SCIENCE AND SOCIETY

Advocacy groups as research organizations: the PXE International example

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Abstract | Advocacy organizations for genetic diseases are increasingly becoming involved in biomedical research, particularly translational research, in order to meet the needs of the individuals that they serve. PXE International, an advocacy organization for the disease pseudoxanthoma elasticum, provides an example of how research can be accelerated by these groups. It has adopted methods that were pioneered by other advocacy organizations, and has integrated these along with new approaches into franchizable elements. The model has been followed for other conditions and has led to the establishment of a common infrastructure to enable advocacy groups to initiate, conduct and accelerate research.

The greatest challenge for research into genetic disease in the genomic era is to understand the molecular abnormalities that underlie disease processes and translate these insights into clinical interventions[1]. In some respects, moving from bench to bedside to practice might be easier for Mendelian disorders than for common complex conditions. For example, it is relatively easy to clone the genes for single gene disorders and understand the related disease pathways, and it might also be easier to find ways to manipulate those pathways in the case of Mendelian disorders. Another motivation for studying Mendelian disorders is the fact that this research often benefits the study of common conditions[2], because the pathways that are affected might be related. However, there are many roadblocks to translational research for rare diseases, in particular a lack of funding and the small sizes of patient cohorts.

Disease-specific advocacy organizations (BOX 1; formerly known as 'support groups'), support and educate affected individuals and their families, and engage in research at various levels (TABLE 1). These organizations can overcome some of the problems of carrying out translational research for rare disorders. They can also accelerate this research by taking a novel approach that focuses specifically on moving from understanding the genetic basis of the disease to developing prognostic, diagnostic and therapeutic strategies that are of direct benefit to patients. As long ago as 1983, Nancy Wexler — who led the research efforts of the Hereditary Disease Foundation — collected samples from people who, like her mother, are affected by Huntington Disease. Wexler worked with scientists to find the gene that is disrupted in this condition. Later, in 1996, the National Breast Cancer Coalition recruited women to take part in clinical trials for Genentech's validation of Herceptin.

Here we describe the work of one advocacy organization, PXE International, which provides a replicable model for the role of such groups in translational research. This organization initiates, funds and conducts research on the autosomal recessive disease pseudoxanthoma elasticum (PXE). In doing so, its founders have provided resources for research, created research consortia and patient registries, banked biological samples, conducted bench science for gene and protein discovery, conducted natural-history studies and initiated several clinical studies. These activities have resulted in tangible advances, from gene discovery to the development of a diagnostic test, and have provided progress towards clinical therapeutic trials. Other organizations have followed this model and, together with PXE International, have created common infrastructure, including templates of documents, agreements, protocols and procedures to allow affordable and efficient replication of these successes.

In this article we discuss the role of disease-specific advocacy organizations as meaningful contributors to the research enterprise, using PXE International as

Box 1 | **The history of advocacy organizations**

The disease-specific advocacy movement began in the United States. Various forces — the early American ethos of self-reliance, familiarity, informality and pioneer mentality — laid the groundwork for the development of disease support organizations, perhaps beginning with Alcoholics Anonymous in the mid-1930s. In the context of genetic diseases, support groups such as the Cystic Fibrosis Foundation, Tay Sachs and Allied Diseases Foundation and a few others began to emerge about 50 years ago, as mechanisms to support patients and families with diseases[44]. Although these early foundations were initially intended to provide emotional and social support, in the 1980s and 1990s foundations began to offer more than psychosocial benefit[45]. In one of the most striking examples, the Hereditary Disease Foundation spearheaded the Venezuela Collaborative Huntington's Disease Project in 1968, which in 1983 led to the identification of a genetic marker for Huntington disease, and in 1993 established a research consortium that has recently made remarkable strides in a collaborative effort — discovering the gene and establishing a longitudinal study and clinical trials[46–48]. This early work of the charismatic leader Nancy Wexler[49] and the Hereditary Disease Foundation was seminal, but not truly replicated until the mid 1990s.

When some of the foundations that are described in this article appeared in the mid-1990s, it was still uncommon for foundations to initiate and conduct research. In fact, some foundations were told quite clearly by researchers and other advocates that reasearch was not the role of an advocacy organization and that their sole purpose should be to provide support for families[50]. In the early years, each of these organizations found their own way, but later discovered that there were common methods that could be leveraged, both in information and infrastructure. One remarkable pioneer in this area, Brad Margus, the father of two boys with ataxia telangiectasia (AT), founded AT Children's Project. Margus not only set up this research foundation and mentored many advocacy organizations, but went on to co-found a biotechnology company[51], even though his background was in shrimp farming.

Another outstanding example of advocates conducting research is that of the Chromosome 18 Registry and Research Society. Jannine Cody, when faced with the birth of a daughter with a chromosome abnormality, did not accept a doctor's declaration that her daughter would never develop past a 'frog-like state'. She established a foundation, went to university and obtained a Ph.D., and now runs the largest research laboratory in the country for diseases associated with chromosome 18. Her daughter is a sophomore in college — able to succeed because of Jannine's discovery that human growth hormone makes a difference in these children[52]. Today many foundations engage in research, and systems have been established to create mentoring infrastructure and to capitalize on the individual by-products of the work of these organizations[53]. This phenomenon has been studied, and the term 'genetic citizenship' has been coined to describe individuals who are bound by a common mutation coming together and taking an active role in changing the course of research for a given disease[54]. This activity was certainly born of necessity, particularly for the orphan diseases, but even for common complex conditions, as affected individuals have demanded more immediate solutions.

an example. We describe the challenges of rare-disease research and how advocacy organizations can respond to these challenges. We conclude with a discussion of the potential for translational research in general to benefit from the involvement of advocacy organizations.

The need for novel approaches

Rare diseases have distinct challenges in the research realm. Some of these problems are obvious, such as limited sample sizes[3]. Other problems are not as obvious. For example, research into genetic disease is generally incentivized by competition for funding from sources (such as the National Institutes of Health (NIH) in the United States and the Medical Reasearch Council (MRC) in the United Kingdom) that require preliminary data, a focus on results that are not necessarily tied to health outcomes, and the publication of papers that describe positive outcomes rather than negative data. These requirements are unlikely to be fulfilled in the case of many rare diseases that have not attracted previous research interest. Furthermore, rare-disease research does not enjoy the advantage of strong funding and interest from the biotechnology and pharmaceutical industries that studies of common diseases often benefit from. Although it is valid to focus research resources on basic discovery, as this is the fuel of the research enterprise, it is also important to consider the products of research in terms of health outcomes. However, most research is not focused on immediate translational benefits[4], and there are not well trodden pathways for the expeditious integration of innovation into health-care delivery[5]. For instance, although the gene that is associated with cystic fibrosis was cloned in 1989 (REF. 6), there is still no effective treatment for the condition. The need to move towards translational benefits is one of the main challenges for rare genetic conditions[7].

The advocacy approach

Although basic scientific research, which is fueled primarily by public funding, is focused on discovery and knowledge, advocacy foundations look for ways to accelerate the pathway from basic science to treatments and technologies that will benefit the lives of affected individuals. These groups are able to take more risks in the search for treatments for rare diseases. Furthermore, they are usually smaller and less encumbered by bureaucracy than traditional research organizations, and are therefore able to respond with agility to the incremental steps in translational research. As we discuss below using the example of PXE International, advocacy organizations can combine their ability to coordinate the communities of individuals they serve with the engagement of research scientists to drive forward research that is aimed at translational goals (FIG. 1).

PXE International. PXE is a rare genetic disorder that causes vision, skin and arterial defects. PXE International is a small research foundation that is funded by the donations of many individuals and run by advocates, with the purpose of supporting people with PXE and educating clinicians about the condition. This organization has also achieved success in accelerating translational research into PXE, and can be used as a model for other such organizations[8,9].

Shortly after its inception, the founders of PXE International met with other members of the advocacy community who challenged the status quo regarding translational research. Among others, these people included Gail Zimmerman, President and CEO of the National Psoriasis Foundation, Vicki Kalabokes, President and CEO of the National Alopecia Areata Foundation, and Brad Margus of the AT Children's Project (for ataxia telangiectasia). Most striking in those early conversations was the definition of success for these leaders and their foundations. This was to achieve positive health outcomes for their members — to "work until we turn the lights off and go home," as Margus said[10], — rather than focusing on the wealth and longevity of the organization. Most organizations that the PXE International founders had met with until this point were focused primarily on building a strong organization as an end point, rather than as a means to an end.

Table 1 | **Examples of advocacy organization achievements**

Organization	Condition(s)	Achievements	Year research began
Hereditary Disease Foundation	Huntington disease	Established blood and tissue bank; lead research consortium; gene discovery; initiated clinical trials	1983
Tuberous Sclerosis Alliance	Tuberous sclerosis complex	Coordinate blood and tissue bank; coordinated gene discovery; facilitated commercialization of molecular diagnostic test; created *TSC1/2*-variation database and natural-history database; coordinated development of TSC Clinic network; supported development of animal models; initiated and supported clinical trials	1987
Cornelia de Lange Syndrome (CdLS) Foundation	Cornelia de Lange syndrome	Established DNA bank; collaborated with NIH on a sleep study; discovered first and second CdLS genes; developed genetic test as part of the CETT programme	1990
Huntington's Disease Society of America	Huntington disease	Coordinated research consortium	1993
AT Children's Project	Ataxia telangiectasia	Established patient registry, and cell and tissue banks; identified mutated gene; created animal models; initiated target discovery and compound screening; established CLIA certified genetic test; developed clinical end points and standardized scale; orchestrated clinical trials.	1994
National Psoriasis Foundation	Psoriasis	Founded blood and tissue bank; established registry; lead research consortium	1994
Chromosome 18 Registry and Research Society	Chromosome 18 abnormalities	Established registry, biobanks and Chromosome 18 Clinical Research Center; coordinated clinical trial	1995
PXE International	Pseudoxanthoma elasticum	Founded blood and tissue bank; led research consortium; discovered gene; established genetic test; created animal models, initiated clinical trial	1995
National Urea Cycle Disorders Foundation	Urea cycle disorders	Initiated drug development; recruited for clinical trials; partnered in research consortium and research registry	1996
PC Project	Pacyonychia congenita	Established registry, research consortium, research infrastructure and shared resources; involved in drug development, orphan drug status and sponsored IND application; recruited patients; collected patient samples	2004
Alpha-1 Foundation	Alpha-1 antitrypsin deficiency	Established research consortium and research infrastructure; recruited for clinical trials	1999
Pediatric/Adolescent Gastroesophageal Reflux Association (PAGER)	Gastroesophageal reflux disease (GERD)	Initiated gene-mapping project and DNA donor recruitment	2000
Alström Syndrome International	Alström Syndrome	Established patient registry; coordinated research clinics and data collection; recruited DNA donors	2001
CARES Foundation	Congenital adrenal hyperplasia	Recruited for clinical trials; initiated natural-history study in conjunction with NIH; initiated study on psychosocial adjustment; collaborator in rare-disease consortium	2001
National Tay-Sachs and Allied Diseases Association (NTSAD)	Tay-Sachs, Canavan and related lysosomal storage and leukodystrophy disorders	Founded NTSAD Research; co-founded the Lysosomal Storage Disease Research Consortium with other patient organizations	2001
Angioma Alliance	Angiomas	Established biobank	2003
CFC International	Cardiofacio-cutaneous syndrome	Established biobanks; discovered gene; established test	2003
Cutis Laxa Internationale	Cutis laxa	Established registry; DNA and biopsy donor recruitment	2004
Progeria Research Foundation	Hutchinson–Gilford progeria	Founded blood and tissue bank, and clinical database; initiated and participated in gene discovery; established genetic testing programme; initiated natural-history study with NIH; initiated clinical trial.	2004
SMA Foundation	Spinal muscular atrophy	Established *in vivo* screening facility for proof-of-concept testing; established drug development 'toolkit' with favourable licensing terms for commercial investigators; establishing a biomarker screen in animal models and patients; established regional clinical trial network	2004
Barth Syndrome Foundation	Barth syndrome	Established clinical database and biorepository; created gene mutation database	2005

In addition to funding research and organizing research workshops, these organization led these research achievements, either with staff scientists of the advocacy organization or in collaborations with scientists from academic institutions or industry. IND, Investigational New Drug application; CETT, The Collaboration, Education and Test Translation (CETT) programme; CLIA, Clinical Laboratory Improvement Amendments; NIH, National Institutes of Health.

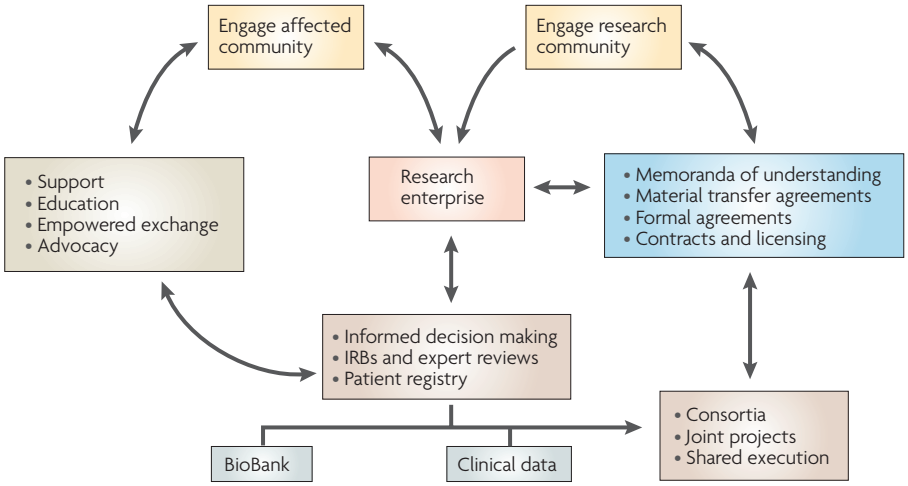

Figure 1 | **The PXE International strategy.** PXE International uses a variety of approaches to bring the PXE community together with research scientists to accelerate translational research. IRB, institutional review board.

The shift in viewpoint in these discussions catalysed a new model and established the essence of the research advocacy foundation. This could be characterized as a "disruptive innovation,"[11] similar to changes in the marketplace that redefine solutions, pushing to accelerate the research enterprise beyond its usual pace and involving new players, the advocates. Such a solution could be construed as conflicting with the view of researchers, who might want to control all the elements of the research enterprise. Unsurprisingly, there have been concerns that such actions would add another layer to the research process and slow it down[12]. Instead, applying the skills of both advocates and scientists has added new levels of engagement for scientists and professionalism for advocates. PXE International has adopted aspects of academic models (rigorous science), commercial enterprises (commodification and accountability) and advocacy organizations (trust and agility), and has used them to create a hybrid model for advancing research.

Community engagement. Early on, the founders of PXE International knew that there was a need to incentivize research into PXE by leveraging the available resources. It seemed that this would be best achieved by establishing a community, developing a commodity through this community, making the foundation an essential part of the academic enterprise, and aiming towards the industrialization of a treatment or technology, with the goal of improving the lives of affected individuals. They determined that biological samples would serve as the commodity, and established the PXE International Blood and Tissue Bank as an important first step.

A novel and essential component at this stage was the establishment of a community of trust — a gathering of individuals bound by the effects of mutations in the *ABCC6* gene that underlies PXE, who could share their experiences and appreciate the feeling of no longer 'being alone' in the way that individuals with rare disorders have often experienced. The language that is used by the advocacy community epitomizes this culture. Research participants are not 'subjects', affected individuals are not 'patients', and the process of becoming engaged in research is not reduced to 'informed consent', but instead involves an informed decision-making process. Drawn together in a community that was designed to represent their needs, individuals who were affected by PXE generously and eagerly donated biological samples and the annotation that was needed (in the form of medical records, questionnaires and longitudinal data), in collaboration with the research community.

Motivating accelerated participatory research. At the same time as building a community of affected individuals, in 1996 PXE International brought together a range of researchers — including geneticists, pathologists, biochemists, dermatologists and ophthalmologists — at a meeting that the organization planned together with Jefferson Medical College, which was supported by the NIH Office of Rare Diseases[13]. This meeting was the catalyst for the formation of the PXE International Research Consortium, now numbering 33 scientists in 20 laboratories. Memoranda of understanding (MOU) (BOX 2) allowed the scientists to work together without being overly concerned about sacrificing advantages for funding and publications.

The founders of PXE International, despite having no scientific training, engaged in bench science as members of the research team that studied PXE, resulting in discovery of the causative gene. Scientists, particularly postdoctoral fellows who worked late at night in the laboratory alongside the founders of PXE International, appreciated 'putting a face on the disease'. Once the PXE locus was identified, an initial decision was made to sequence unknown genes in the locus, purely because they were novel. However, the intense focus of the founders specifically on the quest for the gene associated with PXE reversed this decision, and ultimately led to the identification of the correct gene.

The coordination of research by PXE International allowed the continued aggregation of both negative and positive findings, and dissemination of those results. Furthermore, PXE International helped to bring advocacy organizations and patients to basic science meetings, such as one at the Jackson Laboratory that concentrated on hair and skin research. This gave scientists the opportunity to meet affected individuals and to understand more deeply the reasons for their work. Researchers were also invited to meetings of affected individuals and their families, and subsequently became more motivated to work on PXE.

Research achievements of PXE International. PXE International has initiated a wide variety of research projects. A major breakthrough came in 2000, when the founders and collaborating researchers used samples from the PXE International Blood and Tissue Bank to identify *ABCC6* and the mutations that cause PXE[14,15]. PXE International also engaged in several other projects, including a collaboration with a scientist at the Jackson Laboratory in which the organization funded the search for naturally occurring angioid streaks (breaks in the membrane beneath the retina that are commonly seen in PXE) and the development of a genetically engineered animal model of the disease. Although neither project provided a specific model for PXE, the data that were gleaned from these projects resulted in the discovery of naturally occurring subretinal neovascularization in the mouse, an important finding that has implications for all retinal diseases[16].

Further to accelerating the basic science of PXE, or perhaps because of it, PXE International has been an important catalyst in the first steps toward translational research. Because the founders of PXE International materially participated in the research that led to the identification of the relevant gene, they were able to pursue inventorship. The founders are named as co-inventors on the patent for *ABCC6*, along with four scientists[17], and PXE International is able to act as steward of the gene — representing the interests of the PXE community in the process of moving from gene discovery to commercialization in the form of diagnostics or therapeutics. The founders assigned their rights to the foundation, as did the scientists who were involved in identifying the gene.

Another benefit of the involvement of advocacy organizations in the research enterprise is their ability to forge collaborations with industry, owing in part to their ability to respond quickly, which mirrors that of corporations, and to the fact that companies are eager to contribute to the 'good cause' of a non-profit organization. PXE International coordinated the development of a genotype-based diagnostic test and licensed the patent to a company called Transgenomic, which in turn donated hundreds of thousands of dollars in time and materials towards developing the test. In partnership with Transgenomic, PXE International coordinated three laboratories (based at Jefferson Medical College in Philadelphia, the University of Gent in Belgium and the University of Witwatersrand in South Africa) to genotype hundreds of samples as part of the initial effort to develop a genotyping assay. The participating research groups signed memoranda of understanding, agreeing to publish all data from this work together, and to recognize the contributions of all of the researchers in each of the laboratories. PXE International will license the test to a laboratory that is working with them to create a system by which patients who undergo the test will have the option to bank their clinical information and genotype in the PXE International Blood and Tissue Bank. PXE International will offer pre- and post-genetic counselling to these patients, something that is not commonly offered nor subsidized by rare-disease testing laboratories.

Finally, PXE International has initiated and conducted a number of clinical studies with lay and scientific members of the foundation as investigators[18–26]. Most recently, extensive work with the 19 research groups that currently collaborate with PXE International and the 3,000 individuals who have the condition has culminated in plans for a clinical trial of treatments for the eye defects that are seen in PXE. Various treatments that were initially developed as therapies for macular degeneration have been anecdotally reported to delay vision loss by hundreds of individuals in a natural-history study. The foundation has raised enough money to test these treatments in a double-blind clinical trial, which is set to begin in early 2007.

Future challenges for the PXE effort. At present, PXE International is working to fund a large multicentre project to integrate the efforts of all the scientists in the consortium, managing a coordinated and dynamic process to drive the science towards an intervention for the disease. From its central position, the organization is able to give recommendations for partnerships between laboratories, methods of sharing data that allow researchers to protect their interests, the collection of negative data and resource sharing to accelerate a focused translational agenda. As the research moves into this translational phase, the foundation can look for ways in which the various laboratories that are involved can leverage each other's resources. In addition, it can assure researchers of sufficient patient accrual for clinical trials of treatments during the planning stages, as it has constant contact with the PXE community through the PXE International listservs, web site and newsletter. Furthermore, it is able to raise money from the PXE community to ensure that the previously mentioned trial occurs in early 2007, rather than relying on NIH grant funding, which could take 9 months or more.

The broader influence of the PXE model

Mentoring other advocacy groups. PXE international is transparent about its accomplishments, offering posters, talks and workshops at conferences and encouraging other foundations to follow the same model. In addition, throughout the late 1990s and early 2000s, PXE International mentored numerous other advocacy organizations. The Autosomal Recessive Polycystic Kidney Disease and Congenital Hepatic Fibrosis

Box 2 | **Memoranda of understanding**

A legal instrument, which is known interchangeably as a memorandum of understanding (MOU), a letter of agreement or a research collaboration agreement, is often used to formalize the terms under which researchers and advocacy organizations conduct or fund particular research activities of mutual interest.

Typical MOU terms include:

Non-disclosure terms for the sharing or non-sharing of proprietary information
These provisions often also address what constitutes acceptable uses of sole and joint data and materials, as well as stipulating specific timelines for public release of new jointly generated data or materials (for example, through the use of embargo periods, or through specific terms for the disposition of data into databases or biomaterials into repositories).

Transfer of materials
This describes the use of a particular material transfer agreement (MTA) for the transfer of tangible biological or other materials such as reagents, cell lines, plasmids, vectors, antibodies and chemical compounds, as well as some types of software, between parties for research purposes. Commonly, non-commercial use of materials by third parties is also permitted as long as the model MTA is used.

Authorship provisions
Authorship versus acknowledgement determinations should be clear (for example, suppliers of biomaterials should not automatically be made authors). Procedures for deciding who will be an author and under what circumstances, along with a description of the typical anticipated order of authors, must be jointly decided well before the research commences and any draft manuscript is written.

Intellectual property and licensing-related issues
The criteria by which individuals and their employers will be considered co-inventors and co-owners, respectively, if patent protection is sought on inventions, and which entity will pay patenting costs and control or lead any future licensing negotiations should be determined upfront.

Research plan
The MOU should contain a detailed description of the research project with delineation of the roles and responsibilities of each party.

Box 3 | **Functions of the Genetic Alliance BioBank**

- Recruits donors to the bank, in the context of the community of the advocacy organization, using state-of-the art methods that emphasize trust, privacy protections, data security, empowerment of participants and the members advocacy groups and ongoing education[55,56].
- Provides a robust and dynamic method for the informed donor decision-making process, leading to truly informed consent that is tailored to specific uses of the samples and the related information. The system provides for dynamic re-contacting and re-consenting as the need arises.
- Provides a state-of-the-art storage facility and system for the collection and archiving of DNA, tissue and cell lines.
- Provides an informatics core that encodes identifiers in a centralized database. The database, similarly to the sample repository, is owned and maintained by each advocacy organization, and enables re-contact by the researchers to the (anonymous) donors.
- Raises the resources necessary to develop both the infrastructure and the enrolment of the biobank.
- Facilitates collaboration of academic, government and industrial partnerships[57].

Alliance, Angioma Alliance, Aneurysm Outreach, Progeria Research Foundation and many other foundations emulated the methods of PXE International, and were successful in creating blood and tissue banks, forming research consortia, gene discovery and developing genetic tests. In one of the more prominent examples, the Progeria Research Foundation founders emulated elements of the PXE International model to establish their own sample repository and registry, and participated in the gene discovery process for Hutchinson–Gilford progeria[27]. They are also among the assignees who are filing a patent application for the gene that is associated with this syndrome[28], and have gone on to conduct a clinical study[29] and plan a therapeutic trial.

Creation of the Genetic Alliance Biobank. Although mentoring other organizations was fruitful, it became clear that there was high demand for such input and a need for the information and infrastructure that is required for advocacy organizations to participate in research to be made more widely accessible. The founders of PXE International began to work in earnest with Genetic Alliance, a coalition of over 600 disease advocacy organizations, and used its infrastructure as a repository for their model and methods. They published the Interactive Guide to Building Advocacy Organizations[30] in 2002, under the auspices of Genetic Alliance. This guide addresses many of the questions that advocacy organizations have about running effective research-support organizations. It soon became apparent that, in addition to the basic suggestions, templates and documents in the Interactive Guide, there was a need for a common infrastructure that advocacy organizations could use, beginning with a biorepository.

In recent decades, biorepositories have tended to illustrate science at its worst: they have been characterized by insufficient, uninformed patient consent, an inability to gain re-consent, and small, redundant collections that have no statistical power[31]. Furthermore, inadequate informatics systems that do not document the flow of information have prevented future assurance of the 'chain of custody' (the paper trail that is needed to assure regulators that protocols have been followed). Problems have also been caused by variable nomenclature, which makes it difficult to compare information from patient to patient, and legal structures that provide insufficient protection for the rights of both patients and researchers[32,33]. Too often, the result has been orphaned collections, disillusioned and disenfranchised patients and frustrated scientists who lack the tools that are necessary for their work[34].

The Genetic Alliance BioBank, which was founded in 2003 (REF. 35), was built on these lessons of the past, while keeping an eye on the technology that will change the future (BOX 3). It is a centralized repository of biological samples and data (relating to consent along with clinical and environmental information) to enable translational genomic research on rare genetic diseases. This repository presents a new model in which the needs and rights of all parties are acknowledged and protected. The BioBank infrastructure includes training for the advocacy organizations in all facets of operations (from recruiting donors to managing requests for samples) and a complete compendium of documentation (institutional review board (IRB) application forms, consent forms, researcher application forms and templated memoranda of understanding). It also provides access to its own IRB for approval to collect and archive DNA and tissue samples, and all of the components that are necessary to do this. The BioBank also includes a state-of-the-art informatics core with a web-based user interface, which is suitable for clinical studies and product development that comply with the regulations of the US Food and Drug Administration (FDA).

The centralized management and infrastructure of the biobank provides a relatively cost-effective mechanism by which individual advocacy organizations can, for the first time, pursue sophisticated, novel research collaborations. Member organizations decide what research will be conducted with the samples using a proposal and review process that is modelled on the NIH-grant decision-making process. All organizations have IRB approval as a result of following protocols that were established by the IRB, and all member organizations retain the identifiers for their donors in the bank, ensuring confidentiality by distributing only coded samples. Re-consent and follow-up data collection are possible as a result of this coding. The biobank and its members comply with all of the current human participant regulations, and with the US Health Insurance Portability and Accountability Act (HIPAA), and in fact participate in national advisory committees that are setting guidelines for research participants. In addition to PXE International, members include the Angioma Alliance, CFC International, the Inflammatory Breast Cancer Research Foundation, the Joubert Syndrome Foundation, the National Psoriasis Foundation and the NBIA Disorders Association.

The success of CFC international

The work of CFC International, an advocacy group for the rare disorder cardiofaciocutaneous syndrome (CFC), exemplifies the effectiveness of the Genetic Alliance BioBank. In 1999, there were 21 families enrolled in the organization; by 2003, the number of members swelled to 100 because of interest in gene-discovery research, allowing the collection of extensive clinical data. CFC International joined the Genetic Alliance BioBank and received extensive training in how to collect clinical data so that the samples were well annotated, along with template documents for everything from informed consent to material transfer agreements. After working with their medical advisory board to determine the various clinical characteristics on which they wanted to collect information and creating a clinical data questionnaire to facilitate this, they

engaged phlebotomists to draw blood at their international conference. By autumn of 2005, DNA samples from 45 children with CFC and their biological parents had been collected. This information, along with clinical data and photographs, was stored electronically in the Genetic Alliance Biobank, setting the stage to advance research on this disorder.

The research effort began when Katherine Rauen, a researcher who had previously worked on a similar rare genetic syndrome, Costello syndrome, teamed up with CFC International. The Genetic Alliance BioBank was a valuable, high-quality source of research material, especially in light of tight research budgets and resources. During Rauen's work on Costello syndrome, the procurement of approximately 40 patient samples took over 5 years, including obtaining consent, carrying out phlebotomy, sample isolation, and data collection and organization. Utilizing the Genetic Alliance BioBank was the equivalent of having the biological material handed on the proverbial 'silver platter'. What took Rauen 5 years to accrue with the Costello syndrome study was accomplished in just days with CFC International, including the submission of a research proposal, peer review and receipt of the biological samples and clinical information from an extremely well characterized cohort. With candidates in mind from previous work, Rauen was able to start sequencing genes in the same week that she received the DNA samples, and subsequently identified the genes that are mutated in CFC. CFC International's President and Vice President, both non-scientists, were also authors on the gene-discovery paper[36]. CFC International has consulted extensively with PXE International throughout this process, and its use of elements of the PXE model has been instrumental in establishing clinical genetic testing.

The future: translational research

As biomedical research matures, especially at a time when publicly funded research faces reductions, research that has long-term benefits for understanding general disease mechanisms must be balanced with research that has more immediate applications — both are crucial. Public pressure and influence on research priorities and objectives has accelerated in recent years[37]. As we have indicated, the basic research model is shifting because of the involvement of advocacy organizations, which offer new objectives and deliverables as measures of success.

Further to their direct roles as research organizations, advocacy organizations influence both public policy and capital allocation for various diseases in other ways. In fact, it has been noted that advocates should look beyond their narrow constituencies to consider the health needs of the broader public[38]. These organizations continue to influence open access to the literature[39], efforts to avoid genetic discrimination in order to increase participation in genetic testing and clinical trials[35,40], and stem-cell studies[41], to name a few areas of consequence for research. Advocates are also challenging regulatory bodies, from institutional review boards to the FDA, asking if these entities are accelerating research development or bogging it down with onerous regulations that are designed to protect universities and companies.

In the future, advocacy organizations are also likely to encourage personalized medicine, challenging traditional research and therapeutic paradigms. Advocates will quickly understand the utility and value of emerging diagnostics that enable targeted therapies to be used with increased specificity, and will demand adoption of them. We have witnessed this in the breast cancer[42] and AIDS[43] communities. It is important for advocacy organizations to continue to forge methods to accelerate translational research and influence clinical practice, so that the potential of basic biomedical science can be realized. It is crucial that funding organizations and researchers recognize the potential of collaboration with advocacy organizations and create opportunities for partnership, the value of which is measured in terms of real progress toward therapies for individuals who are living with genetic conditions.

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Competing interests statement
The authors declare no competing financial interests.

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The following terms in this article are linked online to:
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ABCC6
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ataxia telangiectasia | cardiofaciocutaneous syndrome | Costello syndrome | cystic fibrosis | Huntington disease | Hutchinson–Gilford progeria | pseudoxanthoma elasticum

FURTHER INFORMATION

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