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Original Research

Emerging roles and opportunities for rare disease patient advocacy groups

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Amy M. Patterson, Megan O'Boyle, Grace E. VanNoy and Kira A. Dies

Abstract

Background: Patient advocacy groups (PAGs) serve a vital role for rare disease patients and families by providing educational resources, support, and a sense of community. Motivated by patient need, PAGs are increasingly at the forefront of policy, research, and drug development for their disease of interest.

Objectives: The study explored the current landscape of PAGs in order to guide new and existing PAGs on available resources and challenges to research engagement. We aim to inform industry, advocates, and healthcare personnel about PAG achievements and ways they are increasingly involved in research.

Design: We chose PAGs from the Rare Diseases Clinical Research Network (RDCRN) Coalition for Patient Advocacy Groups (CPAG) listserv and the National Organization for Rare Disorders (NORD) 'Find a patient organization'.

Methods: We surveyed eligible PAG leaders about the demographics, goals, and research activities of their organization. For analysis, PAGs were bucketed by size, age, prevalence of disease, and budget. Data were de-identified for cross-tabulation and multinomial logistic regression analysis with R.

Results: Research engagement was an extremely important goal for most PAGs (81%), though ultra-rare disease and high-budget PAGs were most likely to cite it as the top priority. In total, 79% reported research engagement in some capacity, including registries, translational research, and clinical trials. 'Ultra-rare' PAGs were less likely than 'rare' PAGs to have an ongoing clinical trial.

Conclusion: While PAGs of varying sizes, budgets, and maturity levels reported an interest in research, limited funding and lack of disease awareness continue to create barriers to achieving their goals. While support tools exist to make research more accessible, often their utility depends on the funding, sustainability, maturity of the PAG itself, and the level of investment of collaborators. Despite the availability of current support systems, there are challenges related to both the start-up and sustainability of patient-centric research efforts.

Keywords: clinical trial, drug development, patient advocacy group, registry, research, support

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Correspondence to:
Amy M. Patterson
Department of Genetic Medicine, Johns Hopkins Hospital, Baltimore, MD 21287, USA.
apatte42@jh.edu

Megan O'Boyle
Coalition of Patient Advocacy Groups, Rare Diseases Clinical Research Network, Arlington, VA, USA

Grace E. VanNoy
Center for Mendelian Genomics and Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA

Kira A. Dies
Rosamund Stone Zander Translational Neuroscience Center, Boston Children's Hospital, Boston, MA, USA

Introduction

Based on current reports, there may be well over 10,000 rare diseases, and an estimated 80% have a genetic basis.[1,2] There is no current global, standard definition for rare diseases; the United States considers a disease rare if it affects fewer than 200,000 individuals, while the European Union (EU) defines rare as affecting fewer than 1 in 2000 persons.[3] Collectively, rare diseases are not uncommon as they affect over 300 million persons globally.[4] While each rare disease is unique in phenotype and physiology, patients and families across disease groups often report experiencing commonalities related to the low prevalence of their disease. These may include, but are not limited to, feelings of isolation and being overwhelmed with complex information regarding the disease.[5,6] Publicly available genetic

information often has low readability due to the complexity of information, and is continuously evolving.[7] Therefore, recently diagnosed families are often referred to rare disease patient organizations (RDPO), also known as patient advocacy groups (PAGs), for comprehensive, up-to-date information. These organizations typically serve as all-encompassing support communities for patients and families.

As genetic technology and public data-sharing practices evolve, new rare genetic variants and Mendelian conditions (MCs) are being discovered at increasingly rapid rates.[2] OMIM and Orphanet, two databases of curated clinical and genetic information, each reported more than 250 novel rare and ultra-rare genetic disease discoveries between 2012 and 2015.[8] This number is continuing to increase due to advances in NextGen Sequencing, and it is thought that the majority of MCs have yet to be discovered.[2] To meet the demand of more ultra-rare variants being discovered and more patients being diagnosed, patients and families are tasked with creating novel rare disease PAGs. The EU defines ultra-rare diseases as affecting fewer than 1 in 50,000 patients.[3] The literature on existing ultra-rare disease PAGs is sparse due to the relative youth of these organizations and the size of their patient populations.

In both the community of rare disease patients and patient organizations, the adage, 'alone we are rare, together we are strong', holds true. Rare disease PAGs are uniquely challenged not only to spread awareness and build a community, but also to engage in research, create a registry, and advocate for drug development and therapy access. There can be barriers to entry and steep learning curves for patients and families with novel genetic variants who are looking to create and sustain a new PAG. Once PAGs are ready to engage in research, it is important to understand and appreciate the mixed experiences of industry–PAG collaboration, challenges with data collection/sharing practices, and resource availability. Our study sought to provide an overview of rare disease PAG activities, challenges, and lessons learned by the leaders, to better support new and existing organizations through the process of research development and collaboration.

Methods

Participants

Participants were recruited for the study through multiple methods, including the distribution of information about the study through the National Institutes of Health (NIH) Rare Diseases Clinical Research Network (RDCRN) Coalition of Patient Advocacy Groups (CPAG) listserv and the Chan Zuckerberg Initiative's (CZI) Rare As One Project (RAO) listserv, manual email recruiting using the National Organization for Rare Disorders (NORD) 'Find a patient organization' directory, and snowball sampling. The CPAG listserv is made up of approximately 200 PAGs and the RAO listserv reaches 30 PAGs. Additional PAGs were contacted by email by the study PI using contact information found on the NORD directory. PAGs were contacted from the directory if they represented one or more rare diseases. In total, 690 organizations from the database were contacted about study recruitment once by email directly by the study PI. Following initial contact, PAGs had 2 months, starting in February 2021, to either request additional information from the study PI or to complete the survey. Participants were eligible if they reported that they were at least 18 years of age, a representative of a rare disease PAG, and could read and write in English. In all, 225 organizations were deemed eligible by the survey criteria and participated in the study. Responses were excluded if less than 10% of the survey was completed or if there were multiple responses from one organization. In total, 159 participants were deemed eligible to participate based on the above criteria and their responses were included in the data set.

Survey

Representatives of rare disease PAGs participated in a survey-based study using Qualtrics (www.qualtrics.com). The survey comprised of 28 questions, broken up into five categories, Eligibility, Patient and Organization Demographics, Goals and Priorities, Research Activities, and Challenges and Lessons Learned (see supplemental section for full survey). It was an original survey, developed by the study team and piloted by three members of the RDCRN CPAG, as well as the director of Engage Health, Inc. Questions on demographics and goals of the organizations were

taken and modified from the work by Pinto *et al.*[9] Participants responded through multiple choice, multiple selection, and open-text responses. Eligibility was determined through three multiple choice questions (see *Participants* above). Within Demographics, participants were asked 16 questions about their role in the PAG, the size, budget, age, operations, and structure of the PAG, as well as the prevalence of disease that the PAG serves. These demographic variables were adapted from the work by Pinto *et al.*[9] To define the prevalence and incidence of the disease that each PAG represents, the survey used three different measures including birth frequency, number of affected individuals worldwide, and open-text response. In data analysis, the birth frequency metric was used as a proxy measure of disease prevalence.

The Goals and Priorities section (three questions) also used adapted PAG goal statements from the work by Pinto *et al.*[9] Participants were asked to rate their PAG goals using a validated Likert-type scale from 'not at all important' to 'extremely important'.[10] They were then asked to choose one of the goals as top priority. PAGs were only given the option to choose from the goals that they rated as 'extremely important'. Within the Research Activities category (three questions with forced routing to sub-questions based on answers), participants used multiple choice and multiple selection responses to depict research engagement and research support activities. 'Research support activities' were defined for the purpose of this study as any activity that promotes research, such as patient education, consulting, funding, and dissemination of clinical research opportunities. Within the Challenges and Lessons Learned section (three questions), participants were allowed to use an open-text response to describe any successes and lessons learned since founding or joining their organization in a leadership capacity. In addition, PAGs were given the option of disclosing the name of their organization in an open-text response. Participants were informed that the data would be de-identified, aggregated, and not linked to their specific organization, even if they chose to disclose the organization name. This information was used to screen out duplicate responses from one organization. The qualitative data collected from the survey are not included in this publication.

For analysis, PAGs were bucketed into 'rare' and 'ultra-rare' based on birth frequency as a proxy measure of disease prevalence. The 'rare' PAGs were categorized as representing diseases that affect 1 in 2000–200,000 births, while 'ultra-rare' PAGs represented diseases that affect fewer than 1 in 200,000 births. Data were de-identified for cross-tabulation and multinomial logistic regression analysis with R. Multinomial modeling was used to identify significant predictors of the top priority for PAGs; McFadden's pseudo-R^2 coefficients were used to indicate likelihood of choice. The power analysis was conducted by MSSP Consulting at Boston University, with statistical significance considered as $p < 0.05$.

Results

Organization characteristics and patient demographics

Of the 225 respondents, 159 participants were deemed eligible to participate and included in the data set. Eligible survey respondents were asked to select one or more of a provided list of roles that define them within their organization, with the top reported roles being leader (84%, $N = 158$), founder (47%), and caregiver (43%). Of note, 13% reported that they are diagnosed with the disorder represented by the PAG (Appendix A). The most common organizational demographics reported include having no paid staff (47%), being in existence longer than 15 years (46%), representing conditions with a birth frequency of 1 in 2000–50,000 (31%), and serving between 1000 and 10,000 members (28%). The most common annual budget ranges were \$10,000–\$50,000 (18%) and \$100,000–\$200,000 (18%) per year. Primary funding sources included charitable donations (93%, $N = 158$), fundraising events (74%), and corporate/industry sponsors (52%). When organizations were bucketed into 'rare' and 'ultra-rare' by birth frequency, the organizations serving 'ultra-rare' disease patients tended to be younger and smaller (<10 years old; <300 members), while organizations serving 'rare' disease patients tended to be older and larger (>10 years old; >1000 members) (Appendix E). There were nearly twice the number of 'rare' disease PAGs, compared with 'ultra-rare'.

Priorities

We asked respondents to rate goals from most important to least important, then choose one goal as the top priority for their organization. The most popular goal among PAGs was 'to support or

promote research on the disease'; 81% (N = 153) of respondents rated it as 'extremely important' (Table 1). Furthermore, 42% of participants ranked this research-oriented goal as the top priority for their PAG. The goal 'to provide information or education to patients and/or families' was the next most chosen; 78% rated it as 'extremely important' and 36% ranked it as the top priority. 'Rare' disease PAGs were more likely choose the goal 'to provide education to patients and/or families' as the top priority, while 'ultra-rare' disease PAGs were more likely to choose 'to support research on the disease' as their top priority (Appendix B). In addition, organizations with the highest annual budgets (more than US$500,000) were most likely to choose research as the top priority compared with lower budget PAGs.

Research activities

In total, 79% (N = 155) of respondents reported that their PAG engages in research, which could include initiation of research, contribution to external research, and/or research support activities (Table 2). Of the organizations that were not reported to engage, the most cited reason was lack of funding (58%, N = 31) (Table 2). The majority of PAGs that engage in research contribute to research conducted outside of their organization (92%, N = 123), and 47% have initiated their own research (Table 2). 'Contributing to' research is defined for the purpose of this study as providing biospecimens/data to external research groups, encouraging participation in external trials, assisting research study design, and more.

Of the PAGs that initiated their own research (N = 58), 64% created their own patient registry, 43% conducted a natural history study, and 40% initiated a translational research study (Table 2). Nine PAGs have initiated their own clinical trial (16%). For the PAGs that were reported to contribute to external research (N = 113), the majority have contributed to a clinical trial (81%), a natural history study (73%), and/or a patient registry (54%). For patient populations with a clinical trial in progress, a commonly cited support activity involved providing support to participants in a clinical trial (53%). The support offered to these patients was not described. Of the PAGs that do not engage in research (N = 31), limited funding was noted as the primary barrier (58%).

Engagement in clinical trials and drug development

While respondents reported that their PAG contributed to (81%, N = 123) or initiated (16%, N = 58) a clinical trial, 30% (N = 152) of respondents reported having an approved treatment/therapy associated with their rare disease (Appendix C). In this study, an approved therapy is meant to encompass any drug that is approved by the Food and Drug Administration (FDA) or an equivalent international regulatory agency. Of the respondents that reported an approved therapy, 48% reported that their organizations were involved in the development of the therapy, while 46% were not. To help patients gain access to an approved treatment, 63% (N = 46) of the PAGs reported that they educate healthcare professionals on the disease and associated therapy (Appendix C). In all, 61% of PAGs were reported to teach patients self-advocacy skills to help them gain access to treatment.

For the PAGs serving diseases that do not have an approved therapy (N = 82), 51% reported that there were no clinical trials in progress at the time of this study (Appendix C). 'Ultra-rare' disease PAGs were less likely than 'rare' disease PAGs to have a clinical trial in progress (p = 0.04) (Appendix D). Through qualitative analysis, six themes emerged as barriers to drug development and approval. Limited or a lack of research on the organization's represented disease was reported by 61% (N = 41) of respondents as the primary reason for the lack of clinical trials. In addition, 20% mentioned symptom management as the primary treatment for the disease at this time, which may not be gene/disease-specific.

Challenges and lessons

While each PAG faces its own set of unique hurdles, most respondents reported that funding (83%, N = 152) and public awareness (72%, N = 152) were still the greatest challenges for their organizations (Figure 1). The next most reported challenges for PAGs were patient engagement (41%) and healthcare professional engagement (32%). Considering that many of these groups operate on an international scale, 26% responded that resource distribution and language translation pose a significant challenge to their organization, followed by international

Table 1. Goals and priorities of PAGs.

Common Goals of PAGs[a] (*N* = 153)	Not at all important (%)	Slightly important (%)	Moderately important (%)	Very important (%)	Extremely important (%)	Chosen as top priority (%)[b]
To raise community awareness and knowledge of the disease(s)	1 (0.65)	8 (5.23)	11 (7.19)	33 (21.57)	99 (64.71)	15/88 (17.05)
To provide information/education to patients and/or families	0 (0)	2 (1.31)	5 (3.27)	25 (16.34)	120 (78.43)	35/97 (36.08)
To provide information/education to healthcare professionals	1 (0.65)	5 (3.27)	21 (13.73)	40 (26.14)	85 (55.56)	2/74 (2.70)
To provide social support or networking opportunities for patients and families	4 (2.61)	8 (5.23)	14 (9.15)	39 (25.49)	87 (56.86)	14/74 (18.92)
To provide services (i.e. respite care), financial assistance, or other resources (i.e. equipment) to patients and families	54 (34.29)	43 (28.10)	24 (15.69)	12 (7.84)	19 (12.42)	2/16 (12.50)
To support or promote research on the disease	1 (0.65)	6 (3.92)	7 (4.58)	15 (9.80)	124 (81.05)	39/93 (41.94)
To advocate to government or other authorities for research funding, research resources, or research policies	12 (7.84)	11 (7.19)	36 (23.53)	46 (30.07)	47 (30.72)	2/40 (5.00)
To advocate to government or other authorities on other matters (e.g. access to services or existing therapies)	15 (9.80)	23 (15.03)	35 (22.88)	40 (26.14)	39 (25.49)	1/32 (3.13)
Have the priorities of the organization changed since the founding of the organization? *N* = 153 (%)						
Yes	47 (30.32)					
No	108 (69.68)					

PAG, patient advocacy group.
[a]The list of goals was adapted from the work by Pinto *et al.*[9]
[b]The denominator of the top priority ranking was determined based on the number of respondents that rated the goal as 'extremely important'. Only those that rated the goal 'extremely important' had the opportunity to rank it. Shading indicates a scale of 0-100%, with darker shade indicating that a higher percent of PAGs ranked the goal as a top priority.

policy restrictions (11%). Approximately 12% of respondents reported leadership turnover and/or leadership voids as a significant hurdle.

Discussion

While PAGs are traditionally viewed as patient and family networks that provide social and educational support, our study confirms and extends previous findings that the missions and values encompass a more holistic approach to patient support. In recent years, the importance of PAGs and their involvement in research have received global attention due to patient advocacy efforts and increasingly accessible genetic technology.[9,11] Through this study, we hoped to further elucidate the factors that influence a PAG's chosen mission and goals as well as their level of involvement in research. Based on previously published literature on translational and clinical research efforts in addition to our findings, we discuss many of the current challenges facing PAG involvement in research and the existing supports available. The organizations, toolkits, and programs in this article are not an exhaustive list, but are meant to provide examples of what is currently available to PAGs.

Current landscape of PAGs

The results from this study reflect similar findings from the work by Pinto *et al.*[9] on Australian rare disease PAGs that show that limited funding and

Table 2. PAG research activities.

Is the organization engaged in research? (*N* = 155)		**Responses (%)**
Yes		123 (79.35)
No		32 (20.65)
Research activities of PAGs that are engaged in research (*N* = 123)		
Activity	**Initiated own research (*N* = 58) (%)**	**Contributed to research (*N* = 113) (%)**
Patient Registry	37 (63.79)	61 (53.98)
Biobank	18 (31.03)	35 (30.97)
Natural History Study	25 (43.10)	83 (73.45)
Clinical Trials	9 (15.52)	91 (80.53)
Translational Research Study	23 (39.66)	55 (48.67)
Quality Improvement	23 (39.66)	N/A
Other	14 (24.14)	10 (8.85)
For the PAGs that are not engaged in research, why not? (*N* = 31)		**Responses (%)**
Research is handled by a group that supports the same condition		4 (12.90)
Lack of interest from researchers		3 (9.68)
The organization is young and growing		7 (22.58)
Limited funding		18 (58.06)
Research is not the top priority at this time		7 (22.58)
Research is not part of the mission		8 (25.81)
Other		12 (38.71)
Activities that support research progress (*N* = 146)		**Responses (%)**
Provided grants/funding for research		109 (74.66)
Advocated to government or other on research issues		71 (48.63)
Participated in research decision-making		48 (32.88)
Provided support to participants in clinical trials/research studies		77 (52.74)
Disseminated information about research findings and opportunities		125 (85.62)
Other		7 (4.79)
Unknown		5 (3.42)

PAG, patient advocacy group.

lack of public awareness are top challenges facing PAGs. The PAGs in our cohort (which may overlap with the Australian cohort) had a higher average budget range than the Australian PAGs, but, similarly, are primarily volunteer run. Both cohorts reported that their primary funding sources were fundraising events and charitable donations. The budget discrepancy could be

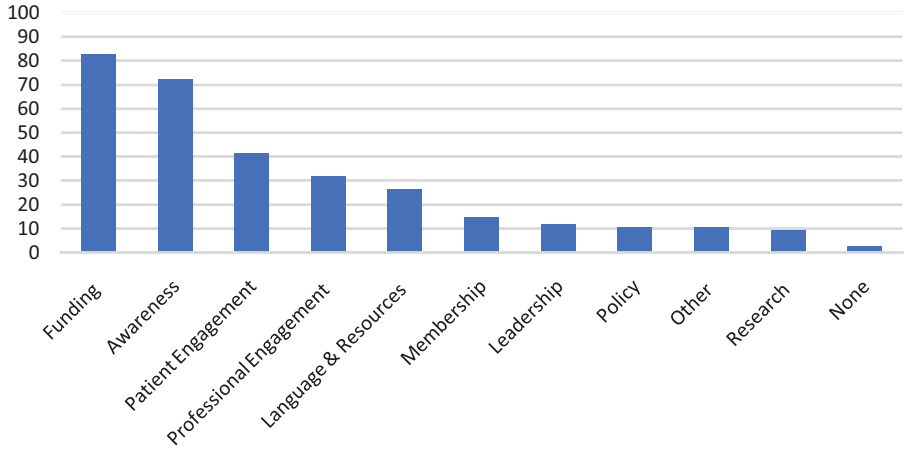

Figure 1. Current challenges facing rare disease PAGs. Participants could select all challenges that they feel apply to their organization. Challenges may include issues for which a PAG has needed to advocate for change, or has kept them from achieving a strategic goal or priority. Funding and awareness remain challenges that affect the majority of organizations.

associated with varying degrees of government support and attention from policymakers, the size of the organizations, and public awareness of rare diseases. In addition, more than half of the PAGs in our study also reported receiving funding from an industry sponsor. According to our results, organizations with budgets above US$500,000 were more likely to choose research as a top priority ($p < 0.05$). Therefore, organizations that are interested in engaging with research in the future may prioritize collaboration with industry while continuing their fundraising, awareness, and grant application efforts. Large alliances and collaborative research networks such as NORD, Global Genes, EURODIS, Genetic Alliance, NIH RDCRN have increased their efforts to improve access to research networks, grants, government advocacy, and training in recognition of the complicated cycle of awareness and funding which may allow individual PAGs to focus their more limited time and resources on research and support. In addition, many of these larger organizations have developed guidelines and toolkits to support PAG administration and management, as the majority of PAG leaders have limited prior experience running a nonprofit organization. Patient-centered research by PAGs is not possible without first establishing a strong, sustainable organization.

Research and drug development

Since the passing of the Orphan Drug Act in 1983, 5% of rare diseases have an FDA-approved treatment.[12] Knowledge of rare disorders is increasing exponentially as new sequencing technologies identify novel rare diseases and pathogenic variants while advances in molecular biology have led to the development of promising new therapeutic modalities.[13] With this lag in translation of knowledge into therapies available to patients, rare disease PAGs are taking more active roles in translational and clinical research. In our cohort, research engagement was ranked as the top priority, followed by awareness and patient education. In addition, our findings showed that 'ultra-rare' disease PAGs were more likely than 'rare' disease PAGs to prioritize research. It is possible that PAGs are shifting their missions toward research to keep up with new opportunities related to NextGen Sequencing and/or cell and gene therapeutic advances. Landy *et al.*[14] suggest that many PAGs are shifting focus from translational research to more direct clinical outcomes based on feedback from their constituents.

Approximately one-third of the organizations in our cohort have initiated their own research, primarily in the form of natural history studies, patient registries, and/or biobanks. Having a biobank and/or registry was associated with an increase in research activity, publications, and clinical trial participation according to a systematic review of studies conducted between 1991 and 2016.[15] Most organizations in our cohort that are engaged in research have contributed in some capacity to a clinical trial. This increased interest

in translational research has influenced biotech/pharmaceutical companies, as well as nonprofit companies, to increase accessibility of data collection and analysis by creating public and private infrastructure for registries (Table 3). One registry platform developed by RARE-X promotes secure data storage, options for data sharing, and assisted analysis for PAGs at any stage of organization. The registry platform developed by AllStripes allows for patient submission of data, which means that the PAG does not need to collect all the data themselves. Through the Data and Analytics Platform from NORD and C-Path's program, the Rare Disease Cures Accelerator, PAGs pay for a data collection platform with built in tools to promote data cleaning and standardization of data from multiple sources. Similarly, Prometheus IQVIA provides both a paid platform and hands-on consulting for database management. The costs and levels of expert support on these platforms are variable, which allows PAGs to pick and choose a platform that fits their needs and/or budgets (Table 3).

Despite the existence of public and private database and analytic infrastructure (Table 3), the long-term success of a registry and/or natural history study ultimately falls on the level of support surrounding the PAG itself. With limited financial, expert, and personnel resources to continue to maintain the database, collect and analyze data, and ultimately interpret the data, registries, and studies may have less utility than expected. To address this disparity, Global Genes created 'Data DIY', to serve as a primer for PAG leaders on collecting and working with data. This tool is meant to empower groups to continue their own data management through self-paced education. Another set of self-paced guidelines includes the NIH National Center for Advancing Translational Sciences Toolkit for Patient-Focused Therapy Development. This toolkit was created with a similar goal of empowering PAGs to better understand the therapeutic development process and seek out appropriate resources.

Importantly, regarding databases, there are discrepancies between the US and EU informed consent and data protections for clinical research. De-identified data that are protected under HIPAA in the United States is not considered anonymous under the Data Protection Act in the EU.[16] Because regulations differ between countries, collecting patient data from a country with additional restrictions may constitute a violation of informed consent and/or patient protection. These regulatory discrepancies create barriers for international collaborations. While there may be a robust natural history database for a specific disease in Europe, it is possible that US clinicians/patients will not be able to contribute. PAGs must take these regulatory discrepancies into account when considering multinational research initiatives.

As an alternative to initiating their own research and managing their own databases, PAGs can encourage informed consent and participation in external clinical research activities through the dissemination of outreach and educational materials. Registries, trials, and natural history studies for specific rare populations may already be occurring through academic medical centers and pharmaceutical companies. Often, the cohorts for rare disease clinical research and trials are recruited through specialty clinics that are supported by their associated PAG.[17] Especially, for rare disease patients of some racial, ethnic, and economic groups, two known barriers to enrollment in clinical research are lack of awareness and mistrust.[18] PAGs may be able to mitigate these concerns by acting as effective liaisons between patients and trusted clinical researchers. Over half of the PAGs in our cohort report that they educate healthcare professionals and teach patients self-advocacy skills to help them gain access to approved therapies. In addition, improved transparency, communication, and education from a trusted support community may help break down barriers to clinical research.

The involvement of rare disease PAGs and patients as consultants represents a growing trend toward patient-centric research.[19] The patient voice in research and drug development provides insight into clinically meaningful endpoints, which is valuable for both the patient community and the sponsor company. Chopra *et al.*[17] proposed an evaluation framework to determine the suitability of a MC for a successful gene therapy development program. The GENE TARGET framework includes 10 scoring criteria to help assess suitability, 3 of which include evaluating the interest, engagement, and perspectives of the target patient population.[17] This framework may help newly formed PAGs to prioritize research efforts and

Table 3. Examples of existing supports available to PAGs (2023).[a]

Category	Organizations and Programs	Target Groups	Link
Guidelines for Patient Engagement in Research	• EveryLife Foundation: Guide to Patient Involvement in Rare disease Therapy Development	*All stakeholders* (i.e. PAGs and sponsors)	https://everylifefoundation.org/pfdd-compendium/
	• Clinical Trials Transformation Initiative (CTTI): Patient Group Engagement	*All stakeholders* (i.e. PAGs and sponsors)	https://ctti-clinicaltrials.org/our-work/patient-engagement/patients-groups-clinical-trials/
	• NIH National Center for Advancing Translational Sciences: Toolkit for Patient-Focused Therapy Development (NCATS Toolkit)	*New* PAGs with limited resources and experience, interested in research	https://toolkit.ncats.nih.gov/about/
Guidance for PAG Development and Growth	• NORD: Mentorship for growing a patient organization/nonprofit	*Existing* organizations (platinum member is already engaged in research; gold member is not engaged in research)	https://rarediseases.org/for-patient-organizations/ways-partner/grow-organization/
	• Global Genes: Guide on Starting a Non-Profit	*New/interested* rare disease advocates	https://globalgenes.org/wp-content/uploads/2018/11/Building-a-Foundation_spread_DIGITAL.pdf
	• Rare Advocacy Movement: Roadmap for Equity Pledge	*Any PAG* interested in working toward diverse, equitable, and inclusive programming	https://www.rareadvocacymovement.com/roadmapforequitypledge
PAG Leadership Development	• FasterCures Milken Institute: LeaderLink Program (builds leadership skills and network through mentorship, capstone project, and virtual collaboration) • YARR Leadership Academy (series of online classes)	*New* leaders of nonprofit organization with interest in research (new leadership within 3 years) *Young adults* in the rare community who are interested in future leadership roles	https://milkeninstitute.org/centers/fastercures/fastercures-leaderslink-program https://everylifefoundation.org/young-adult-representatives/yarr-leadership-academy/
Registry/Data Infrastructure and/or Health Record Collection	• RARE-X: Data storage, sharing, standardization, and analysis	*Any PAG* interested in collecting data	https://rare-x.org/about/
	• AllStripes: Health record collection and storage infrastructure (individual patients can contribute their own data to database)	*Any PAG* interested in collecting data; *any patient* interested in contributing personal data	https://www.allstripes.com/patientorgs
	• Citizen: Health record collection and storage infrastructure (individual patients can contribute their own data to database)	*Any PAG* interested in collecting data; *any patient* interested in contributing personal data	https://www.ciitizen.com/
Guidance on Data Collection	• Global Genes: Data DIY (guidance for collecting and working with data) • Prometheus IQVIA: Registry Platform & Consulting Service	*Any* nonprofit leader interested in collecting data *Existing/mature* PAG interested in creating a registry/considering therapeutic development	https://globalgenes.org/data-diy/ https://www.prometheusresearch.com/advocacy-resources/
Research Networks and Research Funding	• FasterCures Milken Institute: The Research Acceleration and Innovation Network (TRAIN)	*Mature/Advanced* organizations with paid staff, budget for research, and research initiatives	https://milkeninstitute.org/centers/fastercures/train/about
	• NIH Rare Diseases Clinical Research Network: Coalition of Patient Advocacy Groups (CPAG)	*Mature* organizations with an interest in research	https://www.rarediseasesnetwork.org/patient-advocacy-groups/cpag
	• Chan Zuckerberg Initiative (CZI): Rare As One Project (provides research grants and collaborative network)	*Existing* nonprofit PAGs with less than US$2 million budget	https://chanzuckerberg.com/science/programs-resources/rare-as-one/

DIY, do-it-yourself; NIH, National Institutes of Health; NORD, National Organization for Rare Disorder; PAG, patient advocacy group.
[a]Table 3 contains a sample listing of resources currently available (January 2023) and is not meant to be an exhaustive or comprehensive list.

funding toward criteria that may be lacking, such as preclinical models or reliable biomarkers.

To promote mutually beneficial collaborations between PAGs, their patient populations, and industry, Stein *et al.* created publicly available recommendations and guidelines. Biopharmaceutical companies can provide the infrastructure and technical/logistical knowledge to develop a rare disease therapy, but often lack or have difficulty incorporating heterogeneous patient perspectives on research and drug development. Meanwhile, PAGs can bring together diverse rare disease stakeholders and provide a comprehensive and cohesive patient voice to the drug development process, which can counterbalance paternalistic top-down policy.[20] EveryLife Foundation's 'Guide to Patient Involvement in Rare Disease Therapy Development' is meant to be used by all stakeholders, including industry and PAGs, to guide interactions through the patient-centered therapeutic advancement process. Our findings reinforce the potential value of collaboration between industry and PAGs to promote patient-centered drug development and improved patient health outcomes.

While previous reports show that only 5% of known rare diseases have an FDA-approved therapy, one-third of our cohort reported having an approved therapy for their disease of interest.[12] Due to regional differences in drug-approval processes and policies, a specific rare disease therapeutic may be approved by a regulatory agency outside the United States, and not approved by the FDA (and vice versa).[21] In addition, some patient populations benefit from off-label drug utilization due to nonspecific symptoms or similarities among diseases. More research is necessary to understand the discrepancy in the proportion of approved therapeutics. One of our recruitment strategies targeted PAGs that are connected with the NIH RDCRN, which may have skewed our sample toward PAGs with a particular interest in research.

Ultra-rare PAGs

Our data also show that the birth frequency of the disease represented by the PAG is not a predictor of research engagement in general, but, rather, is a predictor of research prioritization. To initiate a clinical trial, there must be years of translational research, natural history studies, and proof of concept. A dichotomy exists in which motivated, ultra-rare PAGs are less likely to have a trial in progress, which may reflect the relative youth of these organizations. With time, it is possible that more 'ultra-rare' PAGs will engage with therapeutic development and approval processes. Due to advances in NextGen Sequencing and increasing usage of whole exome sequencing, more ultra-rare variants are being discovered and diagnosed. Still, many more MCs are predicted to be described in years to come.[2] Each new PAG may need to consider advocating for and identifying interested research groups to study their novel MC. Before providing support and education to families, research may need to be conducted to identify other patients and understand the natural history of the novel MC.

Another factor that will continue to challenge drug development for all PAGs, and especially ultra-rare PAGs, is research funding. The lowest budget organizations were less likely to have a clinical trial in progress. Due to the nature of ultra-rare diseases, associated PAGs typically have a limited patient population, less public awareness of the disease, and a lower budget than rare disease PAGs. The costs of most FDA-associated clinical trials in progress between 2015 and 2016 ranged from approximately US$12 to $33 million.[22] This does not take into account the grants that are necessary to conduct translational research and the costs of developing a registry or biobank prior to reaching a clinical trial. The high financial burden of research acts as a barrier to drug development for ultra-rare and lower budget PAGs.

These results have policy implications with regard to research funding, incentive programs, and collaborative research networks that target PAGs associated with novel MCs. Consortiums like NIH RDCRN bring together patients, researchers, and advocacy organizations to initiate more patient-focused research.[9] The CZI's[23] 'Rare As One' project was created in 2015 to help selected, established organizations promote collaboration, build capacity to engage in research, and provide research funding. While this program targets established but often younger or lower budget PAGs, others like the FasterCures Milken Institute's 'The Research Acceleration and Innovation Network (TRAIN)' support more mature organizations with an established research budget. TRAIN helps PAGs take a

more entrepreneurial and strategic approach as their research progresses. The NIH RDCRN's 'Coalition of Patient Advocacy Groups (CPAG)' brings together mature organizations with an interest in research that would benefit from shared education and expertise. By increasing the reach of these networks and the funding available to organizations, research may continue to become more accessible for global PAGs.

Future directions

This study sought to provide an update on the current, global landscape of rare disease PAGs. In total, 159 eligible organizations took part in this study out of an estimated 600+ organizations that were contacted for recruitment. Additional outreach is needed to broaden the scope of our findings. Future directions may also include surveying PAGs on racial and ethnic disparities in patient engagement, research involvement, government advocacy, and health outcomes. In addition, further research is necessary to elucidate details about PAG collaborations with the biopharmaceutical industry to promote drug development. Future research could involve interviewing PAG leaders to gather narratives and further contextualize their experiences with industry, the support tools reviewed above, and drug development.

Conclusion

Our results reflect prior findings that PAGs serve as holistic patient support communities, often tackling community building to drug development. As gene discovery continues to accelerate, so too will the development of novel PAGs. We provide an update on current challenges facing rare and ultra-rare PAGs, research activities, and lessons learned by their leaders. Patient-centered clinical research and precision-medicine will continue to create new opportunities for these organizations to drive drug development. With increasing attention from pharmaceutical companies, long-term collaborations with PAGs can be mutually beneficial. PAGs can provide perspectives on meaningful outcomes, recruit for trials, and educate families and healthcare professionals, while industry can provide the infrastructure, logistics, and technical expertise to create novel therapeutics and advance research.

Our findings also provide insight into the current challenges and needs of these organizations, despite the available support systems and tools. Funding and lack of awareness in research are primary concerns of the majority of PAG leaders in this cohort. Ultra-rare disease PAGs may have additional support needs. While ultra-rare PAGs often prioritize research in their missions, they face additional hurdles to engaging in clinical research and drug development. From the leaders' lessons learned, many emphasized the need for collaboration, prioritization, strong infrastructure, and involvement of patients in PAG and research development. In addition, there are reports of short-term support, training, and funding from research networks and industry, which is meant to help PAGs begin their research journey. This temporary support may fall flat after the period ends because of lack of continued support. For instance, if a registry is built using infrastructure and expertise from industry, lack of continued support from industry for data collection and analysis may weaken the utility of the registry. To better support rare disease PAGs and their patient population, this study indicates a need for information-sharing and collaboration across similar groups to avoid duplicated efforts and to conserve resources. It also indicates a need for increased accessibility to collaborative research and advocacy networks. Our findings can inform support initiatives and policies, while providing valuable information to future PAG founders and leaders.

Limitations

There are important limitations to this study with regard to the generalizability of the results. Eligibility only extended to participants who could read and write in English, which limits the global scale of the study. The true number of rare disease PAGs is currently unknown, which makes it difficult to understand the reach of the study. Because of the varied recruitment methods, we are unable to calculate an exact response rate for the survey. In addition, geographic data were not collected for the organizations that participated, so the geographic reach of the study is not well understood. The tools and resources cited in Table 3 and throughout the discussion are current as of January 2023, and we recognize that support resources and needs will change with time.

There is no standard definition of a 'rare' or 'ultra-rare' disease across the world with regards to prevalence and incidence. While the United States defines rare as affecting fewer than 200,000 individuals in the United States, the EU defines a 'rare disease' as having a prevalence of less than 1 in 2000 people. There are country- and continent-specific definitions that vary across the world that make comparing the relative prevalence of rare diseases difficult. Therefore, in this study, it is difficult to assess the accuracy and validity of the measures of disease prevalence (which included birth frequency, number of individuals affected, and open-text response). In addition to the incompatibility of these measures, the survey relied on participant response and knowledge of frequency and prevalence rates. In addition, the drug development and approval process varies from country to country. While questions in the Research section of the survey used vague language that could be applied to international drug development and approval processes, it was originally written based on the US FDA approval process. A future study on global PAGs should consider regional differences in drug-approval processes and policies.

Another notable limitation of this study is that it did not inquire directly about PAG interactions with industry. More than half of the PAGs in the study reported that they received funding from an industry/corporate sponsor, but we are not aware of the nature and quality of the PAG–industry collaboration. A future study could focus on the nature of these interactions to better inform support and policy moving forward.

Declarations

Ethics approval and consent to participate

The study was approved by the Boston University Institutional Review Board (H-40857) on 6 September 2021. Participants agreed to take part in the study following an informed consent process; they were given an informed consent document in English. Participants were only eligible if they could speak and read English. Participants were made aware that their data would be de-identified for analysis and publication. Participants had the opportunity to remove themselves from the study and strip their data from publication if they were uncomfortable throughout the duration of the study.

Consent for publication

Not applicable, as data were de-identified and did not contain private and protected health information. Specific identifying PAG information was not included.

Author contributions

Amy M. Patterson: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing.

Megan O'Boyle: Conceptualization, Investigation, Methodology, Resources, Visualization, Writing – review & editing.

Grace E. VanNoy: Conceptualization, Investigation, Methodology, Resources, Supervision, Visualization, Writing – review & editing.

Kira A. Dies: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization.

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Primary data can be made available by author, Amy M. Patterson, MS, CGC. Please contact her with questions and/or data request at apatte42@jh.edu.

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Appendix A. Organization demographics reported by PAG leaders.

Organization demographics (*N* = 157)	**Responses (%)**
Active nonprofit status	
Yes	144 (91.1)
No	13 (8.2)
Birth frequency of disease	
Greater than 1:2000 births	7 (4.5)
1:2000–50,000 births	48 (30.6)
1:50,000–200,000 births	28 (17.8)
1:200,000–500,000 births	12 (7.6)
1:500,000–1,000,000 births	8 (5.1)
Fewer than 1:1,000,000 births	25 (15.9)
Unknown	29 (18.5)
Worldwide prevalence of disease	
Fewer than 100 persons	5 (3.2)
100–1000 persons	33 (21.1)
1000–10,000 persons	34 (21.7)
10,000–50,000 persons	14 (8.9)
50,000–200,000 persons	10 (6.4)
Greater than 200,000 persons	20 (12.7)
Unknown	41 (26.1)
Paid staff members	
None	75 (47.5)
1–5 paid staff	62 (39.2)

(Continued)

Appendix A. (Continued)

Organization demographics (*N* = 157)	**Responses (%)**
5–10 paid staff	14 (8.9)
More than 10 paid staff	7 (4.4)
Unknown	0
Age (years)	
Less than 5	28 (17.7)
5–10	34 (21.5)
10–15	24 (15.2)
Greater than 15	72 (45.6)
Unknown	0
Size	
Fewer than 60 members	23 (14.7)
60–300 members	33 (21.1)
300–1000 members	41 (26.3)
1000–10,000 members	43 (27.6)
More than 10,000 members	9 (5.8)
Unknown	7 (4.5)
Budget	
None	7 (4.5)
US$0–10,000	18 (11.5)
US$10,000–50,000	28 (17.8)
US$50,000–100,000	15 (9.6)
US$100,000–200,000	28 (17.8)
US$200,000–500,000	25 (15.9)
US$500,000–1,000,000	18 (11.5)
Greater than US$1,000,000	13 (8.3)
Unknown	5 (3.2)

PAG, Patient advocacy group.

Appendix B

Frequency	Budget	Advocacy	Awareness	Fam edu	Fam resource	Provider edu	Research	Research policy	Fam support	Highest class
Ultra-rare	Highest	0.0000000	0.1013682	0.0716338	0.0000000	0.0000000	0.7711473	0.0000000	0.0558507	Research
Ultra-rare	Medium-High	0.0000000	0.0812025	0.3004123	0.2500016		0.3432249	0.0000000	0.0251587	Research
Ultra-rare	Medium-Low	0.0000000	0.2455405	0.3731442	0.0000000	0.0000000	0.3322549	0.0000000	0.0490604	Fam edu
Ultra-rare	Lowest	0.0000000	0.1634376	0.3874991	0.0000000	0.0000000	0.4185895	0.0000000	0.0304739	Research
Rare	Highest	0.0666671	0.1062991	0.1142240	0.0000000	0.0000000	0.4610289	0.0000000	0.2517809	Research
Rare	Medium-High	0.0000000	0.0964583	0.5426242	0.0000000	0.0000000	0.2324405	0.0000000	0.1284770	Fam edu
Rare	Medium-Low	0.0000000	0.1897301	0.4384306	0.0000000	0.0624997	0.1463684	0.0000000	0.1629712	Fam edu
Rare	Lowest	0.0000001	0.1274219	0.4593822	0.0000000	0.0000000	0.1860558	0.1250023	0.1021377	Fam edu

Appendix B. Multinomial modeling of PAGs and their top priority goals. PAGs were bucketed by prevalence ('Rare' and 'Ultra-Rare') as well as by budget size ('Highest', 'Medium-High', 'Medium-Low', and 'Lowest'). Results show that ultra-rare disease and high-budget organizations are more likely to prioritize research, while rare disease organizations are more likely to prioritize family education. Multinomial modeling conducted by MSSP Consulting (Boston University).

Appendix C

Yes, there is an approved treatment for the disease that the PAG supports (*N* = 46)	
	Responses
Was the organization involved in the development of the treatment?	
Yes	22 (47.83)
No	21 (45.65)
Unknown	3 (6.52)
Does the organization assist patients with access to therapy?	
Advocate to insurance companies on behalf of the patient	14 (30.43)
Provide funding to cover the cost of treatment	2 (4.34)
Teach patients self-advocacy skills	28 (60.87)
Write letters of medical necessity	13 (28.26)
Educate healthcare professionals	29 (63.04)
Other	7 (15.22)
We do not assist at this time	11 (23.91)
No, there is not an approved therapy at this time (*N* = 82)	
Why not?	
Trials are in progress	33 (40.24)
Trials are NOT in progress	42 (51.22)
Unknown	7 (8.54)
No, trials are NOT in progress at this time (*N* = 41)	
Themes that emerged as barriers to drug development & clinical trials	
Lack of research on the disease	25 (60.98)
Symptom/phenotype challenges	8 (19.51)
Clinical trial is in a preparatory phase	7 (17.57)
Patient population is very small	4 (9.76)
Limited communication and collaboration	2 (4.88)
Limited funding	2 (4.88)

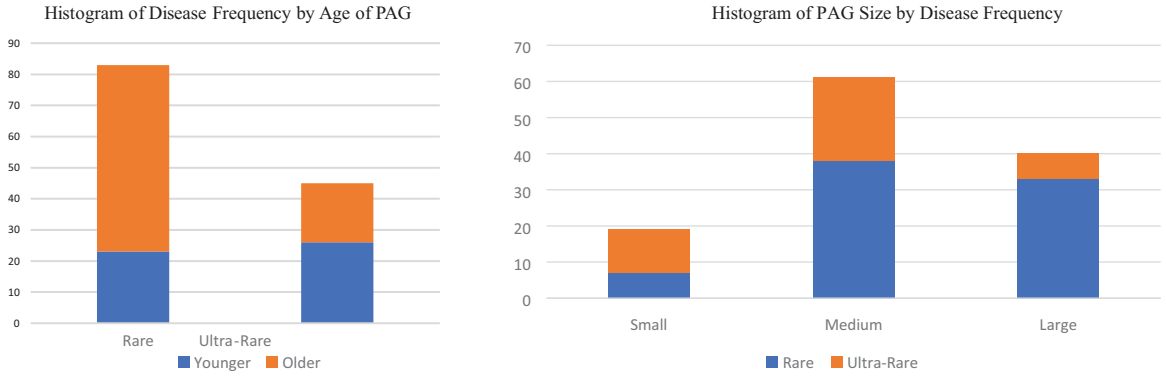
PAG, patient advocacy group.

Appendix D

y. level	Term	Estimate	Std. error	Statistic	*p* value	Conf. low	Conf. high
Not in progress	(Intercept)	−0.80	0.65	−1.22	0.22	−2.08	0.48
Not in progress	Frequency Ultra-Rare	1.34	0.64	2.10	0.04	0.09	2.58
Not in progress	Budget Lowest	1.72	1.01	1.69	0.09	−0.27	3.71
Not in progress	Budget Medium-High	1.54	0.79	0.68	0.50	−1.01	2.09
Not in progress	Budget Medium-Low	0.65	0.84	0.78	0.43	−0.99	2.29

Appendix D. Multinomial modeling of PAGs and their likelihood of NOT having a clinical trial in progress. PAGs were bucketed by prevalence ('Rare' and 'Ultra-Rare') as well as by budget size ('Highest', 'Medium-High', 'Medium-Low', and 'Lowest'). The model shows one significant coefficient estimate at $p < 0.05$ ($p = 0.04$) for 'ultra-rare' PAGs and the likelihood that they do not have a trial in progress. Multinomial modeling conducted by MSSP Consulting (Boston University). PAG, patient advocacy group.

Appendix E



Histogram of disease frequency by age of PAG and histogram of size of PAG by disease frequency. When organizations were bucketed into 'rare' and 'ultra-rare' disease PAGs by birth frequency, the organizations serving 'ultra-rare' disease patients tended to be younger and smaller (<10 years old; <300 members), while organizations serving 'rare' disease patients tended to be older and larger (>10 years old; >1000 members). Visualization and modeling by MSSP Consulting (Boston University).