Living With Neuroendocrine Tumors: Assessment of Quality of Life Through a Mobile Application

Jared R. Adams, MD, PhD[1]; David Ray, PharmD, MBA, MPH[2]; Renee Willmon, MSc[1]; Sonia Pulgar, MPH[3]; and Arvind Dasari, MD, MS[4]

PURPOSE To understand the quality of life (QoL) for patients with neuroendocrine tumors (NETs) through comparison of QoL questionnaires and symptom tracking as well as journaling via the Carcinoid NETs Health Storylines mobile application (app).

PATIENTS AND METHODS This was a 12-week prospective, observational study of US patients with NET who were taking long-acting somatostatin analogs. National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS) and European Organisation for Research and Treatment of Cancer (EORTC) questionnaires were administered three times. Patients also monitored symptoms, mood, bowel movements, food, activity, and sleep, and they journaled in their app, which was coded by theme and sentiment for qualitative analysis.

RESULTS Of the 120 patients with NET, 78% were women (mean age, 57 years); 76% had gastro-enteropancreatic NETs, and 88% had metastases. Lanreotide depot and octreotide long-acting release (LAR) were used by 41% and 59%, respectively. The most common symptoms at baseline were fatigue (76.7%), diarrhea (62.5%), abdominal discomfort (64.1%), and trouble sleeping (57.5%). The majority completed five of six survey assessments (median, 5; mean, 5.1) and tracked four symptoms in the app (median, 4; mean, 5.5); the average frequency was 41.6 days for each symptom (median, 43; mean, 41.6; range, 1 to 84 days [12 weeks]). Without treatment change, most EORTC-assessed physical symptoms decreased from baseline to midpoint (eg, 59.3% at baseline v 33% at midpoint reported "quite a bit" or "very much" diarrhea; P = .002). App-based symptom tracking revealed large day-to-day variation, but weekly averages correlated well with survey scores. Journal entries showed that more patients made predominantly negative unsolicited entries about their injection experience with octreotide LAR compared with lanreotide (13 of 17 v two of 13; P < .001).

CONCLUSION Patients with NET experience a large symptom burden that varies daily. A decrease in physical symptoms on QoL surveys suggests an effect from daily app-based monitoring or journaling, which may reduce recall bias and benefit the patient's experience of symptoms.

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of solid tumors that can greatly affect health-related quality of life (HRQoL) through symptoms associated with tumor burden and excess hormone production. Although commonly reported symptoms include flushing and diarrhea, the true impact on HRQoL can be far reaching.[1-4]

Patient-reported outcome (PRO) instruments evolved in the era of pen and paper to enable investigators to report the impact of disease on patients and have been recognized for their increasingly important role in drug development to evaluate treatment efficacy and patients' HRQoL.[5] Traditionally, PRO data has been collected through recall-based paper surveys[6-13]; however, this methodology suffers from several limitations that range from the cumbersome tasks of manual data collection and processing to biased data related to the limitations of human memory.[14,15]

Electronic means of collecting PRO data have been investigated to evaluate their equivalence to paper.[16] However, the data collection capabilities of ubiquitous smartphones have eclipsed the utility of traditional pen and paper HRQoL questionnaires at variable follow-up time points, and the concept of "bring your own device" increasingly is used to conduct direct-to-patient research studies.[17] With the ability to journal about a patient's lived experience, in the moment, in the context in which it is experienced, application (app)-based HRQoL instruments have the capability to capture much finer granular details and may reveal

CONTEXT

Key Objective

Generate new knowledge about quality of life (QoL) in neuroendocrine tumor when assessed through mobile application versus standard QoL questionnaires.

Knowledge Generated

The act of documenting symptoms daily, facilitated by a mobile app, may alter responses to validated QoL instruments in the absence of any other intervention. In this study, the reported impact of symptoms decreased over time. Unstructured qualitative data can reveal insights into group differences not picked up by quantitative QoL instruments alone.

Relevance

Mobile apps offer a new way to understand longitudinal QoL experiences that may benefit clinical care as well as research methodology.

limitations in existing validated instruments. The aim of this study was to understand the HRQoL of patients with NETs through validated instruments—such as the PROMIS-29, the European Organisation for Research and Treatment of Cancer (EORTC) 30-question QoL questionnaire (QLQ-c30), and GI.NET21—as well as through daily symptom tracking and patient journaling via the Carcinoid NETs Health Storylines mobile app, developed in collaboration between Self Care Catalysts and the Carcinoid Cancer Foundation.

PATIENTS AND METHODS

This was a prospective, observational study conducted in the United States with English-speaking patients age 18 and older who were diagnosed with NETs and being treated with a somatostatin analog (SSA; ie, octreotide long-acting release [LAR] or lanreotide depot) during the course of 12 weeks. Patients brought their own devices, although owning a smart device and technologic familiarity were not

part of the inclusion/exclusion criteria, and the app could be accessed via Web site browser as well. Patients were surveyed at baseline, week 6, and week 12 with the PROMIS-29 profile v2.0[18] and at baseline, week 4, and week 8 with a subset of the EORTC QLQ-c30 and QLQ-GI.NET21[19,20] single-item symptom questions (Fig 1; Data Supplement) that were selected to explore symptoms relevant to NET but minimize the administrative burden on respondents. The PROMIS-29 defines seven HRQoL subdomains (physical functioning, participation in social roles, anxiety, depression, fatigue, pain interference and sleep disturbance) that are based on four 5-point Likert-style questions per domain (and one additional question on pain intensity). The PROMIS assessment of psychological impact, positive and negative, also was administered to provide an additional dimension to the HRQoL results. Raw PROMIS scores were normalized against a representative sample from the general population and scaled to 100, in which 50 represented the general population average and
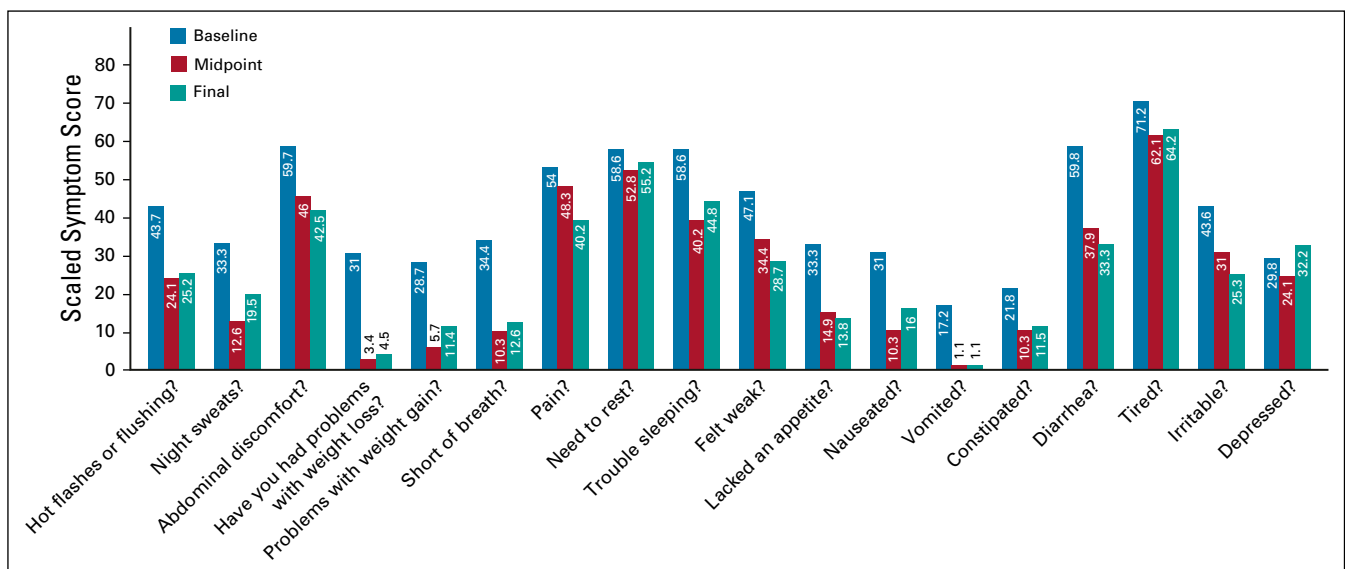

FIG 1. Quality of Life Questionnaire - Neuroendocrine Carcinoid Module (QLQ-GI.NET21) physical symptom scores at baseline, 4-week, and 8-week time points.

every 10-point difference reflected one standard deviation. The EORTC QLQ-C30 is a validated questionnaire that consists of questions with a 4-point Likert scale (from "not at all" to "very much"). A subset of EORTC QLQ-C30 questions specific to symptoms and global HRQoL was combined with symptom items from the disease-specific module created specifically for NETs (Quality of Life Questionnaire - Neuroendocrine Carcinoid Module [QLQ-GI.NET21]).

Institutional review board approval was obtained from Salus (Austin, TX), and all participants signed an informed consent document. Surveys were administered through the Carcinoid Health Storylines mobile application. Carcinoid Health Storylines is a customized version of the care management app Health Storylines designed to specifically support patients with carcinoid tumors. Users can download the app for free on mobile devices (both Android and Apple) or access the program through a Web site portal. Surveys were administered through the app only to consented patients, and only their data were analyzed. Patients also reported on their condition using tools embedded in the Carcinoid Health Storylines mobile application to collect regular and timely data about symptom burden and HRQoL. Data collected included medications, symptoms, mood, free-text journaling, stools, vitals, activity and sleep-tracking data from wearables, as available. Frequency and severity of symptoms were captured through patient report on 5 or more days per week. Severity was captured on a 0 to 10 visual analog scale each time a symptom was documented (0, not currently present). Data captured from the patients' qualitative journaling allowed identification of additional themes that affect patients with NETs.

Descriptive statistics were used when appropriate. The convergent validity of single-item in-app symptom trackers, EORTC single-item scales, and PROMIS-29 scales was assessed using Pearson correlation coefficient tests. Group differences were examined using the t test, the Mann-Whitney U test, and the χ^2 test, as appropriate. App scores were averaged to create weekly summary scores per symptom reflective of the recall time period assessed by EORTC and PROMIS-29 (the week before assessment) with changes over time, and the effect of sociodemographic variables was assessed using repeated measures analysis of covariance.

In the exploratory qualitative analysis, journal entries written by patients in the "thoughts on my therapy" field of the Health Storylines treatment reflections tool were analyzed. Journal entries were stripped of the treatment group identifier before they were coded to identify the themes discussed. Coding was conducted independently by authors J.A. and R.W. and was reconciled through discussion to confirm and revise the emergent coding structure. Journal entries related to injection experience were assessed more to evaluate the emotional quality of patient experiences. Individual responses were assigned a score

between 1 and 5, for which 1 was negative and 5 was positive. Patient-adjusted mean scores of emotional quality were compared between treatment groups using a t test. All statistical analyses were performed using SPSS (SPSS, Chicago, IL).

RESULTS

Overall, 120 patients who received SSAs were recruited for the study; 82 patients completed all assessments. Most patients were women (n = 95; 79%), and most had a GI primary tumor (n = 73; 61%; Table 1). Lanreotide users accounted for 41% of the study population; octreotide LAR users, 59%. The mean length of diagnosis was 5.9 years; 59% and 51% started the SSAs lanreotide and octreotide, respectively, within the past 2 years. The sample was largely white, married, and educated; 55% held a college degree. The mean (standard deviation) age was 56 years (9 years).

PROMIS-29 Results

The PROMIS-29 HRQoL domains, which are related to more abstract social and psychological constructs than the EORTC domains are, did not vary significantly across all three surveyed time points (Fig 2; Data Supplement). HRQoL, as measured by the PROMIS-29, found that patients had worse scores by one half to one full standard deviation compared with the general population across all measured domains (Fig 2). When raw responses on the more extreme end of the scale (4 or 5 on the PROMIS questions' 5-point Likert response scale) were assessed, PROMIS questions revealed that a sizeable minority struggled with depression (17.7%), anxiety (24.2%), fatigue (58.8%), insomnia (34.9%), and dissatisfaction with social role (47%). However, a high percentage of patients reported their lives as meaningful (72.3%).

EORTC Results

The most common baseline symptoms experienced "quite a bit" or "very much" reported on the EORTC were fatigue (76.7%), diarrhea (62.5%), abdominal discomfort (64.1%), and trouble sleeping (57.5%). The baseline scores often were higher before they decreased and stabilized across symptoms at the 4- and 8-week time points (Fig 1). Similar patterns were observed for all physical symptoms assessed by the EORTC; reports of depression remained stable during the course of the study.

Carcinoid Health Storylines

Of the 120 patients recruited, 105 patients (88%) recorded at least one or more symptoms in the mobile app (Data Supplement). Pain of any kind was reported by every patient who used the symptom tracker at some point during the study. Of the 105 patients who reported symptoms, diarrhea (n = 67; 64%), fatigue (n = 52; 50%), and flushing (n = 44; 42%) were most commonly tracked in the app (Appendix Fig A1). This was a similar percentage to those who experienced diarrhea (63%) and flushing (42%) "quite

TABLE 1. Baseline Demographics

| | Total Population | | SSA Treatment | | | |
| | | | Octreotide LAR | | Lanreotide | |
Demographic	No.	%	No.	%	No.	%
No. of patients	120		71		49	
Mean (SD) age, years	56.3 (9.3)		56.5 (9.3)		56.1 (12.6)	
Mean (SD) time since diagnosis, years	5.9 (5.9)		5.1 (4.5)		5.9 (5.3)	
Female sex	95	79	57	80	38	78
Tumor site						
GI	73	61	42	60	31	63
Pancreatic	21	18	11	16	10	20
Lung	9	7	7	10	2	4
Other	5	4	0	0	0	0
Metastatic	105	88	63	90	42	86
Brain involvement	1	1	1	1	0	0
Previous chemotherapy treatment	35	29	19	19	16	33
Surgical treatment	109	91	63	89	46	94
Married	89	74	51	73	38	78
Employed	80	67	41	59	25	51
Race/ethnicity						
White	107	89	63	90	44	90
Black	5	4	3	4	2	4
Asian	2	2	1	1	1	2
Hispanic	6	5	4	6	2	4
College degree	66	55	40	57	26	53
Household income > $50,000	79	66	47	67	32	65

Abbreviations: LAR, long-acting release; SD, standard deviation; SSA, somatostatin analog.

a bit" or "very much" on the baseline EORTC, but fatigue tracking was lower than those who reported feeling "tired" (77%) on the EORTC survey (Data Supplement).

Daily Variation Compared With Weekly Scores

Large daily variation in the experience (or absence) of any given physical symptom was typical of most individuals. Figure 3 shows one individual's example of daily variation in symptom tracking for diarrhea mapped against the EORTC scaled scores for diarrhea. However, when symptom tracker scores were averaged for a week and matched against the recall period for the PROMIS and EORTC, all three symptom subdomain scales correlated well with each other ($R > 0.8$; Fig 4).

Connection Between App-Reported Daily Symptoms, PROMIS, and EORTC Scores

There was a high degree of symptom interconnectedness, with significant correlation between the average daily intensity of diarrhea (captured in the app during PROMIS questionnaire recall periods) and anxiety ($r = 0.32$; $P = .02$), depression ($r = 0.4$; $P = .003$), satisfaction with role ($r = -0.44$; $P = .001$), pain interference with daily living

($r = 0.39$; $P = .005$), and fatigue ($r = 0.49$; $P < .001$) measurements on PROMIS-29. Multiple regression indicated that three PROMIS domains explained 50% of the variance in (EORTC) global QoL ($R^2 = .502$; $F(3,116) = 38.9$; $P < .001$): satisfaction with social role ($\beta = 0.26$; $P < .001$), fatigue ($\beta = -0.43$; $P < .001$), and pain interference ($\beta = -0.19$; $P = .03$; Data Supplement).

Qualitative Insights

We also conducted an exploratory qualitative analysis of patient's open-ended health journals. Among the 120 patients, 69 patients journaled about their therapy within the mobile app in 1,399 entries (responses per patient: mean, 20.3; median, six). Treatment effectiveness, adverse effects, and injection experience were the most common qualitative themes touched on at least once by patients (Data Supplement). The assessment of the emotional quality of journal entries on treatment experience indicated a more negative experience with octreotide than with lanreotide (2.1 [95% CI, 1.9 to 2.3] v 3.0 [95% CI, 2.5 to 3.5]; $P < .001$; Table 2). The negative association with octreotide relative to lanreotide also was reflected in the distribution of patients who journaled about the injection
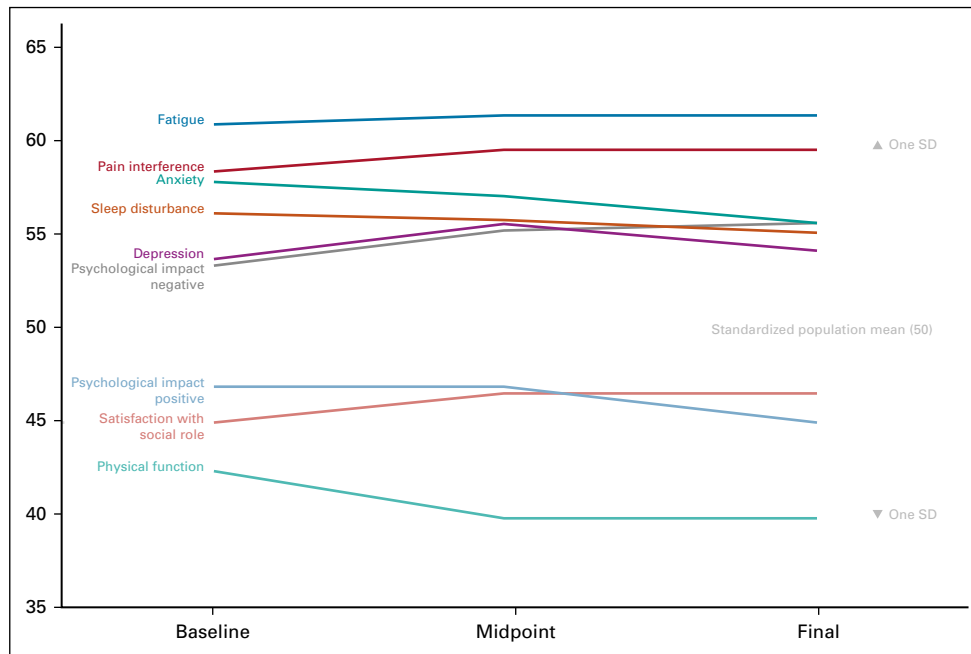
FIG 2. Patient-Reported Outcomes Measurement Information System (PROMIS) quality-of-life domains at baseline, 6-week, and 12-week time points normalized against the general population. SD, standard deviation.

experience: 13 of 17 patients who used octreotide had a mean emotional quality score worse than 2.5 compared with only two of 13 who used lanreotide. Unsolicited octreotide verbatims included "sometimes it is so sore that I cannot lie on that side for a week," "injection site remains painful for too many days," "Today I received my shot in one injection. Hurrah! My worse [sic] experience was 6 attempts, usually it takes 3-4 attempts," and "I wish there was more consistency in the administration of the shots." Conversely, "The injection needle for lanreotide hurts a lot" was the most negative example for lanreotide.

DISCUSSION

This 3-month prospective observational study demonstrated that patients with NETs suffer from daily symptoms that significantly affect their HRQoL, although the intensity of their symptoms can vary greatly from day to day. The most common symptoms at baseline in our study were fatigue, diarrhea, abdominal discomfort, and trouble sleeping. In a recent principal component analysis of the ELECT (Evaluating Lanreotide Efficacy and Safety as a Carcinoid-Syndrome Treatment) study data, diarrhea, flushing, and QLQ-C30 summary score domains accounted for nearly half of the variation in baseline symptom variables.[21] We also found a significant correlation between the intensity of diarrhea logged in the app and decreased mental health. Similarly, Beaumont et al[22] concluded from PROMIS-29 data that incremental improvements in symptom control, especially for flushing and diarrhea, may lead to significant improvements in overall HRQoL. The baseline PROMIS-29 assessment revealed that a large proportion of patients endorsed depression, anxiety,

fatigue, dissatisfaction with social role, difficulty with physical functioning, and insomnia compared with the general population. Despite this, few clinical trials in NETs have assessed HRQoL in a rigorous way, if at all.[23] Although physicians may be concerned primarily with the progression-free survival benefits of treating NETs,[24] these symptomatic improvements may matter greatly to patients.

Other solid tumors, including prostate cancer, colorectal cancer, non–small-cell lung cancer, and breast cancer, have found PROMIS pain interference (52.4), fatigue (52.2), and physical function (44.1) significantly worse than the general population within 13 months of diagnosis.[25] Patients with lung cancer reported the highest symptom burden (pain interference, 55.5; fatigue, 57.3; depression, 51.4), and patients younger than age 65 years reported greater sleep disturbance, anxiety, and depression than did older patients with cancer.[25] The relatively young age of patients with carcinoid NETs may explain in part the higher psychosocial burden of living with the disease compared with reference PROMIS populations,[26,27] and it may explain the longer duration of diagnosis. However, the moderate correlation between the PROMIS domains with EORTC symptoms likely represents the multidimensionality of patients' experiences of NET, which included patients with carcinoid syndrome and noncarcinoid syndrome NETs. By administering the PROMIS-29 instrument and tracking tools, and by offering patients an opportunity to journal freely about their experience and QoL, this study captured a broader picture of QoL experienced by patients with NETs, including information about injection experiences, daily symptoms, and thoughts
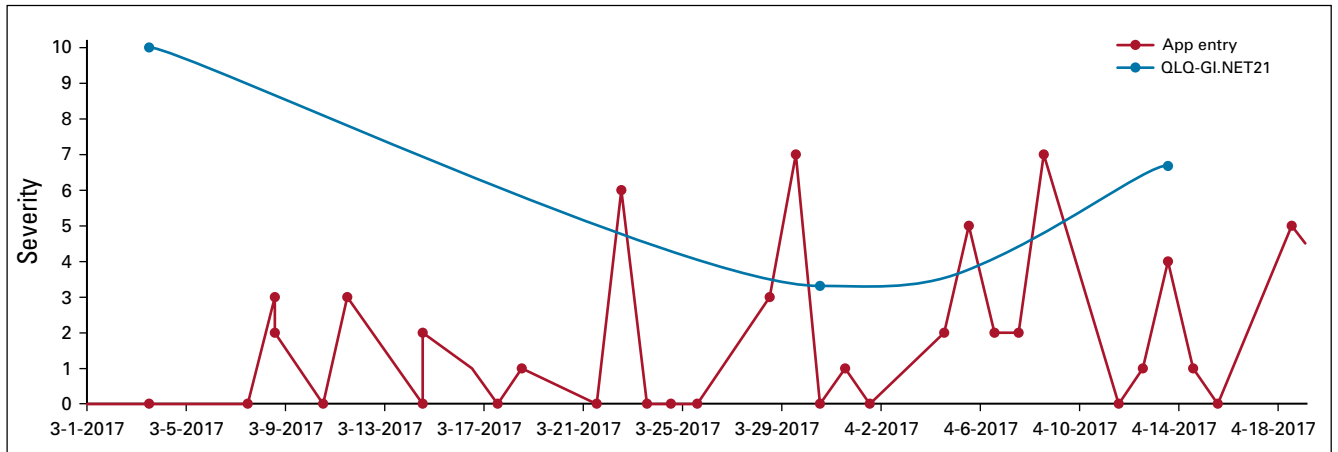
FIG 3. Comparison of diarrhea severity tracked by a single patient in the Health Storylines app and their Quality of Life Questionnaire - Neuroendocrine Carcinoid Module (QLQ-GI.NET21) diarrhea score (scaled to 10).

on therapy that cannot be captured in general HRQoL measures.

Given the importance of overall QoL to a meaningful life with NET, other studies recently have tried to gain a more nuanced understanding of the patient experience in neuroendocrine cancer by conducting individual interviews. This approach is limited by small sample sizes and is time and resource intensive. For example, Gelhorn et al[28] conducted individual interviews and administered validated HRQoL surveys among participants in a phase II clinical trial of telotristat ethyl (a drug intended to treat diarrhea associated with carcinoid syndrome inadequately controlled by SSA therapy). Although the interviews enabled researchers to capture the first-hand experience of patients and identify important changes in symptom experience during the course of a clinical trial, the study was limited by small sample size (n = 11) and restricted geography.[28] Potential advantages of using a mobile app such as Health Storylines to collect such data are the ability to reach larger populations of patients more quickly and the ability to collect real-time qualitative and quantitative data without geographic restrictions.
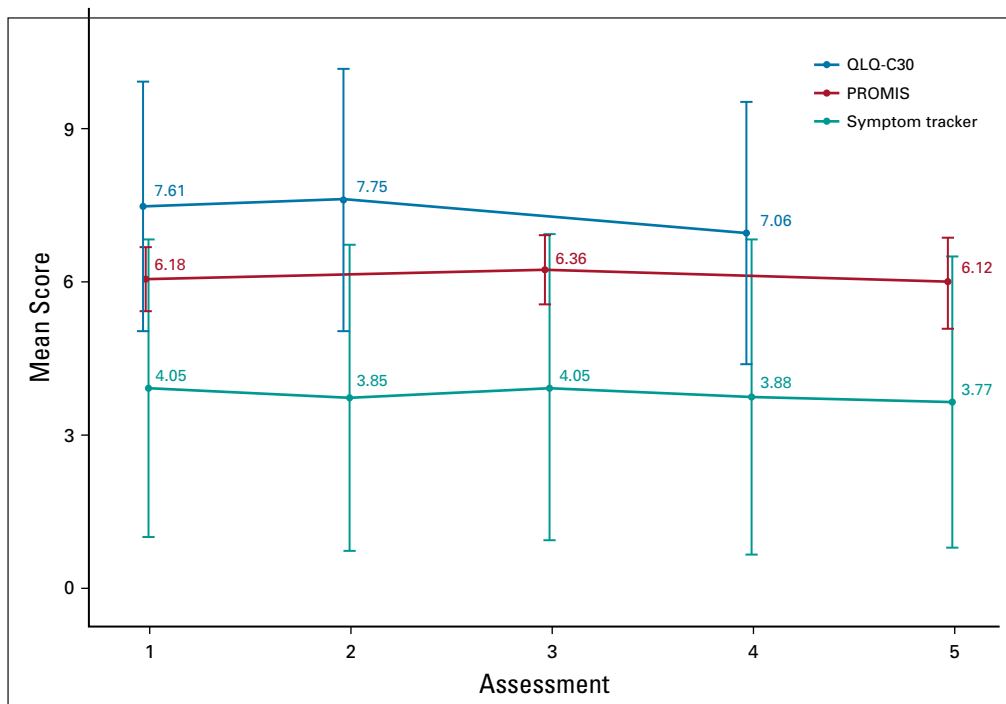

FIG 4. Comparison of fatigue severity measured by the quality of life questionnaire C30 (QLQ-C30; blue), Patient-Reported Outcomes Measurement Information System (PROMIS-29; red), and Health Storylines symptom tracker averaged over the corresponding week (teal).

TABLE 2. Emotional Quality of Injection Experience Journal Entries

Responding Group or Variable by Journal Entry	No. (%)		Total No.
	Octreotide LAR	Lanreotide	
Responses to "thoughts on my therapy"			
Patients	41 (59)	28 (41)	69
Unique responses	1,018 (73)	381 (27)	1,399
Median responses/patient	9	5	6
Mean responses/patient	24.83	14	20.28
Unsolicited comments about injection experience			
Patients	17 (57)	13 (43)	30
Unique responses	102 (73)	37 (27)	139
Emotional quality of injection experience*			
Mean (SD)†	2.13 (0.43)	3.03 (0.88)	2.52
SD	0.43	0.88	0.79

Abbreviations: LAR, long-acting release; SD, standard deviation.

*Quality ratings are as follows: 1, negative; 2, somewhat negative; 3, neutral; 4, somewhat positive; and 5, positive.

†Difference between means: $P < .001$.

The platform also has clinical utility through printable patient reports and health feeds for family and caregivers as well as a physician dashboard for remote patient monitoring—an increasingly important method to improve follow-up care in cancer to detect early adverse events or symptom exacerbation that may lead to hospitalization or emergency department visits.[29] Workflow integration, data silos, and liability concerns represent large barriers to adoption of new technology for data sharing between patients and physicians, but solutions are becoming more viable as proposed requirements under the 21st Century Cures Act: Interoperability, Information Blocking, and ONC Health IT Certification Program (Docket: HHS-ONC-2019-0002-0001, 45 C.F.R. § 170 2019) (and related CMS incentive programs) mandate that EMRs make health data accessible to patients, registries, and third-party solutions, in part through the recently developed FHIR (HL7 Fast Healthcare Interoperability Resources; first draft published in 2014, release 4 submitted to American National Standards Institute as a normative standard in 2019) API data standards to streamline transfer of essential health information.

Our study is important because it introduces a potentially novel method of capturing unique patient experiences through an app that tracks daily symptoms and journals, so it offers a more well-rounded perspective of the patient's cancer journey. For instance, patient journaling offered insights not captured by quantitative QoL metrics and indicated a more favorable injection experience with lanreotide than with octreotide LAR among the small subgroup that spontaneously journaled about the topic. Patients reported more consistent experiences in terms of both pain and duration of efficacy with lanreotide.

Daily symptom logs of patients with NETs revealed a high degree of individual variation in daily symptom experiences.

Patients often reported as many days free of specific symptoms as those with symptoms, and symptom intensity could spike unpredictably. However, weekly symptom tracker averages correlated well with corresponding EORTC and PROMIS-29 subdomain scores, which supported excellent convergent validity. Although both validated PRO instruments delivered a good average overview of patient experiences with carcinoid symptoms, they missed the granular details of the daily ups and downs (Fig 1) and were subject to recall bias. Physical symptoms on the EORTC decreased from baseline despite the lack of an intervention other than the app, which may reflect a potential therapeutic effect of journaling in the app or better alignment of recall because of frequent tracking. Regular tracking may bring a level of mindfulness to thinking about symptoms, and a readily available history on the mobile device may call attention to the abundance of symptom-free days. It is worth mentioning that tracking symptom frequency in the app did not decrease during the course of the study; thus, reported decreases in frequency of symptoms on the EORTC were not reflective of patients neglecting to log their symptoms.

Limitations of this study include cohort recruitment as a convenience sample through a patient advocacy organization (Carcinoid Cancer Foundation), which featured patients with largely stable disease already on long-acting SSA treatment. (As a requirement, though, median treatment duration was less than 2 years.) The sample, therefore, was more likely to include patients highly engaged and educated about the disease. A little more than half of patients had college degrees, and all had a smartphone (although that was not technically required because the service could be accessed through the Web site as well). Use of an app required a modicum of tech literacy

(and some patients required more extensive onboarding than others).

This study demonstrates the promise of incorporation of multiple tools into a single mobile application to collect multiple types of data that pertain to patients' HRQoL, and this approach minimized the burden of trial data collection mechanisms on patients. Apps such as Carcinoid Health Storylines also offer an opportunity to measure health outcomes that are meaningful to patients through the use of open text fields that approximate the unstructured data capture afforded through focus groups or patient interviews. The value of this approach was demonstrated through the unsolicited patient comments about the experience of their drug injection process, which found differences in the consistency of the experience between SSAs and offered valuable insight into the daily patient experience not usually captured in traditional questionnaires. This enables investigators to incorporate novel feedback and patient needs into the design of future studies.

In conclusion, patients with NET experienced a significant symptom burden (most commonly pain, diarrhea, fatigue, and flushing) that had a negative impact on their mental, physical, and social QoL and well-being. The results suggest that the use of tracking apps can complement validated HRQoL and symptom questionnaires and may be an improvement because of reduced recall bias and granular detail into the daily lived experience. Apps such as Carcinoid Health Storylines may help monitor disease and should be investigated more as an important addition to most clinical trials and the therapeutic treatment paradigm.

AFFILIATIONS
[1]Self Care Catalysts, Toronto, Ontario, Canada
[2]Ipsen Biopharmaceuticals, Basking Ridge, NJ
[3]Seattle Genetics, Bothell, WA
[4]MD Anderson Cancer Center, Houston, TX

CORRESPONDING AUTHOR
Jared R. Adams, MD, PhD, Self Care Catalysts, 250 University Ave, Unit 231, Toronto, Ontario, Canada M5H 3E5; e-mail: jared@selfcarecatalysts.com.

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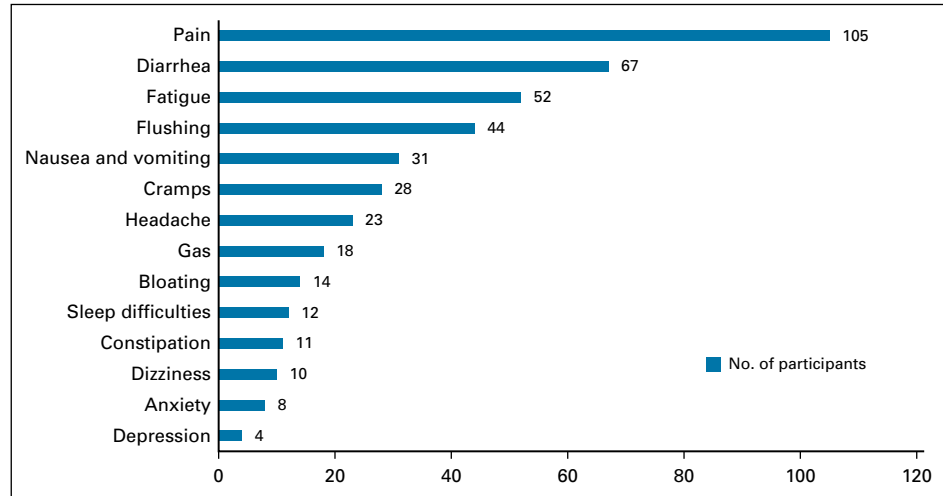
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APPENDIX

FIG A1. Number of participants who tracked symptoms in the Carcinoid NETs Health Storylines app.