of PPIR.

[viii] Specifically, ADNP Kids and ADNP Kids Research Foundation public Facebook pages. Private online groups for parents and families with a child diagnosed with ADNP have not been accessed in the study to avoid collection and storage of potentially sensitive data without informed consent.

[ix] An exception here is that the first parent held a brief email correspondence with one parent a and a half year before the study took place. This exchange was the original source of inspiration for the study.

[x] Program and slides were found online. Presentation text was provided from Peter by email upon request from the first author.

[xi] Rhetoric of parents being together on a quest, mission, or to solve a mystery for the sake of their children is pervasive in the material collected. Related work focusses on the importance of emotional work and role of affect in scientific patient communities 14 (Lindén, 2021).

[xii] In study of patient participation in the Danish Medicines Council patients with rare disease are noted as a group the more have more a voice and easier can influence on medical priority setting because they act as experts on their own disease where the formal, credentialed expertise is lacking due to rareness (Steffensen et al., 2022).

[xiiixiii] It is also notable that this very diagnostic biomarker works to increase the number of children diagnosed, the patient population for which research is conducted, and who serve as very the subjects of research when testing new treatments.

[xiv] Panofsky (Panofsky, 2011) examines sociability and how close relationships are established between members of patient advocacy organizations (PAOs) and scientists to drive PAO's concerns. Here, PAOs representing those with rare genetic disorders drive research to their concerns through 'sociability', forging close relationships with scientists and orchestrating relationships among them. Panofsky analysis shows how the strategic manipulation of sociability can give PAOs substantial influence over the research process.