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Rare disease patient groups as clinical researchers

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In the face of inadequate treatments, rare disease patients have begun acting like scientists and studying themselves. Through online networks, patient groups transform disease experiences into novel research data: exchanging therapeutic anecdotes, willingly self-testing treatments and compiling outcomes into preliminary research hypotheses which are subsequently relayed to professionals. Through such efforts, rare disease patient groups have helped evaluate and validate several new therapeutic modalities. This article specifically explores the process of patient-driven research while considering broader implications of the trend. While issues regarding methodological quality and patient safety must not be overlooked, through future partnerships with academia and the pharmaceutical industry, patient groups could function as a powerful resource in rare disease research.

Introduction

To date, scientists have identified more than 5000 rare diseases, which collectively affect about 10% of the population [1]. Yet few of these diseases have been carefully studied and only a very small proportion can be considered 'treatable' by biomedical standards [2]. Communities of patients have responded to the lack of medical provisions by mobilizing into grassroots organizations, which in addition to providing emotional support to sufferers, often simultaneously pursue research agendas [3,4]. Such groups might lobby Congress for increased federal research funding and/or award their own private grants to scientists. Not all patient groups, however, especially smaller-scale rare disease communities, possess the political or economic capital required for such research strategies. Several of these groups have alternatively begun using their collective lay experiences, knowledge about living with various diseases, as a unique, legitimate, and valuable source of research data [5]. Patient groups hope that by aggregating experiences patient-by-patient, they will further the medical understanding of their diseases and move closer to finding cures and effective treatments [6].

With the growth of online social networking and electronic data collection capacities, patients' ability to share, aggregate and analyze health information is rapidly expanding [7–10], http://www.fergusonreport.com/articles/fr00903.htm. Rare disease patient groups have begun using a variety of online tools to promote research, such as interactive message boards, community forums, and web surveys. Reports of such efforts are documented in the academic literature [6,10–14] and popular media [15,16].

Patients' involvement in medical research challenges normative boundaries between expert and layman. However, among less well-developed research topics (i.e. most rare disease fields), outsiders and new innovations tend to have a relatively greater likelihood of entering into and impacting professional domains [17].

Numerous factors deter public and for-profit agencies from investigating rare diseases, lowering the barriers of entry to research for outsiders. For example, cost-effectiveness and public health interests drive federal and state health departments to prioritize research funding of common over rare conditions [18]. Academics interested in rare diseases are deterred by the ensuing funding shortages and discouraged by the difficulties of patient recruitment and adequate powering of studies [1]. For-profit industry subsequently considers R&D for rare diseases too costly [19] given the paucity of basic science information for the diseases [20,21] and poor financial prospects of selling drugs to such a limited patient pool [22,23]. The ensuring scarcity of rare disease research leaves room for outside players, including patients, to actively participate in research production.

Although several enthusiasts tout the research efforts of patient groups [8,9], other professionals express concern over their

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work [15]. Research scientists for example caution that patient groups might unknowingly engage in data dredging or conflate correlation with causation [16], hold latent, unchecked biases toward specific therapies [24], or compromise safety through excessive risk taking [25]. Professionals additionally express fears that patient involvement in research might be 'inefficient' or disruptive to the work of scientists [11], or might dilute the patient pool for traditional randomized controlled trials [28].

With respect to these concerns, the potential and pitfalls of patient-driven research merit further attention. Although examples of rare disease patient groups developing novel hypotheses regarding disease etiology and treatment exist in the literature [6,10–14], few accounts have reviewed the practical steps required to bridge the gap between patient experience and empirical research.

The goal of this article is twofold, first to present a framework characterizing the step-by-step processes by which patient groups transform experiential information into biomedical research, and secondly to identify the strengths and weaknesses of patient-driven research and consider how and where the practice could prove most impactful to patients and professional researchers. To answer these questions, this article reviews the published literature and presents in Box 1, a detailed example of how one rare disease patient group has used experiential knowledge as a source of research data. This case was gathered from exploratory interviews held with rare disease patient group founders in preparation for writing this article.

Steps in patient-driven research

Although each patient organization follows a unique trajectory in its research, specific research 'steps' were frequently shared or overlapping. A three-step model characterizes the general progression of information generation, from patient experiences to research data (Fig. 1).

Research begins when patient groups learn of possible treatment 'leads' through members' anecdotal reports. The groups then share the anecdotal information with other members, often through their websites or newsletters. Subsequently, many additional patients test the publicized therapy themselves, reporting their outcomes back to the group. Patient groups sort and analyze these responses, then share their data with a broader biomedical audience, by publishing their work in biomedical journals or on their patient websites, asking physicians to publish case reports about their experiences, encouraging researchers to follow up on the groups' preliminary research, or funding their own clinical trials. Each of these steps can be considered in greater detail.

Pursuing possible treatment 'leads'

Within communities of patients suffering from the same disorders, individuals tend to freely share health information [14], including their personal endorsements of various therapies. Patient groups

BOX 1

Case: The Recurrent Respiratory Papillomatosis Foundation.

The Recurrent Respiratory Papillomatosis Foundation (RRPF) was created nearly 20 years ago, after the founder's daughter was diagnosed with the rare condition, which causes continual growth of airway-obstructing tumors. Over the past two decades, the RRPF has mobilized a network of patients and professionals to help promote research into several pharmacotherapies, including indole-3-carbinol/3,3′-diindolylmethane (I3C/DIM, a phytochemical) described below, artemisinin (an antimalarial drug first described in Chinese Medicine), and the mumps vaccine, among others (RRP Foundation: http://www.rrpf.org). Investigation into I3C/DIM began after the founder learned of a research team using the compound to successfully control the disease in mice [52]. The founder requested a sample of the compound from the scientists conducting the study and was told it could be found in high concentrations in cabbage. He subsequently fed cabbage juice to his daughter every night and several months later she entered remission, shocking both him and her doctors. The founder printed the story in the RRPF's newsletter, inciting a rush of patients to try the treatment. A follow-up patient group survey estimated a >50% response rate with a 20% remission rate. Soon after, an affiliated researcher published a case history on the daughter and conducted a pilot study showing similarly promising results [53–55]. The treatment continues in usage with many research studies discussing its potential benefits [56–58]. However, due to funding shortages and lack of professional interest, no formal RCTs have yet been conducted.

-Based on exploratory interviews with RRPF founder, Bill Stern

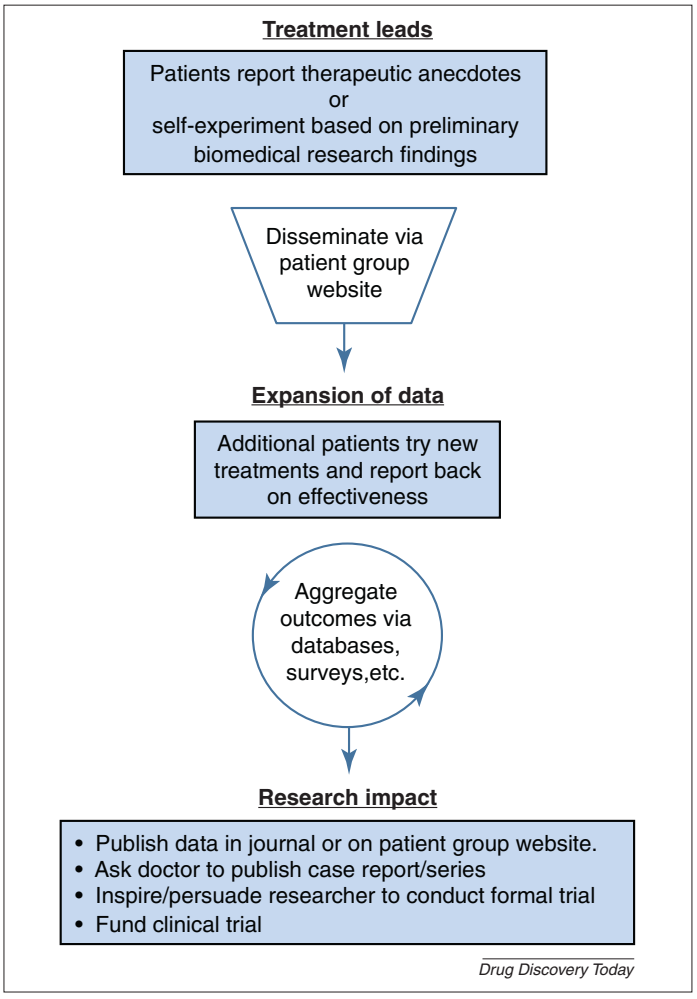

FIGURE 1

To transform experiential knowledge into research data, patient groups gather and disseminate anecdotal treatment endorsements from group members, prompting additional patients to 'self-test' publicized therapies. Ensuing member reports are aggregated and analyzed by patient groups, generating data that can be shared with a broader biomedical audience.

capitalize on this information exchange by listening carefully and openly to the variety of anecdotes coming their way [26,27]. Treatment endorsements arise in a variety of forms. Some come from patients who unexpectedly benefited from an off-label drug prescription or from a medication prescribed for indications other than their primary disease [11]. Others emerge when patients stumble upon intriguing leads through literature reviews of abandoned or incomplete trials; and decide themselves to resurrect a forgotten therapeutic through self-experimentation [7]. Suggestive preclinical or animal evidence alone has also prompted group members to self-test therapies [7,28].

Sharing information and expanding access

Before disseminating treatment leads, patient groups worked to balance timely information release and patient safety, filtering leads appearing disingenuous (i.e. coming from nonpatients abusing a listserv as a promotional tool), exceptionally risky and mechanistically implausible. Treatment modalities remaining after this initial screening process included off-label drug prescriptions [7,11], newly emerging therapeutics [7], and more easily accessible treatments such as phytochemicals, specific diets, and a few complementary and alternative medicines [11,26].

Information circulated in several ways. In addition to online postings by group members, patient group representatives could publish purported treatment benefits and side effects in sponsored newsletters [7]. Dissemination of treatment anecdotes frequently prompted group members to seek out the therapy themselves, and then report back to the patient group through phone calls, emails and message board posts. To formalize this process, patient groups often designed simple surveys with Likert scales inquiring on treatment effectiveness, quality of life variables, adverse effects and complications [12,26,27].

Representatives inputted patient-reported data into computer spreadsheets to run basic statistics. Occasionally, patient group leaders with professional training in other fields (i.e. librarians, engineers, social scientists, business administrators, lawyers, among others) would conduct such analyses themselves [15,16,27,29]; while other groups enlisted assistance from professional colleagues or personal friends with research training [27,30]. Additional patient reports validated or invalidated emerging trends, with groups welcoming confirmatory and disconfirmatory evidence alike [11,26,31]. Effectively these groups were spearheading patient-driven observational trial of the anecdote, their hypotheses 'tested' in real-time through subsequently recorded experiences of patient members.

Broader research contributions

Patients groups pursued at least three different strategies for validating and integrating their findings into the professional biomedical literature. Some groups simply published carefully collected survey data themselves [6,7,32]. Other groups sought to collaborate on follow-up studies with professionals. Such patient groups would market their findings as promising research hypotheses, supported by evidence, with a high likelihood of yielding significant response rates in larger investigations [27]. In a few cases, patients with intriguing responses to novel therapies persuaded professionals witnessing their success to publish the findings as a case history or case report (Box 1). Alternatively, a scientist's interest could be piqued without any effort from the patient group, especially if the finding itself generated attention within a field [11].

Despite this list of successes, however, patient groups frequently are not able to persuade researchers to investigate their hypotheses. At least one report has identified close sociable ties with professionals as an important predictor of patient-driven research success [30]; groups without personal ties to individual scientists and health professionals might have a more difficult time bringing their work into the mainstream. In the meantime, some groups have managed to raise money and fund studies themselves, whereas others continue to search for professional research assistance [27].

Rare disease patient groups fill a unique research niche

In assessing the research efforts of patient groups, attention must be paid to how patient groups produce information insofar as their efforts compare and contrast with conventional scientific research, and also what broader research contributions such actions represent.

Patient groups' resemblance to and departure from scientific norms

Patient group research resembles professional processes in some respects, with additional liberties taken along the way. On the one hand, patient groups, like scientists, make observations and form testable hypotheses. Their efforts to collect and evaluate 'data' through aggregated emails, calls, and surveys, further reflect scientific practice; predetermined, concrete bits of data were being systematically collected and analyzed. As has been reported among other activist groups [17,33,34], such methodological formality often derived from coaching from professional affiliates, if the expertise was not present within the group itself.

On the other hand, patient groups also make fundamental departures from scientific norms. In fact the very foundation of their research model, anecdote, currently sits among the lowest tier of biomedical evidence, surrounded by connotations for being 'unscientific' [35]. Patient groups, however, prize this source of evidence, and act on anecdotes far more frequently than professionals [36,37]. Patient groups secondly demonstrate a relatively higher threshold for uncertainty compared to professionals, especially regarding their dissemination of unproven anecdotes and self-experimentation with untested therapies. Other patient groups have similarly prioritized the prospective benefits of research over risk management, by fighting to expand access to experimental treatments [3], even invasive ones [38].

On a more critical note, the liberal research methods of patient groups also tended to lack many of the stringent elements of experimental design scientists employ to minimize biases. Their 'observational trials' rely heavily on patient self-reported medical history, proceeding without baselines or experimental controls. Patient groups might be overestimating the efficacy of treatments as a result. Although professionals attribute this oversight to oblivion or a lack of professional training [15,16,25], an alternative interpretation considers that patient groups might simply be rejecting aspects of scientific practice incompatible with their own goals. When they perceive lives to be on the line, some patient groups knowingly prioritize expedient results over pristine

or cautious science. In any case as discussed below, the procedural liberties of patient groups, although methodologically problematic, might simultaneously be instrumental to the successful generation of useful treatment-related information.

Expediting the R&D pipeline

Traditional research models depict a linear progression from bench-to-bedside, whereby basic science and mechanistic studies pave the way for animal testing and finally, human trials. Through their generation of clinical data, patient groups expedite several bottlenecks in the R&D pipeline, nimbly maneuvering through research steps that frequently cause delays for professionals [39].

Patient groups' continuous flow of anecdotal reports is firstly instrumental in this effort. Iterative feedback from members enables patient groups to essentially mimic the start-up stages of biomedical research, which tend to be highly labor intensive and expensive for experts [40]. Through their online networks, patients can find out early on which treatments warrant further scrutiny and which do not, and relay the most promising findings to scientists.

Patient groups can also expediently bypass stages of translational research, obviating the need to perform such unglamorous research tasks as drug specificity and toxicity testing in animals, which neither academics nor industry have much incentive to perform [41]. As described in Box 1, one method by which patients bypass translational research steps is by testing novel therapies supported only by preclinical evidence on themselves. Although not without risk, such efforts can dramatically expedite research.

Patient groups can additionally circumvent the laborious process of patient recruitment, another common obstacle in rare disease research [20]. Recruitment is a relatively easy endeavor for patient groups, as cohorts form organically on online networks. Ultimately, by efficiently assessing therapeutic anecdotes within an organized group of patients, then directing the most promising research findings to professionals, patient groups can arguably save valuable biomedical research dollars [7].

Patients' generation of clinical data challenges the linear model of research, especially when generated before a therapy's mechanistic elucidation. This scenario is not, however, entirely uncommon: the anti-inflammatory and anesthetic effects of aspirin were known well before the discovery of its effect on prostaglandins. In fact, some argue that for therapies already in widespread use, for which there is scarce research, and little or no regulatory or financial gatekeepers controlling their usage, research might more reasonably proceed in reverse order, with clinical evaluation preceding mechanistic understanding [42]. Rare disease patient groups are well positioned to contribute to such practices.

Patient group research topics reflect patient group research values

Prior work demonstrates how the personal values of research participants can impact the nature of knowledge derived from a study [43]. Accordingly, as patients' health goals differ from professionals' so too might their research emphasis. Although professionals frequently pursue academic, mechanistic questions relating to health and disease, patients prioritize more pragmatic questions—i.e. which therapies work best and how these therapies might affect their lives. Subsequently, patient groups tend conduct more multifaceted evaluations of therapeutic efficacy than professionals [27,29]. They record patients' perceptions of effectiveness and adverse effects (which can be at odds with professionals') [37], use open-ended questions enabling yet-unreported treatment effects to surface [31], assess how therapies impact daily living [21], and simultaneously compare efficacy rates across several different treatments [1]. Such research proves widely generizable and possesses high external validity, yielding a unique form of research likely unattainable through more stringent, professionally designed trials. Ground level information about treatment impact could also be of use when making health care reimbursement decisions in the future.

The patient survey compiled by one rare disease organization provides a demonstrative example of the above-mentioned points. This organization tracks patient responses across a range of treatment categories, reporting on length of hospital stay, complications, tumor regrowth, and pre and post comparisons of the presence/absence, frequency, and duration of multiple symptoms, including cognitive and psychiatric variables (Acoustic Neuroma Association: http://anausa.org/index.php/patient-surveys). Such a resource can be immensely instrumental to the medical decision making of patients.

Also in contrast to professionals, patient groups often endeavor to track treatment effectiveness over long durations [26]. Current federal law requires drug developers to prove short-term treatment efficacy over a span of years, whereas in the 'real world' patients often take these drugs for decades. While government agencies recognize this issue and have asked nonprofit and for-profit organizations to extend the duration of their investigations [44], without proper legal enforcement, these organizations have no incentive for following through. Because the issue of long-term effectiveness is more relevant to patients, patient groups might be well positioned to carry out this type of postmarket drug regulation.

Patients driving research also tend to explore a broader range of therapeutic modalities than academics or pharmaceutical researchers. Firstly, through patient group investigations of off-label prescriptions and open-ended survey questionnaires, new uses for old drugs are being discovered [11]. Outside of patient groups, investigators tend to evaluate treatments for narrow therapeutic purposes; trial designs do not encourage emergence of serendipitous findings [45]. Even in the presence of government subsidies [1], evaluation of unexpected benefits of current drugs is uncommon among professionals [46]. Patient groups' interest in the unforeseen benefits of old drugs can thus serve as an important means for exploring new treatment options for rare disease sufferers [11].

Patient groups also fill a research gap through their evaluation of unconventional therapies. In professional spheres, stigmas [47] and biases [48] against alternative modalities can deter academic interest; while the inability to patent readily available herbs or natural products dissuades pharmaceutical interest [39]. As such, patient groups might be uniquely positioned to conduct research in these areas, studying overlooked, but potentially beneficial, natural therapeutic modalities. In fact several biomedical articles have recently encouraged research organizations to return their attention to natural product research, because historically,

medicinal plants and micronutrients in food were lucrative contributors to drug development [49–51].

Conclusion

Using tools of social networking, rare disease patient groups have helped transform patient-reported treatment anecdotes into biomedical knowledge. Through the iterative sharing, aggregation, and evaluation of therapeutic outcomes, patient groups initiate open observational studies on novel therapeutics, information which can be subsequently relayed to professionals for further formal assessment. Although patient group efforts' resemble scientists' in many respects, their work also differs in important ways. Patient groups demonstrate a greater tolerance of risk taking, openly explore a variety of therapeutic options regardless of biomedical acceptability and economic profitability, and make modifications to the experimental design of their studies.

On the one hand such departures from conventional practice raise legitimate concerns: self-experimentation with untested treatments could be risky, and the absence of experimental controls might cause an overestimation of treatment efficacy. But these same methodological liberties appear, on the other hand, to be instrumental to patient groups' success.

A review of the literature demonstrates numerous research contributions of rare disease patient groups: (i) They conduct expedient research, efficiently tackling the start-up phases of research, bypassing translational research steps, and quickly negotiating the process of patient recruitment; (ii) They compile information that is pertinent to patients, documenting exhaustive lists of treatment benefits and adverse effects, including quality of life issues; making across-treatment comparisons, conducting post-market treatment testing, and producing results with high external validity; (iii) Finally they investigate novel treatments by evaluating new uses for off-label drugs and natural products, such as medicinal plants and micronutrients in food.

The current structures of the biomedical research establishment do not sufficiently incentivize the development of new rare disease treatments. Because of their unique motivations and research approach, patient groups are well positioned to fill important gaps in rare disease research. Many of the treatments tested will not yield promising results, but occasionally some will. It is with these cases, that through future partnerships with academia and the pharmaceutical industry, patient groups could function as a powerful resource in rare disease research. In fact, in appropriate settings, such efforts could be expanded to other more common, but still understudied diseases as well.

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References

1 Griggs, R.C. *et al.* (2009) Clinical research for rare disease: opportunities, challenges, and solutions. *Mol. Genet. Metab.* 96, 20–26
2 Wastfelt, M. *et al.* (2006) A journey of hope: lessons learned from studies on rare diseases and orphan drugs. *J. Intern. Med.* 260, 1–10
3 Epstein, S.G. (2007) Patient groups and health movements. In *The Handbook of Science and Technology Studies* (3rd edn) (Amsterdamska, O. *et al.* eds), pp. 499–539, MIT Press
4 Boon, W. and Broekgaarden, R. (2010) The role of patient advocacy organisations in neuromuscular disease R&D – the case of the Dutch neuromuscular disease association VSN. *Neuromuscul. Disord.* 20, 148–151
5 Ayme, S. *et al.* (2008) Empowerment of patients: lessons from the rare disease community. *Lancet* 371, 2048–2051
6 Rabeharisoa, V. (2003) The struggle against neuromuscular disease in France and the emergence of the 'partnership model' of patient organisation. *Soc. Sci. Med.* 57, 2127–2136
7 Ferguson, T. (2002) e-Patients as medical researchers. *The Ferguson Report* 9 (September)
8 Ferguson, T. and Frydman, G. (2004) The first generation of e-patients. *BMJ* 328, 1148–1149
9 Hoch, D. and Ferguson, T. (2005) What I've learned from E-patients. *PLoS Med.* 2, E206
10 Rabeharisoa, V. and Callon, M. (2002) The involvement of patients' associations in research. *Int. Soc. Sci. J.* 171, 57–65
11 Caron-Flinterman, J. *et al.* (2005) The experiential knowledge of patients: a new resource for biomedical research? *Soc. Sci. Med.* 60, 2575–2584
12 Callon, M. and Rabeharisoa, V. (2003) Research 'in the wild' and the shaping of new social identities. *Technol. Soc.* 25, 189–204
13 Oliver, S. *et al.* (2004) Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach. *Health Technol. Assess.* 8, 1–148
14 Terry, S.F. *et al.* (2007) Advocacy groups as research organizations: the PXE International example. *Nat. Rev. Genet.* 8, 157–164
15 Arnquist, S. (2009) *The New York Times*. August, D1
16 Landro, L. (2007) *Wall Street J.* 13 June, D1
17 Epstein, S. (2005) Democracy, expertise, and AIDS treatment activism. In *Science, Technology, and Democracy* (Kleinman, D.L., ed.), State University of New York Press
18 Dresser, R. (1999) Public advocacy and allocation of federal funds for biomedical research. *Milbank Q.* 77, 257–274
19 *Pharmaceutical R&D: Costs, Risks and Rewards*. U.S. Congress Office of Technology Assessment http://www.fas.org/ota/reports/9336.pdf
20 Heemstra, H.E. *et al.* (2009) Translation of rare disease research into orphan drug development: disease matters. *Drug Discov. Today* 14, 1166–1173
21 Serrano-Aguilar, P. *et al.* (2009) Patient involvement in health research: a contribution to a systematic review on the effectiveness of treatments for degenerative ataxias. *Soc. Sci. Med.* 69, 920–925
22 Trouiller, P. *et al.* (2002) Drug development for neglected diseases: a deficient market and a public-health policy failure. *Lancet* 359, 2188–2194
23 Smits, R.E.H.M. and Boon, W.P.C. (2008) The role of users in innovation in the pharmaceutical industry. *Drug Discov. Today* 13, 353–359
24 Entwistle, V.A. *et al.* (1998) Lay perspective: advantages for health research. *BMJ* 316, 463–466
25 Solovich, S. (2001) The citizen scientists.
26 Frost, J.H. and Massagli, M.P. (2008) Social uses of personal health information within PatientsLikeMe, an online patient community: what can happen when patients have access to one another's data. *J. Med. Internet Res.* 10, E15
27 Capek, S. (2006) *Building Partnerships that Work: Grassroots, Science, and Social Change*. The Endometriosis Association
28 Anand, G. (2010) *The Cure: How a Father Raised $100 Million – and Bucked the Medical Establishment – in a Quest to Save His Children* (1st edn), William Morrow
29 Ferguson, T. (2000) Online patient-helpers and physicians working together: a new partnership for high quality health care. *BMJ* 321, 1129–1132
30 Panofsky, A. (2011) Generating sociability to drive science: patient advocacy organizations and genetics research. *Soc. Stud. Sci.* 41, 31–57
31 Brownstein, C.A. *et al.* (2009) The power of social networking in medicine. *Nat. Biotechnol.* 27, 888–890
32 Call, J. *et al.* (2010) Evaluation of self-reported progression and correlation of imatinib dose to survival in patients with metastatic gatrointestinal stromal tumors: an open cohort study. *J. Gastrointest. Cancer* 41, 60–70
33 Epstein, S. (1995) The construction of lay expertise: AIDS activism and the forging of credibility in the reform of clinical trials. *Sci. Technol. Human Values* 20, 408–437
34 Epstein, S. (1996) *Impure Science: AIDS, Activism, and the Politics of Knowledge*. University of California Press
35 Herman, J. (1991) Anecdote and objectivity. *J. Clin. Epidemiol.* 44, 725–726

36 Pickering, W. (1992) The negligent treatment of medical anecdote. *BMJ* 304, 1516
37 Basch, E. (2010) The missing voice of patients in drug-safety reporting. *N. Engl. J. Med.* 362, 865–869
38 Grady, D. (2010) *The New York Times* 29 June, p. D1
39 Matter, A. and Keller, T.H. (2008) Impact of non-profit organization on drug discovery: opportunities, gaps, solutions. *Drug Discov. Today* 13, 347–352
40 Moses, H., III *et al.* (2005) Financial anatomy of biomedical research. *JAMA* 294, 1333–1342
41 Begley, S. and Carmichael, M. (2010) *Newsweek* 24 May, 38–42
42 Fonnebo, V.F. *et al.* (2007) Researching complementary and alternative treatments – the gatekeepers are not at home. *BMC Med. Res. Methodol.* 7, 7
43 Yearly, S. (1994) Understanding science from the perspective of the sociology of scientific knowledge: an overview. *Public Underst. Sci.* 3, 245–258
44 Carpenter, D.P. (2010) *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton University Press
45 Klein, D.F. (2008) The loss of serendipity in psychopharmacology. *JAMA* 299, 1063–1065
46 Pulley, J. *et al.* (2010) Identifying unpredicted drug benefit through query of patient experiential knowledge: a proof of concept web-based system. *Clin. Transl. Sci.* 3, 98–103
47 Polich, G. *et al.* (2010) The need to act a little more 'scientific': biomedical researchers investigating complementary and alternative medicine. *Sociol. Health Illn.* 32, 106–122
48 Resch, K.I. *et al.* (2000) A randomized controlled study of reviewer bias against an unconventional therapy. *J. R. Soc. Med.* 93, 164–167
49 Koehn, F.E. and Carter, G.T. (2005) The evolving role of natural products in drug discovery. *Nat. Rev. Drug Discov.* 4, 206–220
50 Li, J.W. and Vederas, J.C. (2009) Drug discovery and natural products: end of an era of an endless fronteir? *Science* 325, 161–165
51 Rishton, G.M. (2008) Natural products as a robust source of new drugs and drug leads: past successes and present day issues. *Am. J. Cardiol.* 101, 43D–49D
52 Newfield, *et al.* (1996) Estrogen metabolism and human papillomavirus-induced tumors of the larynx: chemo-prophylaxis with indole-3-carbinol. *Anticancer Res.* 13, 337–342
53 Coll, D.A. *et al.* (1997) Treatment of recurrent respiratory papillomatosis with indole-3-carbinol. *Am. J. Otolaryngol.* 18, 283–285
54 Rosen, C.A. and Bryson, P.C. (2004) Indole-3-carbinol for recurrent respiratory papillomatosis: long-term results. *J. Voice* 18, 248–253
55 Rosen, C.A. *et al.* (1998) Preliminary results of the use of indole-3-carbinol for recurrent respiratory papillomatosis. *Otolaryngol. Head Neck Surg.* 118, 810–815
56 Higdon, J.V. *et al.* (2007) Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. *Pharmacol. Res.* 55, 224–236
57 Elackattu, A.P. *et al.* (2009) A controlled safety study of diindolylmethan in the immature rat model. *Larynogoscope* 119, 1803–1808
58 Rogan, E.G. (2006) The natural chemopreventive compound indole-3-carbinol: state of the science. *In Vivo* 20, 221–228