DOI: 10.1002/cncr.35184

COMMENTARY

Making progress against rare cancers: A case study on neuroendocrine tumors

Michael O'Rorke PhD | **Elizabeth Chrischilles PhD** | **the NET-PRO Study Investigators**

Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, Iowa, USA

Correspondence
Michael O'Rorke and Elizabeth Chrischilles.
Email: michael-ororke@uiowa.edu and e-chrischilles@uiowa.edu

Funding information
Patient-Centered Outcomes Research Institute, Grant/Award Number: RD-2020C2-20329

Abstract

In April 2023, the National Cancer Institute offered a roadmap for cancer research to achieve Cancer Moonshot goals. To reach these goals requires making progress for all cancers, not just those that are most common. Achieving progress against rare cancers, as well as common cancers, requires involvement of large clinical research networks. In 2020, the Patient-Centered Outcomes Research Institute (PCORI) launched an initiative on Conducting Rare Disease Research using PCORnet, the National Patient-Centered Clinical Research Network. The purpose of this commentary is to introduce the broader community of cancer researchers to the PCORnet NET-PRO study (comparing the effects of different treatment approaches for neuroendocrine tumors on patient-reported outcomes) thereby demonstrating how researchers can use the PCORnet infrastructure to conduct large-scale patient-centered studies of rare cancers.

KEYWORDS
carcinoid tumor, epidemiology, humans, neoplasms, neuroendocrine tumors, patient-reported outcome measures, rare diseases

The members of the NET-PRO Study Investigators include the following: Alanna M. Chamberlain, PhD (Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota); Elizabeth A. Chrischilles, PhD (Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, Iowa); Lindsay G. Cowell, MS, PhD (O'Donnell School of Public Health, UT Southwestern Medical Center, Dallas, Texas); Joseph S. Dillon, MB, BCh, BAO (The University of Iowa, Iowa City, Iowa); Carol Early, BA (University of Kansas Medical Center, Kansas City, Kansas); Tobias Else, MD (Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, Michigan); T. Clark Gamblin, MD, MS, MBA (Medical College of Wisconsin, Milwaukee, Wisconsin); David Geller, MD (University of Pittsburgh, Pittsburgh, Pennsylvania); Elyse Gellerman, MHS (Neuroendocrine Tumor Research Foundation, Boston, Massachusetts); Brian Gryzlak, MSW, MA (Department of Epidemiology, College of Public Health, University of Iowa); Thorvardur R. Halfdanarson, MD (Mayo Clinic, Rochester, Minnesota); Harley C. Hamilton, BS (Ohio State University Wexner Medical Center, Comprehensive Cancer Center, Columbus, Ohio); Fiona C. He, MD (Allina Health Cancer Institute, Minneapolis, Minnesota); Juan Pablo Hourcade, PhD (Department of Computer Science, College of Liberal Arts and Sciences, University of Iowa, Iowa City, Iowa); Kamran Indrees, MD, MSCI, MMHC (Vanderbilt University Medical Center, Nashville, Tennessee); Syed M. Kazmi, MD (University of Texas Southwestern Medical Center, Dallas, Texas); William Lancaster, MD (Department of Surgery, Medical University of South Carolina, Charleston, South Carolina); Amoni Lewis-Hughes, BS (Ohio State University Wexner Medical Center, Comprehensive Cancer Center, Columbus, Ohio); Mei Liu, PhD (Department of Health Outcomes and Biomedical Informatics, College of Medicine, University of Florida, Gainesville, Florida); Josh A. Mailman, MBA (NorCal CarciNET Community, Ripon, California); Bradley McDowell, PhD (Holden Comprehensive Cancer Center, University of Iowa, Iowa City, Iowa); Michael O'Rorke, PhD (Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, Iowa); Robert A. Ramirez, DO (Vanderbilt University Medical Center, Nashville, Tennessee); Brian H. Ramnaraign, MD (University of Florida, Gainesville, Florida); Hanna K. Sanoff, MD (Division of Oncology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina); Heloisa P. Soares, MD, PhD (Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah); Vineeth Sukrithan, MD (Ohio State University, Columbus, Ohio); Bradley W. Taylor, MBA (Medical College of Wisconsin, Milwaukee, Wisconsin); Mia S. Tepper, MBA (The Healing NET Foundation, Los Angeles, California); Maryann Wahmann (Neuroendocrine Cancer Awareness Network, Fort Mill, South Carolina); Gideon K. D. Zamba, PhD (Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, Iowa).

Ensuring that effective treatment with minimal side effects is accessible to all people, including those with rare cancers, is embraced in one of eight goals of the National Cancer Institute (NCI) National Cancer Plan[1] which was released April 3, 2023. The Plan's aspirational statements respond to the Cancer Moonshot and offer a roadmap for cancer research. An NCI-led study,[2] published immediately following the Plan's release, reviewed opportunities to achieve the Moonshot's 50% mortality reduction goals. The study focused solely on common cancers because these account for the largest number of cancer deaths.[2] An accompanying commentary[3] highlighted that if little or no progress is made for the combined category of uncommon cancers (accounting for 14.2% of age-adjusted cancer mortality), an unrealistic 3.44% yearly decrease in mortality from common cancers would be required to achieve Moonshot goals. To begin to address this challenge, the Cancer Moonshot supports NCI's Participant Engagement and Cancer Genome Sequencing Network[4] focused on rare cancers or rare cancer subsets and other understudied populations. NCI's National Clinical Trials Network (NCTN), formerly the Cooperative Group Program, also includes Phase 1–3 rare cancer protocols.[5] Consisting of four adult and one pediatric group, NCTN groups receive infrastructure funding and are able to reduce the costs of conducting trials by sharing resources. The overall NCTN budget of $171 million enrolls 17,000–20,000 participants annually, across all rare and common cancer protocols.[6] The Congressionally mandated Rare Diseases Clinical Research Network (RDCRN) includes 20 topically focused research consortia,[7] none of which focuses on rare cancers. Clearly, to do this work, still more large-scale networks will be needed.

The US Patient-Centered Outcomes Research Institute (PCORI) has been an active participant in Moonshot activities. [8] PCORI funded the development of PCORnet, The National Patient-Centered Clinical Research Network, to conduct large-scale patient-centered outcomes research faster and more efficiently through a reusable research infrastructure and patient partnerships. Participating health systems gather data from electronic health records and standardize them into a common data model. In 2020, PCORI launched an initiative on Conducting Rare Disease Research using PCORnet to answer important questions about the treatment and management of rare diseases or conditions through observational cohort studies. An important part of the vision of PCORnet was that its scale (more than 60 centers within eight clinical research networks) would allow for improved research on rare diseases. The purpose of this commentary is to introduce the goals and methods of one PCORnet rare cancer study to the broader community of cancer researchers and to demonstrate how the infrastructure can make large-scale research accessible to and for people with a rare cancer as well as common cancers.

The PCORnet NET-PRO Study—comparing the effects of different treatment approaches for neuroendocrine tumors on patient-reported outcomes—is an observational study with aims to examine treatment sequencing, quality of life, progression-free survival (PFS), and comparative safety outcomes. Neuroendocrine tumors, or NETs, are a rare type of cancer that can occur anywhere in the body. NETs often occur in the stomach, intestines, pancreas, or lungs. Fewer than 20,000 people in the United States are diagnosed with a NET each year[9] and there are approximately 175,000 prevalent cases.[10] Several treatments are available for NETs,[11] but questions remain about which treatments work the best and the order in which to use them.

NETs are typically slow-growing in nature with prolonged survival and significant symptom burdens; however, few studies have examined quality of life impacts. The complex and confusing nomenclature of NETs contributes to a thin evidence base for optimal management. Somatostatin analogues (SSAs) are established first-line agents for most well-differentiated gastroenteropancreatic (GEP) NETs, largely because of their demonstrated improvements in overall survival in two placebo-controlled randomized trials. However, there is no consensus guideline as to the optimum sequencing of other therapeutic options. Interestingly, an assessment of the clinical benefit of systemic treatments in GEP-NETs found that currently used treatments had low health benefit scores according to the American Society of Clinical Oncology Net Health Benefit (ASCO-NHB), and none could be graded as meaningfully beneficial clinically according to the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (ESMO-MCBS).[12] Therefore, one of the greatest challenges in the current NET oncology management landscape is how best to optimally sequence these many therapeutic options (if warranted at all), and how to tailor treatment selection on the basis of individual characteristics of the tumor and patient. This was underscored in a network meta-analysis of 30 randomized trials finding that severe and life-threatening adverse effects ranged from 3.0% to 83.9% depending on the treatment combinations used, underlining the importance of mitigating toxicity and optimizing sequencing of therapy for patients with prolonged survival.[13]

The NET-PRO Study is composed of 14 partnering PCORnet sites, from four clinical research networks that together saw an estimated 6010 patients with NETs during 2019–2021 (Table 1). The study was planned and designed with patients with NETs, four US patient advocacy organizations focused on NETs (Table 1), and physicians with expertise in treating NETs.

Enrollment of patients in NET-PRO began in May 2022 and will continue for at least 21 months. Patients 18 years and older with a new diagnosis of a NET during 2018 or after are eligible and are being identified from electronic health records with a computable phenotype developed for the study, validated to have a positive predictive value in excess of 90%. Across all sites, approximately 3000 patients will be enrolled; there are 1494 enrolled to date) using low-touch methods. Patients are largely invited by email that includes a link to the study portal and unique user log-in credentials. Informed consent is administered through the study portal after which patients are presented a baseline survey to complete online. Flexible recruitment methods allow sites to supplement low-touch email methods with mailed surveys, phone calls, and in-clinic recruitment.

Three types of data are being collected for the NET-PRO study: four patient surveys (at baseline, 6, 12, and 18 months), electronic

TABLE 1 Estimated total population and number of patients with GEP or lung NETs diagnosed during 2019–2021.

Partner type	Collaborating organization	Total NET population	No. of GEP-NETs	No. of lung NETs
GPC clinical research sites	Allina Health	155	122	33
	University of Iowa	228	158	70
	University of Kansas Medical Center	398	283	115
	Medical College of Wisconsin	275	210	65
	University of Texas Southwestern Medical Center	363	230	133
	University of Utah	238	155	83
One-Florida clinical research site	University of Florida	224	167	57
STAR clinical research sites	Medical University of South Carolina	84	62	22
	University of North Carolina at Chapel Hill	460	322	138
	Vanderbilt University Medical Center	355	195	160
	Mayo Clinic	1972	1590	382
PaTH Toward a Learning Health System (PaTH) clinical research sites	University of Pittsburgh Medical Center	355	195	160
	Ohio State University	649	437	212
	University of Michigan	254	202	52
Patient advocacy organization	NorCal CarciNET Community (https://norcalcarcinet.org/)			
Patient advocacy organization	The Neuroendocrine Cancer Awareness Network (NCAN) (https://www.netcancerawareness.org/)			
Patient advocacy organization	The Neuroendocrine Tumor Research Foundation (NETRF) (https://netrf.org/)			
Patient advocacy organization	The Healing NET Foundation (https://www.thehealingnet.org/)			

Abbreviations: GEP, gastroenteropancreatic; GPC, Greater Plains Collaborative; NETs, neuroendocrine tumors; NorCal CarciNET, Northern California CarciNET; STAR, Stakeholder, Technology, and Research.

health records, and chart reviews. The patient surveys (available on request) and a study portal/NET personal health record were designed with patient partners. The survey has been designed to assess a broad range of topics that are best reported by patients (Table 2). Clinical and tumor variables will be measured from the electronic health record data in each site's instance of the PCORnet common data model or from chart reviews (Table 3).

The NET-PRO study has major strengths that distinguish it from prior observational studies of neuroendocrine cancers. Patients are being enrolled from multiple regions and health care systems. The clinical and patient perspectives are merged by combining in-depth patient surveys with detailed clinical data extracted from electronic health record systems and selected clinical data abstracted from manual chart reviews to create one of the most comprehensive data sets for understanding the experiences, treatments, and outcomes of patients with neuroendocrine tumors. Additionally, the low-touch recruitment methods and efficiency of interoperable electronic health record data permits this rare cancer and its subtypes to be investigated at a large scale. Finally, NET-PRO is following PCORI's engagement rubric[24] for a rigorous stakeholder engagement plan for the planning, conduct, and engagement phases of the study.

The NET-PRO study also faced a number of challenges that needed to be addressed. Patients with neuroendocrine tumors often have metastatic disease at the time of diagnosis and have a high prevalence of moderate to severe symptoms especially tiredness (44%–50%), lack of well-being (37%–49%), and anxiety (30%–40%).[25] Special efforts are being made to recruit these patients, including multiple modes and a REDCap recruitment monitoring tool deployed to all participating clinical sites. Additionally, to enable low-touch recruitment, a computable phenotype was needed that could be efficiently deployed for cohort identification with high fidelity against the PCORnet common data model. Working within the common data model to search for pre-specified diagnostic codes, we can essentially use the search strategies that would be otherwise implemented in a variety of institutional electronic medical record systems and local enterprise data warehouses. Foundational work was done to develop and validate three complementary phenotypes that can be consistently applied across institutions: 1) one that uses high quality institutional tumor registry data; 2) one with demonstrated high positive predictive value (i.e., the low-touch phenotype) that identifies patients with a high degree of certainty with minimal need for chart confirmation of eligibility; and 3) a third high sensitivity algorithm identifying further potential cases but at a lower

TABLE 2 Overview of concepts and measures collected in patient surveys.

Concept/measure	Baseline survey	Follow-up surveys
Sociodemographic data (date of birth, sex and gender orientation, race, marital status, ethnicity, state of residence, household income, highest level of educational attainment, health literacy)	X	
Height and weight	X	X
Health-related quality of life (QLQ-C30, QLQ-GINET21)[14–16]	X	X
Other impacts of cancer (worry, other life events)	X	X
Symptom inventory with frequency and severity (adapted for NETs from ONWARD study)[17]	X	X
History of chronic conditions (20-item checklist)[18]	X	
Preferences and attitudes (quality vs. quantity of life,[19] preferred decision-making role,[20,21] family's role in decision-making)	X	
Attitudes (fatalistic thinking, spirituality)[22]	X	
Experiences of care (physician communication, coordination and responsiveness of care,[23] actual decision-making role adapted from Hawley et al.)[20]	X	X
Self-reported treatments, including over-the-counter	X	X

TABLE 3 Patient, clinical, and tumor variables that will be collected from the PCORnet common data model or chart review.

Concept/variable	Common data model table or chart abstraction
Demographics (date of birth, sex, Hispanic, race)	Demographic table
Toxicity outcomes (acute renal failure, dialysis, liver failure)	Diagnosis table
Vitals (height, weight, systolic and diastolic blood pressure, smoking)	Vitals table
Treatments (SSAs, octreotide, lanreotide, pasireotide)	Dispensing, prescribing, procedures, and medications administered tables
Bevacizumab, cytotoxic chemotherapy, everolimus, interferon α, external beam radiation, TARE, TAE, TACE, PRRT-Lutetium Lu-177 DOTATATE, PRRT-Yttrium-90 DOTATOC, small molecule TKIs, telotristat ethyl	
Laboratory indicator and result/abnormal result indicator (ALT, albumin and microalbumin albumin/creatinine and microalbumin/creatinine ratio, ALP, AST, AST/ALT ratio, blood urea nitrogen, chromogranin A, cystatin C, hemoglobin, Ki-67, lymphocytes, pancreastatin, serum or blood creatinine, somatostatin, total bilirubin)	Lab results
Comorbid conditions (chronic pulmonary disease, congestive heart failure, coronary artery disease, diabetes with complications, diabetes without complications, hypertension, end-stage renal disease, mild liver disease, severe liver disease, peripheral vascular disease, renal disease, myocardial infarction)	Diagnosis table, conditions table (for conditions in the 2 years before GEP-NET/lung NET diagnosis)
Vital status (death date, cause of death)	Death table; death cause table
Linkage (patient ID, token)	Hash token table (Datavant link module)
Tumor characteristics (NAACCR required variable list [i.e., tumor grade, stage, nodal status and other pathological characteristics])	Tumor table
Status of disease progression, mitotic count, CgA, and Ki-67 index (where available) and clinical variables found to be insufficiently populated in the common data model.	Chart extraction

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CgA, chromogranin A; GEP, gastroenteropancreatic; ID, identification; NAACCR, North American Association of Central Cancer Registries; NET, neuroendocrine tumor; SSAs, somatostatin analogues; TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization.

TABLE 4 Rare cancer research challenges and lessons learned from the NET-PRO Study.

Challenge for rare cancer research	Impact on rare cancer research	NET-PRO solution	NET-PRO lesson
Limited existing knowledge, lack of standardized treatment approaches	Uncertain design stage assumptions, especially to guide sample size determination	Quality of life and creatinine clearance selected as co-primary end points with power estimated for the smallest expected treatment group; progression-free survival as secondary end point due to insufficient existing knowledge	Study would have benefited from an adaptive learning stage using interim data from the study to assess uncertain design stage assumptions, especially to optimize sample size
	Need for stakeholders to advise on research questions and outcomes	Partnered with national patient advocacy groups, developed a patient and clinician advisory committee	Time must be allowed for iterating on stakeholder input to develop study measures
Gathering a sufficiently large number of participants	Need for collaboration across institutions	Nested in a clinical research network with interoperable data enabling a computable eligibility phenotype	Common data model and computable phenotype enables effective and efficient low-touch recruitment approaches
Feasibility of multi-institution recruitment	Need for pragmatic methods, local variability in policies	Primarily email invitations with link to study patient portal developed with user-centered design coupled with flexible approaches based on patient/site preferences (i.e., direct-to-patient [in-clinic, EMR messaging], mailed letter/study packet)	Pragmatic recruitment benefits from expertise and support from local and central PCORnet teams
Limited longitudinal studies or registries	Need to plan for funding to sustain cohorts	Launched prospective cohort study	Study would have benefited from longer data analysis and dissemination phase to ensure future funding
Whether meaningful surrogate outcomes are available	If available, surrogate end point can allow for earlier assessment and smaller sample size	Included progression-free survival (rather than overall survival) as a study outcome	Clinician stakeholders determined it was neither feasible nor clinically relevant to apply gold standard RECIST criteria; a novel substitute for use with real-world data will be piloted

Abbreviation: NET-PRO, Neuroendocrine Tumors-Patient-Reported Outcomes Study.

level of e latter requires reviewing more charts to find eligible cases. A third challenge is accounting analytically for potential confounders that may affect both patient treatment choice and outcomes. The detailed patient and clinical data will make it possible to control for a large number of potential confounders in statistical methods. Last, the NET-PRO study will conduct chart abstraction as part of assessing and determining a secondary outcome of PFS as well as select other data elements incompletely populated in the PCORnet common data model. There is currently no accepted framework for developing chart abstracted real-world progression end points. Large observational studies require feasible measurement methods. NET-PRO will test a protocol for applying the PRISSM framework[26] to determine disease progression using data in electronic health records from 14 health systems with varying electronic health record platforms. The PRISSMM framework standardizes collection of pathology, radiology, imaging, signs and symptoms, tumor markers, and medical oncologist assessments.

Research on rare cancers has some unique challenges including limited existing knowledge, lack of standardized treatment approaches, the need for collaboration across institutions to gather a sufficiently large number of participants, and limited longitudinal programs for tracking long-term progress toward understanding the natural history and effectiveness of treatment approaches. Table 4 offers examples of how NET-PRO addressed these challenges and lessons that were learned.

In summary, PCORnet has many advantages for rare cancer research. It offers efficiencies for conducting smaller, multi-site efficacy studies as well as large-scale patient-centered comparative effectiveness trials and outcomes research.[27] The NET-PRO study is the largest and most comprehensive observational study of neuroendocrine tumors that has ever been undertaken. This study is demonstrating the feasibility of conducting large-scale research that is accessible to and for people with a rare cancer. With patients as partners, the NET-PRO study offers an important opportunity to

answer the questions "how is each therapy expected to impact my survival and quality of life," "what therapy would be the best for me to try next," and "if I were to take this option now, what treatment options will be available to me in the future?"

AUTHOR CONTRIBUTIONS

Michael O'Rorke: conceptualization; investigation; funding acquisition; writing original draft; methodology; supervision; project-administration. **Elizabeth Chrischilles**: writing original draft; conceptualization; methodology; resources.

ACKNOWLEDGMENTS

The research reported in this article is funded through a Patient-Centered Outcomes Research Institute Award (RD-2020C2-20329).

CONFLICT OF INTEREST STATEMENT

Tobias Else reports fees for professional activities from Merck. David Geller reports fees for professional activities from Olympus America Inc. Thorvardur R. Halfdanarson reports consulting fees from Advanced Accelerator Applications, Camurus, Ipsen Biopharmaceuticals, Inc, ITM Isotopen Technologien Muenchen, Perspective Therapeutics, and TerSera Therapeutics LLC; and grant and/or contract funding from Advanced Accelerator Applications, Camurus, Crinetics, ITM Isotopen Technologien Muenchen, and Thermo Fisher Scientific. Syed M. Kazmi reports stock with Johnson & Johnson Health Care Systems Inc. Josh A. Mailman reports consulting fees from Carver College of Medicine, University of Iowa, the National Cancer Institute, and the US Nuclear Regulatory Commission. Bradley McDowell reports grant and/or contract funding from the National Cancer Institute. Robert A. Ramirez reports consulting fees from Advanced Accelerator Applications, Curium US LLC, Ipsen Biopharmaceuticals Inc, ITM Radiopharma, and TerSera Therapeutics LLC. Hanna K. Sanoff reports fees for professional activities from Pfizer; and grant and/or contract funding from Biomed Valley Discoveries, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Exelixis Inc, F. Hoffmann-La Roche, Pfizer, and Rgenix. Heloisa Soares reports consulting fees from Ipsen Biopharmaceuticals, Inc and Novartis Pharmaceuticals Corporation; and fees for professional activities from ITM Isotope Technologies Munich SE. Vineeth P. Sukrithan reports consulting fees from Exelixis Inc, General Electric, and Progenics Pharmaceuticals Inc. Mia S. Tepper reports consulting fees from Inter Science Institute Inc. The other authors declare no conflicts of interest.

FUNDING INFORMATION

Patient-Centered Outcomes Research Institute, Grant/Award Number: RD-2020C2-20329

DATA AVAILABILITY STATEMENT

On study completion, the data that support the findings of this study will be openly available in Inter-university Consortium for Political and Social Research.

ORCID

Michael O'Rorke https://orcid.org/0000-0002-2425-3323
Elizabeth Chrischilles https://orcid.org/0000-0002-1843-1955
Hanna K. Sanoff https://orcid.org/0000-0001-8679-4486
Vineeth Sukrithan https://orcid.org/0000-0002-5878-9900

REFERENCES

1. National Cancer Institute. National Cancer Plan. April 3, 2023. Accessed May 1, 2023. https://nationalcancerplan.cancer.gov
2. Shiels MS, Lipkowitz S, Campos NG, et al. Opportunities for achieving the Cancer Moonshot goal of a 50% reduction in cancer mortality by 2047. *Cancer Discov*. 2023;13(5):1084-1099. doi:10.1158/2159-8290.cd-23-0208
3. Bertagnolli MM, Carnival D, Jaffee EM. Achieving the goals of the Cancer Moonshot requires progress against all cancers. *Cancer Discov*. 2023;13(5):1049-1052. doi:10.1158/2159-8290.cd-23-0344
4. Schuster AL, Crossnohere NL, Bachini M, et al. Priorities to promote participant engagement in the participant engagement and cancer genome sequencing (PE-CGS) network. *Cancer Epidemiol Biomarkers Prev*. 2023;32(4):487-495. doi:10.1158/1055-9965.epi-22-0356
5. Bertagnolli MM, Blanke CD, Curran WJ, et al. What happened to the US cancer cooperative groups? A status update ten years after the Institute of Medicine report. *Cancer*. 2020;126(23):5022-5029. doi:10.1002/cncr.33209
6. National Cancer Institute. NCTN: NCI's National Clinical Trials Network; 2023. Accessed November 20, 2023. https://www.cancer.gov/research/infrastructure/clinical-trials/nctn
7. National Center for Advancing Translational Sciences. Current RDCRN Consortia. Accessed on November 20, 2023. https://ncats.nih.gov/research/research-activities/rdcrn/consortia
8. Chrischilles EA, Friedman S, Ritzwoller DP, Selby JV. Patients, data, and progress in cancer care. *Lancet Oncol*. 2017;18(11):e624-e625. doi:10.1016/s1470-2045(17)30796-9
9. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3(10):1335-1342. doi:10.1001/jamaoncol.2017.0589
10. Chauhan A, Kohn E, Del Rivero J. Neuroendocrine tumors-less well known, often misunderstood, and rapidly growing in incidence. *JAMA Oncol*. 2020;6(1):21-22. doi:10.1001/jamaoncol.2019.4568
11. Castillón JC, Gordoa TA, Bayonas AC, et al. SEOM-GETNE clinical guidelines for the diagnosis and treatment of gastroenteropancreatic and bronchial neuroendocrine neoplasms (NENs) (2022). *Clin Transl Oncol*. 2023;25(9):2692-2706. doi:10.1007/s12094-023-03205-6
12. de Hosson LD, van Veenendaal L, Schuller Y, et al. Clinical benefit of systemic treatment in patients with advanced pancreatic and gastrointestinal neuroendocrine tumours according to ESMO-MCBS and ASCO framework. *Ann Oncol*. 2017;28(12):3022-3027. doi:10.1093/annonc/mdx547
13. Kaderli RM, Spanjol M, Kollár A, et al. Therapeutic options for neuroendocrine tumors: a systematic review and network meta-analysis. *JAMA Oncol*. 2019;5(4):480-489. doi:10.1001/jamaoncol.2018.6720
14. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376. doi:10.1093/jnci/85.5.365
15. Davies AH, Larsson G, Ardill J, et al. Development of a disease-specific quality of life questionnaire module for patients with gastrointestinal neuroendocrine tumours. *Eur J Cancer*. 2006;42(4):477-484. doi:10.1016/j.ejca.2005.10.025
16. Yadegarfar G, Friend L, Jones L, et al. Validation of the EORTC QLQ-GINET21 questionnaire for assessing quality of life of patients with

gastrointestinal neuroendocrine tumours. *Br J Cancer*. 2013;108(2):301-310. doi:10.1038/bjc.2012.560
17. Del Vecchio NJ, McDowell BD, Carter KD, et al. Relationships between health literacy, having a cancer care coordinator, and long-term health-related quality of life among cancer survivors. *Support Care Cancer*. 2021;29(12):7913-7924. doi:10.1007/s00520-021-06356-w
18. Fortin M, Almirall J, Nicholson K. Development of a research tool to document self-reported chronic conditions in primary care. *J Comorb*. 2017;7(1):117-123. doi:10.15256/joc.2017.7.122
19. Weeks JC, Cook EF, O'Day SJ, et al. Relationship between cancer patients' predictions of prognosis and their treatment preferences. *JAMA*. 1998;279(21):1709-1714. doi:10.1001/jama.279.21.1709
20. Hawley ST, Griggs JJ, Hamilton AS, et al. Decision involvement and receipt of mastectomy among racially and ethnically diverse breast cancer patients. *J Natl Cancer Inst*. 2009;101(19):1337-1347. doi:10.1093/jnci/djp271
21. Degner LF, Sloan JA, Venkatesh P. The Control Preferences Scale. *Can J Nurs Res*. 1997;29(3):21-43.
22. Powe BD. Fatalism among elderly African Americans. Effects on colorectal cancer screening. *Cancer Nurs*. 1995;18(5):385-392. doi:10.1097/00002820-199510000-00008
23. Ayanian JZ, Zaslavsky AM, Arora NK, et al. Patients' experiences with care for lung cancer and colorectal cancer: findings from the Cancer Care Outcomes Research and Surveillance Consortium. *J Clin Oncol*. 2010;28(27):4154-4161. doi:10.1200/jco.2009.27.3268
24. Patient-Centered Outcomes Research Institute. Engagement Rubric for Applicants. Accessed November 20, 2023. https://www.pcori.org/sites/default/files/Engagement-Rubric.pdf
25. Hallet J, Davis LE, Mahar AL, et al. Patterns of symptoms burden in neuroendocrine tumors: a population-based analysis of prospective patient-reported outcomes. *Oncologist*. 2019;24(10):1384-1394. doi:10.1634/theoncologist.2019-0112
26. Lavery JA, Lepisto EM, Brown S, et al. A scalable quality assurance process for curating oncology electronic health records: the Project GENIE Biopharma Collaborative approach. *JCO Clin Cancer Inform*. 2022;6:e2100105. doi:10.1200/cci.21.00105
27. Patient-Centered Outcomes Research Institute. PCORnet Research. Accessed November 20, 2023. https://pcornet.org/research/

How to cite this article: O'Rorke M, Chrischilles E. Making progress against rare cancers: a case study on neuroendocrine tumors. *Cancer*. 2024;1-7. doi:10.1002/cncr.35184