# Evaluating the Content Validity, Clarity, and Relevance of Two Patient-Reported Outcomes for Use With Adults With *EGFR*-Mutated NSCLC

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## ABSTRACT

**Introduction:** NSCLCs account for most lung cancers; approximately 30% involve a mutation in the *EGFR* gene. This study sought to identify one or more patient-reported outcome (PRO) measures relevant for use in clinical trials to assess symptoms and health-related quality of life in this population.

**Methods:** Patients with NSCLC from the United States, Europe, and Asia and including those with an exon 20 insertion mutation and other *EGFR* mutations participated in a combination of concept elicitation and cognitive debriefing interviews to report symptoms and impacts of their NSCLC and provide feedback on the clarity and relevance of several PRO measures.

**Results:** A total of 30 individuals participated (mean age = 57 years, 87% female, 80% white). The most often reported symptoms included fatigue, shortness of breath, cough, and weight loss. Individuals with the exon 20 insertion mutation (n = 21) more frequently reported negative impacts on daily life, physical functioning, and social functioning but less frequently reported negative impacts to emotional functioning. The PROMIS Short-Form version 2.0—Physical Function 8c and the NSCLC Symptom Assessment Questionnaire were deemed clear, relevant, and easy to complete. The concepts identified during the concept elicitation portion of the interviews were mapped to the content of each PRO, and all items within both PROs were endorsed by at least 20% of the participants.

**Conclusions:** These results support the content validity, clarity, and relevance of the PROMIS Short-Form version 2.0—Physical Function 8c and the NSCLC Symptom Assessment Questionnaire in a population with *EGFR*-mutated NSCLC. Both would be appropriate for inclusion in future studies.

## Introduction

Lung cancer is the most often diagnosed cancer worldwide (11.6% of total cases) and the leading cause of cancer death (18.4% of total cancer deaths).[1-3] NSCLC accounts for 85% of lung cancers.[1] Approximately 30% of these involve a mutation in the *EGFR* gene,[4] with 9% to 11% of these involving the specific exon 20 insertion (exon 20ins) mutation.[5,6] The population of those with the exon 20ins mutation represents a small portion of all NSCLCs and is not well characterized, and patient-reported outcomes (PROs) have not been well investigated.[7] Currently, there is no approved targeted therapy in this population, but new treatments are in development.[8,9] Therefore, there is a need to understand what health-related quality of life (HRQoL) aspects are most relevant to patients and the availability of relevant PRO instruments.

Patients with NSCLC often experience symptoms, such as pain, fatigue, and dyspnea,[1,10] and many have respiratory comorbidities, including comorbid hepatitis B and C, diabetes, and chronic renal insufficiency.[11] Symptoms associated with NSCLC can impose substantial detriments to physical functioning and HRQoL, as can treatment.[10,12,13] Similar impacts have been reported for patients with the exon 20ins mutation within the limited existing evidence: disease-related symptoms of fatigue, pain, and shortness of breath are detrimental to HRQoL and negatively affect daily activities, self-care, social activities, and work.[7] The use of PRO measures in clinical trials and clinical practice is increasing,[14-16] and a variety of PRO measures are available for use in a lung cancer population,[12] which can help reveal more on the experience of these patients.

When planning trials in patients with NSCLC characterized by *EGFR* mutations, we sought to identify one or more PRO measures that would be relevant to this population. Specifically, qualitative research (i.e., interviews) was conducted with adults with *EGFR*-mutated NSCLC to evaluate two specific PRO measures, the PROMIS Short-Form version 2.0—Physical Function 8c (PROMIS-PF-8c)[17] and the NSCLC Symptom Assessment Questionnaire (NSCLC-SAQ),[18-20] to confirm the PRO measures' content validity and ensure that they are clear, relevant, and appropriate for use in this population.

## Materials and Methods

### Site and Participant Recruitment

Patient survey participants were recruited by (1) the exon 20 group, https://exon20group.org, a multistakeholder, pan-tumor international coalition devoted to converting EGFR exon 20ins and HER2 exon 20ins into manageable diseases (a project of the International Cancer Advocacy Network, https://askican.org/) and (2)

the EGFR Resisters, a lung cancer patient advocacy group of EGFR-mutated survivors and care partners (https://egfrcancer.org/). These advocacy groups recruited patients through targeted online announcements and e-mail communications to their respective memberships. Participants were identified from the United States of America (USA), Europe, and Asia.

Eligible and interested patients were provided with an informed consent form to review; when feasible, the treating oncologist completed a clinical case report form, otherwise it was self-administered by the patient. To be considered for inclusion, individuals were required to be at least 18 years of age; have a confirmed diagnosis of locally advanced or metastatic (either a systemic recurrence after previous surgery for early stage disease or a newly diagnosed stage IIIB or IV disease) NSCLC not amenable to curative surgery or radiotherapy; have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; be able to speak, read, and write in English; provide consent; and be willing to take part in an audiotaped Zoom interview lasting approximately 60 minutes. Individuals with a medical or psychiatric condition or who were receiving treatment for a condition that results in a cognitive or other (visual, hearing) impairment that would interfere with participating in the study were excluded. Although not part of the eligibility criteria, the goal was to enroll as many patients with the exon 20ins mutation as possible. The study protocol, interview guide, informed consent, and supporting documents were reviewed and approved by the Copernicus Group institutional review board (Cary, NC).

### Concept Elicitation and Cognitive Debriefing Interviews

A single interview was conducted by means of Zoom with each participant. The interview consisted of the following two parts: it started with concept elicitation (CE) questions followed by a cognitive debriefing (CD) portion. A semistructured interview guide, developed specifically for this study, was used to facilitate the interview. The guide contained CE questions on symptoms and impacts and CD questions to obtain feedback on the clarity and relevance of several PRO measures, including the NSCLC-SAQ, PROMIS-PF-8c, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), and 5-Level EuroQoL-5 Dimension. The NSCLC-SAQ was developed in accordance with the U.S. Food and Drug Administration PRO Guidance[21] and contains seven items that evaluate cough, pain, dyspnea, fatigue, and poor appetite in a 7-day recall period.[18] The EORTC-QLC-C30 is a 30-item tool that evaluates functioning

and common cancer symptoms with recall in the past week.[22] The PROMIS-PF-8c has six items that evaluate physical ability, including walking and climbing stairs, with a 7-day recall period.[17]

Most questions in the debriefing pertained to the NSCLS-SAQ and the PROMIS-PF-8c. Examples of CE questions included the following: "What is it like to live with NSCLC?" and "What symptoms, if any, have you ever experienced as a result of NSCLC? Can you describe each of these symptoms? How, if at all, do these symptoms impact your ability to do your daily activities? Which one symptom would you say is the most difficult to manage?" Examples of CD questions included the following: "Are these questions and response options clear or unclear to you? Are these questions relevant to someone with NSCLC?" and "Now, please look at the fourth question (go up and down stairs at a normal pace). What does 'go up and down stairs at a normal pace' mean to you? How would you respond to this question? Why did you give this response? Is this question clear or unclear? Why?" During the CD portion, the interviewer was able to share his or her screen to display the PROs, so the participant could complete the questionnaires in real time while answering questions on each item.

The interview guide was revised iteratively as interviews were conducted. These revisions were motivated by a desire to add more detailed questions on particular PRO measures, so that the team could consider seeking a PRO label claim with one or more measures. Given the length of the interview, not all questions were asked of all participants. In addition, certain questions were not applicable to all participants (e.g., only those who indicated that symptoms affected daily activities were asked to describe which specific activities), resulting in slightly different denominators when calculating results.

### Analysis

When undertaking qualitative research, it is not possible to use statistical tests to estimate the necessary sample size. Furthermore, with qualitative research, no statistical tests are appropriate to be performed across subgroups. Included individuals should mimic those that will be enrolled in upcoming studies as closely as possible. The intent is to collect information on the concepts that characterize a specific disease or condition and to achieve the point of saturation, defined as the point when little or no new relevant information is provided. Practical guidelines for a sample size calculation are provided in a publication by Turner-Bowker et al.[23] in 2018 and ranged from 13 to 43. All interviews were

recorded and transcribed for analysis purposes. All transcripts were analyzed using VERBI GmbH's MAXQDA (version 2020), a qualitative data analysis software. A coding dictionary was developed and used in the analysis of the transcripts. The codebook was used to organize and categorize concepts of interest from the interviews and included descriptions and examples for each code to ensure consistency across coders. Each transcript was coded by one coder and then reviewed, summarized, and analyzed by a second coder.

A saturation table, which displays the point at which no new concepts are mentioned by subsequent participants, was developed to categorize each symptom mentioned by each participant. Comparisons of participant responses were made between subgroups of interest, specifically those with and without the exon 20ins mutation and USA versus ex-USA participants.

## Results

### Demographic and Clinical Characteristics of Participants

A total of 30 individuals participated; most were female (87%, n = 26 of 30), with a college degree or higher educational level (69%, n = 20 of 29), white (80%, n = 24 of 30), married (60%, n = 18 of 30), and with a household annual income up to $99,999 (53%, n = 16 of 30). A total of 47% were working part- or full-time (n = 14 of 30). The mean age was 57 years of age. Most participants were from the USA (63%, n = 19 of 30).

All but one participant had metastatic NSCLC (97%, n = 29 of 30), 53% (n = 16 of 30) had an ECOG performance score of 1 (restricted activity), whereas the remainder had a score of 0 (fully active) and 70% (n = 21 of 30) had an exon 20ins mutation. Of those with the exon 20ins mutation, six participants also had another mutation (two also had T790M, two also had *ERBB2*, one also had L858R, and one also had S768I and 770D). A total of 63% (n = 19 of 30) had received chemotherapy at some time, of which 42% (n = 8 of 19) were currently receiving chemotherapy. A total of 70% (n = 21 of 30) had ever received other treatments, including erlotinib and osimertinib, of which 90% (n = 19 of 21) were currently receiving. One participant was not currently receiving any treatment. A total of 23% (n = 7 of 30) had undergone a pulmonary lobectomy. Participants had been diagnosed on average 46 months before the interview (median = 41.5 mo), although this average included one patient who had been diagnosed 137 months earlier. Demographic and clinical characteristics of the participants are provided in Table 1.

**Table 1.** Demographic and Clinical Characteristics

| Characteristics | Value (Total, N = 30) |
|---|---|
| Female, n (%) | 26 (87) |
| Age in y, mean ± SD (range) | 57.0 ± 12.0 (25-73) |
| Race and ethnicity, n (%) | |
|   White | 24 (80) |
|   Asian | 4 (13) |
|   Latino Hispanic | 1 (3) |
|   Indian | 1 (3) |
| Country of residence, n (%) | |
|   USA | 19 (63) |
|   Canada | 2 (7) |
|   Germany | 2 (7) |
|   India | 1 (3) |
|   Australia | 1 (3) |
|   Hong Kong | 1 (3) |
|   Finland | 1 (3) |
|   Belgium | 1 (3) |
|   Israel | 1 (3) |
|   Malaysia | 1 (3) |
| Work status, n (%) | |
|   Full-time for pay | 5 (17) |
|   Part-time for pay | 9 (30) |
|   Do not work for pay because of NSCLC | 1 (3) |
|   Do not work for pay, unrelated to NSCLC | 7 (23) |
|   Other (listed as retired) | 8 (27) |
|   Duration of disease in mo, mean ± SD | 46 ± 31 |
| Type of NSCLC, n (%) | |
|   Local | 1 (3) |
|   Metastatic | 29 (97) |
| Activity level—ECOG score,[a] n (%) | |
|   Fully active (0) | 14 (47) |
|   Restricted (1) | 16 (53) |
| Type of EGFR mutation,[b] n (%) | |
|   Exon 20ins | 21 (70) |
|   T790M | 6 (20) |
|     Exon 19del | 5 (17) |
|     L858R | 3 (10) |
|     cMET | 1 (3) |
|     C797S | 0 (0) |
|   Other (ERBB2, RET, S768I, 770D) | 4 (13) |
| Medical treatments, n (%), ever | |
|   Stereotactic radiation therapy | 11 (37); (0 currently receiving) |
|   Radiation therapy | 13 (43); (0 currently receiving) |
|   Chemotherapy[c] | 19 (63); (8/19 currently receiving) |
|   Pembrolizumab (Keytruda)[c] | 6 (20); (1/6 currently receiving) |
|   Other (including TKI)[c] | 21 (70); (19/21 currently receiving) |
|   Other (vitamin C infusion) | 2 (7); (2/2 currently receiving) |
| Surgical procedures, n (%), ever | |
|   Segmental or wedge resection | 3 (10) |
|   Sleeve resection | 0 (0) |

(continued)

**Table 1.** Continued

| Characteristics | Value (Total, N = 30) |
|---|---|
|   Pneumonectomy | 1 (3) |
|   Pulmonary lobectomy | 7 (23) |

[a]ECOG, ECOG performance status developed by the ECOG, grades span from zero (fully active) to five (dead).
[b]Could be more than one mutation.
[c]Could have received more than one treatment.
ECOG, Eastern Cooperative Oncology Group; Exon 19del, exon 19 deletion; Exon 20ins, exon 20 insertion; TKI, tyrosine kinase inhibitor.

### Living With NSCLC

When asked what it is like to live with NSCLC, participants indicated that they were very upset, anxious, and fearful, and some said that they were very surprised by their diagnosis. Some examples include, "you're always wondering when you're going to die, when things are going to get ugly" and "I always feel like I am always scared."

### CE Portion of Combined CE and CD Interviews

Participants were asked to report symptoms they experienced related to NSCLC. The most common symptoms included fatigue (93%, n = 26 of 28), shortness of breath (82%, n = 23 of 28), cough (71%, n = 20 of 28), and weight loss (68%, n = 15 of 22) (Table 2). When comparing the subgroup with the exon 20ins mutation (n = 21 of 30) with those without the exon 20ins mutation (n = 9 of 30), the former had a greater frequency (by at least 10 percentage points) of reported symptoms for shortness of breath, lack of appetite, and difficulty remembering things or concentrating (85%, n = 17 of 20 versus 75%, n = 6 of 8; 24%, n = 5 of 21 versus 11%, n = 1 of 9; and 67%, n = 14 of 21 versus 56%, n = 5 of 9, respectively). Nevertheless, the exon 20ins group reported chest pain less frequently (25%, n = 5 of 20 versus 63%, n = 5 of 8; Table 2). Participants residing in the USA (n = 19 of 30) reported chest pain and headaches with a higher frequency compared with those ex-USA (n = 11 of 30) (47%, n = 8 of 17 versus 18%, n = 2 of 11 and 32%, n = 6 of 19 versus 18%, n = 2 of 11, respectively, data not found). Those who reside outside the USA reported pain in areas of the body other than the chest, cough, and difficulty remembering things or concentrating more frequently compared with those in the USA (64%, n = 7 of 11 versus 53%, n = 10 of 19; 90%, n = 9 of 10 versus 61%, n = 11 of 18; and 73%, n = 8 of 11 versus 58%, n = 11 of 19, respectively, data not found).

Saturation, the point at which no new concepts are mentioned, was reached by the 18th interview overall. Within the subgroups, saturation was achieved by the 15th interview for those with the exon 20ins mutation and by the eighth interview for those without; it was

**Table 2.** Frequency of Symptoms Ever Experienced

| Symptoms | Total Group (N = 30) | With Exon 20 Insertion Mutation (n = 21) | Without Exon 20 Insertion Mutation (n = 9) |
|---|---|---|---|
| Fatigue | 93% (n = 26 of 28) | 95% (n = 19 of 20) | 88% (n = 7 of 8) |
| Shortness of breath | 82% (23 of 28) | 85% (17 of 20) | 75% (6 of 8) |
| Cough | 71% (20 of 28) | 74% (14 of 19) | 67% (6 of 9) |
| Weight loss | 68% (15 of 22) | 67% (12 of 18) | 75% (3 of 4) |
| Difficulty remembering things or concentrating | 63% (19 of 30) | 67% (14 of 21) | 56% (5 of 9) |
| Pain other than chest pain | 57% (17 of 30) | 57% (12 of 21) | 56% (5 of 9) |
| Chest pain | 36% (10 of 28) | 25% (5 of 20) | 63% (5 of 8) |
| Headaches | 27% (8 of 30) | 19% (4 of 21) | 44% (4 of 9) |
| Lack of appetite | 20% (6 of 30) | 24% (5 of 21) | 11% (1 of 9) |
| Weight gain | 13% (4 of 30) | 10% (2 of 21) | 22% (2 of 9) |
| Congestion (head or chest) | 10% (3 of 30) | 14% (3 of 21) | 0% (0 of 9) |
| Hoarseness, throat | 10% (3 of 30) | 14% (3 of 21) | 0% (0 of 9) |
| Weakness | 10% (3 of 30) | 10% (2 of 21) | 11% (1 of 9) |
| Lightheadedness, balance issues | 7% (2 of 30) | 5% (1 of 21) | 11% (1 of 9) |
| Swollen lymph node, lump | 7% (2 of 30) | 10% (2 of 21) | 0% (0 of 9) |
| Vomiting | 7% (2 of 30) | 5% (1 of 21) | 11% (1 of 9) |
| Indigestion | 3% (1 of 30) | 0% (0 of 21) | 11% (1 of 9) |
| Pressure in chest | 3% (1 of 30) | 0% (0 of 21) | 11% (1 of 9) |
| Acne | 3% (1 of 30) | 0% (0 of 21) | 11% (1 of 9) |
| Diarrhea | 3% (1 of 30) | 0% (0 of 21) | 11% (1 of 9) |
| Dry skin | 3% (1 of 30) | 0% (0 of 21) | 11% (1 of 9) |
| Eye, vision issues | 3% (1 of 30) | 0% (0 of 21) | 11% (1 of 9) |
| Neuropathy | 3% (1 of 30) | 0% (0 of 21) | 11% (1 of 9) |
| Water retention, swelling, bloating | 3% (1 of 30) | 0% (0 of 21) | 11% (1 of 9) |

achieved by the 17th interview for those living in the USA and by the ninth interview for those outside of the USA.

When asked about symptoms they were currently experiencing, the most often reported symptoms were fatigue (70%, n = 21 of 30), shortness of breath (53%, n = 16 of 30), and cough (47%, n = 14 of 30), although many participants were currently experiencing few symptoms. In general, participants reported that symptoms affected their ability to do daily activities (range: 50%–86%). Fatigue (38%, n = 9 of 24), cough (25%, n = 6 of 24), and pain in areas other than the chest (25%, n = 6 of 24) were most often identified as the most difficult symptoms to manage, and shortness of breath (43%, n = 6 of 14), pain other than chest pain (29%, n = 4 of 14), and cough (29%, n = 4 of 14) were most often cited as the most bothersome.

A total of 40% of participants (n = 6 of 15) reported that their daily activities are affected by NSCLC, and 13% (n = 2 of 15) reported that their ability to do household chores is affected. One participant each said that they are affected in their ability to bathe, carry heavy groceries, cook, and mow the lawn and that they needed to rest after walking around. A total of 70% of participants (n = 19 of 27) reported impacts in physical functioning, whereas 30% (n = 8 of 27) said that they were not affected. Of those affected, 68% (n = 13 of 19) had difficulty walking up stairs or hills, 37% (n = 7 of 19) had trouble walking long distances, 11% (n = 2 of 19) had trouble walking in general, 11% (n = 2 of 19) had trouble cycling, and 11% (n = 2 of 19) had trouble running. A total of 90% of participants (n = 27 of 29) reported being affected emotionally owing to NSCLC. Furthermore, 70% of these participants (n = 19 of 27) reported being sad

**Table 3.** Impacts of Symptoms

| Impact | Total Group (N = 30) | Exon 20 Insertion (n = 21) | Without Exon 20 Insertion (n = 9) |
|---|---|---|---|
| Daily life[a] | 40% (n = 6 of 15) | 55% (n = 6 of 11) | 0% (n = 0 of 4) |
| Physical functioning | 70% (n = 19 of 27) | 79% (n = 15 of 19) | 50% (n = 4 of 8) |
| Emotional functioning | 93% (n = 27 of 29) | 90% (n = 18 of 20) | 100% (n = 9 of 9) |
| Social functioning | 33% (n = 10 of 30) | 38% (n = 8 of 21) | 22% (n = 2 of 9) |

[a]Patients were not directly probed on daily life; therefore, the sample sizes only include individuals who reported an impact on daily life spontaneously.

**Table 4.** Comparison of Impacts for USA and Non-USA Participants

| Impact | Total Group (N = 30) | USA Group (n = 19) | Ex-USA (n = 11) |
|---|---|---|---|
| Daily life[a] | 40% (n = 6 of 15) | 30% (n = 3 of 10) | 60% (n = 3 of 5) |
| Physical functioning | 70% (n = 19 of 27) | 59% (n = 10 of 17) | 90% (n = 9 of 10) |
| Emotional functioning | 93% (n = 27 of 29) | 100% (n = 19 of 19) | 80% (n = 8 of 10) |
| Social functioning | 33% (n = 10 of 30) | 26% (n = 5 of 19) | 45% (n = 5 of 11) |

[a]Patients were not directly probed on daily life, and therefore, the sample sizes only include individuals who reported an impact on daily life spontaneously.
USA, United States of America.

or depressed, 56% (n = 15 of 27) reported being anxious or nervous, 19% (n = 5 of 27) were scared or fearful, 11% (n = 3 of 27) were angry, 11% (n = 3 of 27) were sensitive or emotional, and 7% (n = 2 of 27) were worried.

A total of 33% of participants (n = 10 of 30) reported that they are negatively affected socially, 57% (n = 17 of 30) not socially affected negatively, and 10% (n = 3 of 30) experienced positive social impacts (e.g., making new friends). Compared with those without the exon 20ins mutation, participants with the exon 20ins mutation reported more frequent negative impacts on daily life (55%, n = 6 of 11 versus 0%, n = 0 of 4), physical functioning (79%, n = 15 of 19 versus 50%, n = 4 of 8), and social functioning (38%, n = 8 of 21 versus 22%, n = 2 of 9); the exon 20ins group less frequently reported negative impacts to emotional functioning (90%, n = 18 of 20 versus 100%, n = 9 of 9) (Table 3). Those located outside the USA reported more negative impacts in daily life, physical functioning, and social functioning compared with USA residents (60%, n = 3 of 5 versus 30% n = 3 of 10; 90%, n = 9 of 10 versus 59%, n = 10 of 17; 45% n = 5 of 11 versus 26% n = 5 of 19, respectively) (Table 4), but USA residents more often reported being affected emotionally (100%, n = 19 of 19) compared with those outside the USA (80%, n = 8 of 10) (Table 4).

### CD Portion of Combined CE and CD Interviews

For both the NSCLC-SAQ and PROMIS-PF-8c, participants were able to accurately paraphrase the instructions and questions and generally found the questions and response options to be clear and relevant (Table 5). Nine participants suggested additional questions for the NSCLC-SAQ related to aspects such as anxiety or worry, emotional well-being, and some additional symptoms, for example, pressure, tingling, nausea, and vomiting. Each recall period was considered appropriate by 74% (n = 14 of 19) (NSCLC-SAQ) and 64% (n = 7 of 11) (PROMIS-PF-8c) of the participants. Almost all participants thought that both questionnaires were easy to complete and found the formatting and layout to be clear and appropriate. More details regarding specific suggestions are available in Table 5.

The concepts identified during the CE portion of the interviews were then mapped to the content of each PRO. All symptoms in the NSCLC-SAQ were endorsed, either spontaneously or after probing, by at least 20% of the participants (range: 20%–93%): fatigue = 93% (n = 26 of 28), pain in areas other than the chest = 85% (n = 17 of 20), shortness of breath = 82% (n = 23 of 28), coughing = 71% (n = 20 of 28), chest pain = 36% (n = 10 of 28), and poor appetite = 20% (n = 6 of 30). All concepts in the PROMIS-PF-8c were endorsed, either spontaneously or after probing, by at least 37% of participants (range: 37%–70%): physical functioning (various) = 70% (n = 19 of 27), walking up stairs or hills = 68% (n = 13 of 19), bathing = 40% (n = 6 of 15), and walking long distances = 37% (n = 7 of 19). To help map the most important concepts, with information obtained from the interviews and published literature[11,24] and online resources, a conceptual model was created to describe the relationship between patient symptoms, comorbidities, treatment, and impacts to patient lives (Fig. 1).

## Discussion

The results of the CE and CD interviews revealed that individuals with NSCLC experience several common symptoms. The most often reported symptoms were fatigue, shortness of breath, cough, and weight loss. When asked to describe the three most bothersome symptoms, the symptoms most often ranked as such were shortness of breath, pain in areas other than the chest, cough, and fatigue. Participants felt the most difficult symptoms to manage were fatigue, cough, and pain in areas other than the chest. Individuals reported that symptoms negatively affected their physical functioning, social functioning, emotional functioning, and ability to perform daily activities. Differences between patients with and without the exon 20ins mutation were found in the reported frequency of certain symptoms (those with the mutation had greater frequency of shortness of breath, lack of appetite, and difficulty remembering things) and the impact on their ability to perform

**Table 5.** Cognitive Debriefing Results

| Attribute | NSCLC-SAQ | PROMIS-PF-8c |
|---|---|---|
| Clarity | 100%[a] of participants were able to accurately paraphrase the instructions<br>All questions were accurately paraphrased by 89% to 100%[a] of participants<br>62% to 100%[a] of participants thought each question was clear | 90% to 100%[a] of participants were able to accurately paraphrase each question<br>71% to 94%[a] thought each question was clear |
| Relevance | 96% (n = 24 of 25) of participants thought all questions were relevant<br>45% (n = 9 of 20) thought there were symptoms missing<br>33% (n = 3 of 9) of these thought it should include a question on anxiety or worry and 22% (n = 2 of 9) would add a question on headaches<br>One participant each would add a question on depression, emotional well-being, sleeplessness, and specific types of pain, such as pressure, aching, and tingling<br>One participant would add questions on diarrhea, nausea, rash, and vomiting | All participants (n = 29) found the questions to be relevant to someone with NSCLC<br>Of these, three participants did not think the questions were relevant for them currently but did feel they could be relevant for others<br>One participant thought the questions were more relevant to an aging population but could be relevant to individuals with NSCLC<br>One participant thought the questions would be relevant to individuals with NSCLC and the broader population<br>One participant thought they would be relevant to individuals with all types of cancer |
| Recall period | 74% of participants (n = 14 of 19) thought the recall period of the past 7 d was appropriate<br>16% (n = 3 of 19) would change the recall period to the past 30 d or past mo<br>One participant would revise it to the past 4 d, and one participant would prefer to be asked on "today" | 64% of participants (n = 7 of 11) thought the recall period of the past 7 d was appropriate<br>One participant thought it was difficult to think on the past 7 d but thought most people would be able to recall the past 7 d.<br>One participant would prefer to think on the past 2 weeks or the past mo<br>One participant thought it was a little difficult to think on the past 7 d and would prefer to think on the past week from a fixed period of time (e.g., Sunday to Saturday)<br>One participant thought the timeframe was appropriate but did not notice it when completing the questions |
| Ease of completion | 93% of participants (n = 27 of 29) thought the NSCLC-SAQ was easy to complete<br>One participant thought it was a little difficult because he or she was not used to thinking on fatigue in the way the question asked<br>One participant thought it was difficult because there were many response options and felt his or her cancer had "not been severe" | 92% of participants (n = 23 of 25) found the questionnaire easy to complete<br>One of the participants found it a little difficult because he or she felt the font size of the text was too small<br>One participant found it a little difficult because his or her answers would vary from day to day, so it was a little hard to average across 7 d (the recall period) |
| Formatting and layout | 90% of participants (n = 19 of 21) thought that the formatting and layout of the questionnaire was clear<br>80% of participants (n = 4 of 5) thought the ordering of the items was appropriate, whereas one participant suggested placing question 4 (shortness of breath) after question 1 (coughing) | 94% of the participants (n = 17 of 18) found the formatting and layout to be appropriate<br>One participant thought the formatting made it a little more difficult to complete (specific details not provided) |

*Note:* Participants were asked on the clarity and to paraphrase the instructions and each question individually. There are seven different sample sizes across the NSCLC-SAQ measures and 12 different sample sizes across the PROMIS-PF-8c measures. NSCLC-SAQ, NSCLC Symptom Assessment Questionnaire; PROMIS-PF-8c, PROMIS Short-Form version 2.0—Physical Function 8c.

daily activities and on physical, social, and emotional functioning (those with the mutation more frequently reported negative impacts on daily life, physical functioning, and social functioning). There were also observed differences in symptom frequency and impact between USA residents and non-USA residents. Although many participants were experiencing few symptoms during data collection, this could be owing to the fact that they had received treatment and, to be eligible for the study, were required to have an ECOG score of 0 or 1.

All symptoms and impacts identified were mapped to the content of the NSCLC-SAQ and PROMIS-PF-8c. For the NSCLC-SAQ, the percentage of participants who
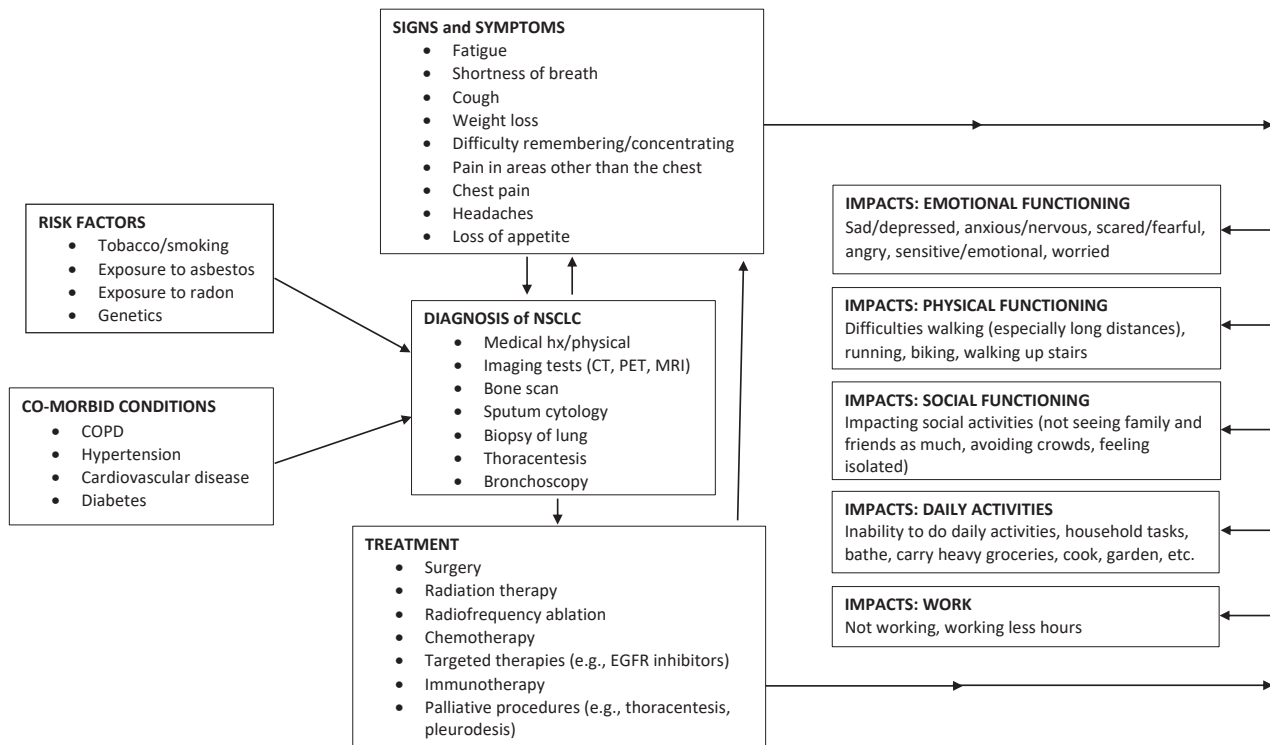
**Figure 1.** Conceptual model based on data from 30 subjects with NSCLC who participated in combined concept elicitation and cognitive debriefing interviews and searches of lung cancer websites (e.g., American Cancer Society) and the publication by Lembircz et al.[24] and Leduc et al.[11] COPD, chronic obstructive pulmonary disease; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

endorsed the concepts covered in that tool ranged from 20% to 93%. For the PROMIS-PF-8c, each concept was endorsed by 37% to 70% of participants. One of the principal impacts identified by participants, difficulty with physical functioning was covered in the PROMIS-PF-8c. The NSCLC-SAQ also covered the most frequently reported NSCLC symptoms. One area not specifically covered by either questionnaire was weight loss, which was endorsed by 68% of the participants (n = 15 of 22).

Another PRO often used in lung cancer studies is the EORTC-QLQ-C30.[25–28] The EORTC-QLQ-C30 covers many of the important impacts and some of the most frequently reported symptoms also covered on the NSCLC-SAQ, but it also includes some less relevant symptoms and does not assess cough or pain in specific areas of the body. The 5-Level EuroQoL-5 Dimension also assesses physical functioning and pain but is not specific to cancer of any type. As a result, the PROMIS-PF-8c and NSCLC-SAQ are thought to be more relevant to a NSCLC population. In addition, both the PROMIS-PF-8c and the NSCLC-SAQ have been listed by the U.S. Food and Drug Administration's Center for Drug Evaluation and Research as qualified for use in NSCLC as a part of their Clinical Outcome Assessment Qualification

Program. The PROMIS-PF-8c was listed as qualified to measure physical functioning in the FDA's 2019 Compendium,[29] and the NSCLC-SAQ was listed as able to measure severity of several symptoms, such as cough, pain, dyspnea, fatigue, and appetite in an updated Compendium.

This study included a relatively large sample, with a total of 30 individuals with *EGFR*-mutated NSCLC. The sample was diverse in terms of most demographic and clinical characteristics, such as education level, household income, and work status. Several countries were represented in the sample, including the USA, Australia, Hong Kong, Canada, Finland, Belgium, Israel, and Malaysia. In addition, on the basis of the scores from the NSCLC-SAQ, there was a fair amount of variability in the responses, suggesting diversity in terms of severity of NSCLC symptoms and impacts. Saturation of concepts was reached by the 18th interview. Because of coronavirus disease 2019, all interviews were conducted by means of Zoom video-conferencing, which allowed the interviewer to interpret body language and probe further if necessary. It also allowed a seamless transition from the CE portion of the interview to the CD portion of the interview. For example, the participants could spontaneously

report all symptoms they experienced during the CE portion, and then they were immediately shown the PROs and could complete them in real time, therefore providing immediate feedback while completing them. This study also contained some limitations. Although there was diversity regarding demographic and clinical characteristics, interviews being conducted in English likely resulted in the inclusion of individuals with a higher income and educational status. Furthermore, only four males were interviewed and most participants had metastatic NSCLC. It would have been preferrable to interview more males and additional individuals with localized NSCLC. In addition, all interviews were conducted in 2020 during the coronavirus disease 2019 pandemic, and therefore, this may have influenced responses to questions of social functioning from some respondents owing to the need for social distancing. Furthermore, although numerous countries were represented in the sample, most were from the USA. There are indeed differences in the prevalence, incidence and treatment patterns between the USA, Europe, and Asia[4,30–32]; the extent to which symptoms and impact can be attributed to receipt of treatment cannot be quantified. Finally, owing to the length of the interview (interviews averaged well more than 1 h), not all interview questions were asked.

This qualitative research study provided evidence to support the content validity, clarity, and relevance of the PROMIS-PF-8c and NSCLC-SAQ in a population with *EGFR*-mutated NSCLC, including those with the exon 20ins mutation. Both measures would be appropriate for inclusion in future NSCLC studies and together provide sufficient coverage of NSCLC symptoms and physical functioning.

## CRediT Authorship Contribution Statement

**Marcia Horn:** Investigation, Resources, Writing—original draft, Writing—review and editing.

**Kevin Liu:** Methodology, Writing—original draft, Writing—review and editing, Visualization.

**Susan D. Mathias:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing—original draft, Writing—review and editing, Visualization, Supervision, Project administration, Funding acquisition.

**Hilary H. Colwell:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing—original draft, Writing—review and editing.

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**Parthiv Mahadevia:** Methodology, Writing—original draft, Writing—review and editing.

**Renee F. Pierson:** Conceptualization, Methodology, Writing—original draft, Writing—review and editing, Visualization, Supervision, Project administration, Funding acquisition.

## References

1. Duma N, Santana-Davila R, Molina JR. Non-small cell lung cancer: epidemiology, screening, diagnosis, and treatment. *Mayo Clin Proc*. 2019;94:1623-1640.
2. World Health Organization. Cancer. https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed January 14, 2021.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
4. Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*. 2016;7:78985-78993.
5. Arcila ME, Nafa K, Chaft JE, et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol Cancer Ther*. 2013;12:220-229.
6. Oxnard GR, Lo PC, Nishino M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. *J Thorac Oncol*. 2013;8:179-184.
7. Burnett H, Emich H, Carroll C, Stapleton N, Mahadevia P, Li T. Epidemiological and clinical burden of EGFR Exon 20 insertion in advanced non-small cell lung cancer: a systematic review. *PLoS One*. 2021;16:e0247620.
8. Riely GJ, Neal JW, Camidge DR, et al. Activity and safety of mobocertinib (TAK-788) in previously treated non-small cell lung cancer with EGFR exon 20 insertion mutations from a phase 1/2 trial [e-pub ahead of print]. *Cancer Discov*. https://doi.org/10.1158/2159-8290.CD-20-1598. accessed June 19, 2021.
9. Sabari JK, Shu CA, Park K, et al. OA04.04 amivantamab in post-platinum EGFR exon 20 insertion mutant non-small cell lung cancer 2021;. 2021;16(suppl):S108-S109.
10. Tishelman C, Degner LF, Rudman A, et al. Symptoms in patients with lung carcinoma: distinguishing distress from intensity. *Cancer*. 2005;104:2013-2021.
11. Leduc C, Antoni D, Charloux A, Falcoz PE, Quoix E. Comorbidities in the management of patients with lung cancer. *Eur Respir J*. 2017;49:1601721.
12. Bouazza YB, Chiairi I, El Kharbouchi O, et al. Patient-reported outcome measures (PROMs) in the management of lung cancer: a systematic review. *Lung Cancer*. 2017;113:140-151.
13. Hirpara DH, Gupta V, Brown L, Kidane B. Patient-reported outcomes in lung and esophageal cancer. *J Thorac Dis*. 2019;11(suppl 4):S509-S514.

14. Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA*. 2017;318:197-198.

15. Cavanna L, Citterio C, Orlandi E. Feasibility and utility of incorporating patient-reported outcomes into surveillance strategies for advanced lung cancer. *Patient Relat Outcome Meas*. 2020;11:49-66.

16. Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-reported outcomes in cancer clinical trials: measuring symptomatic adverse events with the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *Am Soc Clin Oncol Educ Book*. 2016;35:67-73.

17. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol*. 2010;63:1179-1194.

18. McCarrier KP, Atkinson TM, DeBusk KP, et al. Qualitative development and content validity of the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ), a patient-reported outcome instrument. *Clin Ther*. 2016;38:794-810.

19. US Food and Drug Administration. DDT COA qualification review. https://fda.report/media/131690/DDT+009_NSCLC-SAQ_COA+Review.pdf. Accessed June 19, 2021.

20. Liepa AM, Bushnessl D, Atkinson TM, et al. P1.06-004 Evaluating the non-small cell lung cancer symptom assessment questionnaire (NSCLC-SAQ): preliminary results from the quantitative pilot study. *J Thorac Oncol*. 2017;12(suppl):S666-S667.

21. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Accessed June 19, 2021.

22. Montazeri A, Gillis CR, McEwen J. Quality of life in patients with lung cancer: a review of literature from 1970 to 1995. *Chest*. 1998;113:467-481.

23. Turner-Bowker DM, Lamoureux RE, Stokes J, et al. Informing a priori sample size estimation in qualitative concept elicitation interview studies for clinical outcome assessment instrument development. *Value Health*. 2018;21:839-842.

24. Lembicz M, Gabryel P, Brajer-Luftmann B, Dyszkiewicz W, Batura-Gabryel H. Comorbidities with non-small cell lung cancer: is there an interdisciplinary consensus needed to qualify patients for surgical treatment? *Ann Thorac Med*. 2018;13:101-107.

25. Kenny PM, King MT, Viney RC, et al. Quality of life and survival in the 2 years after surgery for non small-cell lung cancer. *J Clin Oncol*. 2008;26:233-241.

26. Li WW, Lee TW, Lam SS, et al. Quality of life following lung cancer resection: video-assisted thoracic surgery vs thoracotomy. *Chest*. 2002;122:584-589.

27. Balduyck B, Hendriks J, Lauwers P, Van Schil P. Quality of life after lung cancer surgery: a prospective pilot study comparing bronchial sleeve lobectomy with pneumonectomy. *J Thorac Oncol*. 2008;3:604-608.

28. Movsas B, Moughan J, Sarna L, et al. Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. *J Clin Oncol*. 2009;27:5816-5822.

29. US Department of Health and Human Services. Center for Drug Evaluation and Research clinical outcome assessment (COA). Compendium. June 2021. https://www.fda.gov/drugs/development-resources/clinical-outcome-assessment-compendium. Accessed June 19, 2021.

30. Sekine I, Yamamoto N, Nishio K, Saijo N. Emerging ethnic differences in lung cancer therapy. *Br J Cancer*. 2008;99:1757-1762.

31. Carbonnaux M, Souquet PJ, Meert AP, Scherpereel A, Peters M, Couraud S. Inequalities in lung cancer: a world of EGFR. *Eur Respir J*. 2016;47:1502-1509.

32. Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). *Am J Cancer Res*. 2015;5:2892-2911.