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# A feasibility exploratory study of a novel modality of using patient-reported outcomes (PROsEXPLOR) in the real world

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## Abstract

**Introduction:** Patient-reported outcomes (PROs) can help clinicians better evaluate chemotherapy and immunotherapy toxicity based on patient perspectives. In this exploratory study, we tested a simplified PRO questionnaire (sPQ) in routine clinical practice and patient satisfaction with this tool.

**Methods:** We included 16 items related to the main toxicities of chemotherapy and immunotherapy to be filled in by patients. A baseline sPQ was completed by patients before starting treatment and then in the interval between courses for a total of 4 sPQs. Patients communicated the results to a data manager, who alerted the referral oncologist in case of replies differing from the basal or previous sPQ. According to the severity of symptoms, the patient was then referred to the team nurse, the general practitioner, or another specialist. A satisfaction survey was also completed.

**Results:** In a 3-month interval, 27 patients were enrolled. Fatigue and nausea were the most frequent symptoms reported as worsening during treatment. The oncologist was involved in the management of adverse events in 4 cases, home therapy variations were recommended by the dedicated nurse in 14 cases, additional visits were performed in 6 patients, and 1 patient was admitted to the oncology ward. None of the patients had unplanned visits to the emergency department or to the hospital. The sPQ was judged to be simple, useful, and satisfactory.

**Conclusions:** Using sPQs in routine clinical practice was feasible and well-accepted by patients. PROs allowed us to recognize and promptly manage adverse events, reducing unplanned emergency department or hospital visits to zero.

## Keywords

Patient-reported outcomes, side effects, toxicity, mesothelioma, melanoma, sarcoma

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## Introduction

Patient-reported outcomes (PROs) consist of direct reporting of a patient's condition, not filtered by clinician interpretation.[1] PROs are currently considered the best tool to describe subjective toxicity during cancer treatments. Several studies highlighted relevant differences between the description of toxicity caught by PROs compared to that reported by clinicians, the latter underestimating both the incidence and the entity of symptoms.[2–4] PROs could be a strategic tool allowing both more accurate reporting

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of adverse events in the clinical research context and better management of patients in everyday practice.[1,4]

A proper and inclusive reporting of symptoms and toxicities by patients was found to correlate with outcomes in a post hoc analysis of survival within a prospective trial: median overall survival in the PROs arm was 5 months longer than that of the standard arm (31.2 vs 26.0 months, $p = 0.03$), maintaining statistical significance in the multivariable model with a hazard ratio of 0.83 (95% confidence interval, 0.70–0.99; $p = 0.04$).[5]

The most plausible explanation for the observed survival advantage of the PROs arm is that the timely identification and management of toxicities could prevent worse consequences and improve treatment compliance and ultimately efficacy. In the trial mentioned above, patients in the experimental arm received active treatment significantly longer than those in the control arm (8.2 vs 6.3 months; $p = 0.002$).

This observation could be valid not only in the research context but also in real-life clinical practice. The instrument used by clinicians to report adverse events and their impact on patients' daily activities in the oncologic setting is Common Toxicity Criteria for Adverse Events (CTCAE), which provide a list of potential side effects and a grading scale to quantify the entity of each toxicity. A specific tool for patients has been developed by the National Cancer Institute (NCI) to capture symptomatic adverse events in patients in cancer clinical trials (PRO-CTCAE) (https://healthcaredelivery.cancer.gov/pro-ctcae). The NCI PRO-CTCAE includes 78 symptomatic treatment toxicities, such as pain, fatigue, and nausea, all of which can be meaningfully reported from the patient's perspective. Both the US Food and Drug Administration (FDA) and European Medicines Agency have issued guidance on the use of PROs in clinical trials, underlying the relevance of including the patients' perspectives as a standard outcome measure and source of information when evaluating the benefit/harm ratio of cancer treatments. The US FDA stressed that some unobservable symptoms such as nausea, pain severity, and itching can only be adequately assessed using PRO measurements.[1,6,7]

Each of the 78 symptom terms included in the PRO-CTCAE item library is assessed relative to 1 or more distinct attributes, including presence/absence, frequency, severity, and/or interference with usual or daily activities. Responses are provided on a 5-point Likert scale and the recall period is "the past 7 days." An Italian version of this toxicity measurement tool has been available since March 2017 (https://healthcaredelivery.cancer.gov/pro-ctcae/instrument.html).

We decided to test this proactive reporting of toxicity in daily clinical activity using an easier-to-handle tool, including some relevant, selected items and an easier modality of interaction with patients, not solely based on the use of informatic devices.

We defined a simplified PRO questionnaire (sPQ) that was tested within a pilot, prospective, observational, single-center exploratory study (PROsEXPLOR): the primary aim was to describe its feasibility and the secondary aim was to assess patient satisfaction. Furthermore, we explored the impact of the sPQ in improving compliance with cancer treatments and in reducing unplanned visits to oncologic and emergency departments.

## Methods

### *Questionnaire definition*

The sPQ was defined using the Italian version of PRO-CTCAE. A dedicated multiprofessional team including 2 oncologists, 2 oncologic nurses, 1 general practitioner, 1 nurse, and 3 patients was asked to choose among the 78 items the ones considered more relevant to describe the effects of chemotherapy and immunotherapy and more likely to require medical interventions or advice. The sPQ was designed including items that received 5 or more votes. Figure 1 shows the items that received at least 1 vote. The 16 items selected were difficulty swallowing, mouth or sore problems, decrease in appetite, nausea, vomiting, constipation, diarrhea, dyspnea, cough, edema, itching, pins and needles in arms and legs, pain, headache, fatigue, burning urination, and other (free items indicated by the patient).

A satisfaction questionnaire (SQ) was prepared by the same team including the following questions: difficulty in filling out the sPQ, difficulty in understanding the items, usefulness of the sPQ for the patient and for other future patients, and time required to fill out the questionnaire. Possible responses were "none," "little," "enough," or "much."

### *Inclusion and exclusion criteria*

Eligibility criteria were age >18 years; histologic diagnosis of mesothelioma, sarcoma, or melanoma; undergoing systemic intravenous treatment; interval time between treatment cycles of at least 15 days; capability to fill in the questionnaire autonomously or with the support of a caregiver; and written informed consent provided.

## Procedures

Each patient signed a specific informed consent and an informative letter was sent to the general practitioner to notify him or her about the study and to ask for collaboration in the management of symptoms.

Each patient was asked to fill out 4 sPQs: 1 soon after study entry (t0) before starting treatment in presence of the referral oncologist and 3 on their own in the interval period between 2 subsequent courses (t1, t2, t3) in a range of dates in the middle of the treatment interval indicated by the oncologist. The t0 sPQ was stored by the study

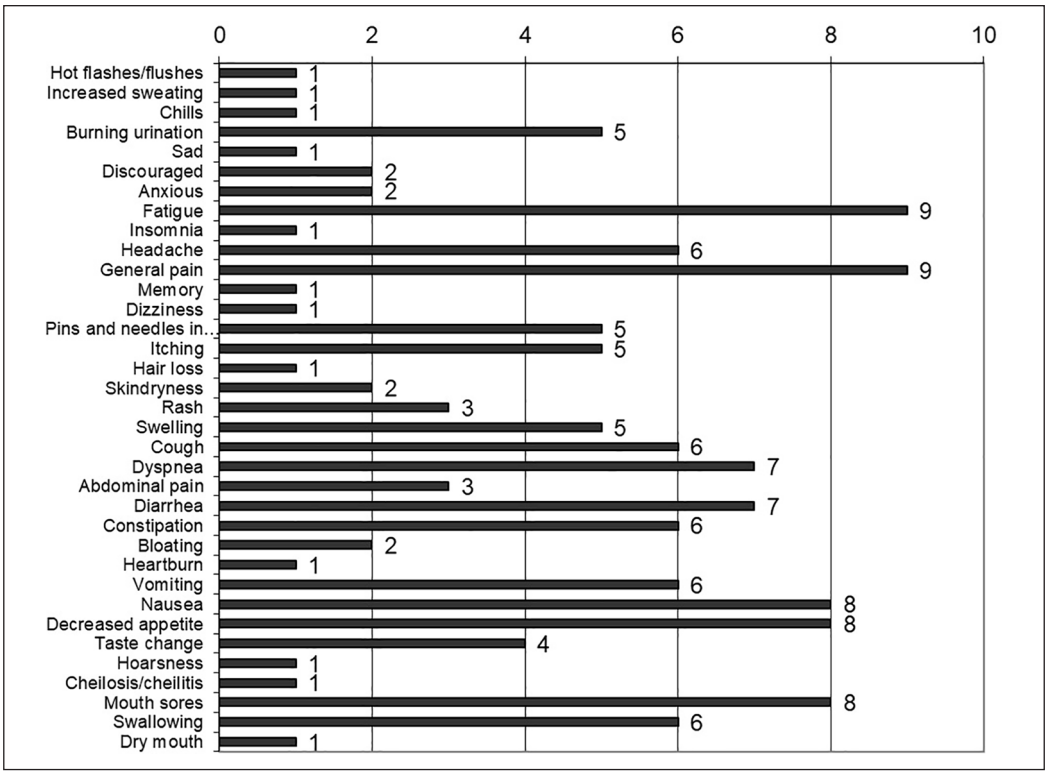


**Figure 1.** Item preferences chosen by the multiprofessional team.

dedicated data manager. The t1–t3 sPQs were sent to the data manager by fax or email or communicated by phone on specific days defined during the visit. If the patients did not contact the data manager in the predefined range of dates, the data manager called the patients. Patients were asked to return the originally filled in sPQ forms during the subsequent visit. The data manager was in charge of checking the replies and alerting the referral oncologist in case they were different from the replies recorded in the baseline or in the previous sPQ. The referral oncologist decided which symptoms and signs required follow-up according to their type and severity and chose a response among the following options: phone call by an oncologic nurse, visit by the general practitioner, or visit by a specialist. When transferring the sPQs in the interval between 2 courses, the patient could also ask to be contacted by a staff nurse or a physician in case he or she needed help in managing toxicities and symptoms. Variations in therapy, visits to the emergency department, or additional unscheduled visits were recorded.

A database was set up to record variables. For each patient, the following variables were recorded: sex, age, education, diagnosis, stage, systemic treatment, line of treatment, comorbidities, ongoing home therapies, PRO items, performance status, active reporting by the patient, time required to fill in the sPQs, and side effects. For each item reported as different from the baseline, the following information were recorded: contact by a nurse, visit by the general practitioner or by the oncologist or other specialists, therapy variations required, and unplanned visits to the emergency department or other visits.

## Measures

The questions related to the 16 items had the same 5 response categories for severity and interference with daily activities—"not at all," "a little," "quite a bit," "much," "very much"—and 5 other response categories for frequency—"never," "seldom," "sometimes," "often," "almost always."

With respect to the variables reporting each level of the 5 response categories, scores were as follows: "not at all" and "never" = 0; "a little" and "seldom" = 1; "quite a bit" and "sometimes" = 2; "much" and "often" = 3; and "very much" and "almost always" = 4. Then each variable was weighted according to the score reported by each patient. Thus if 27 patients reported that they "never" experienced nausea, the weighted value was 0; if 27 patients reported having nausea "almost always," the weighted value was 108; if 27 patients reported having nausea "sometimes," the weighted value was 54.

## Sample size and statistics

This was an exploratory study in which we decided to include a number of consecutive patients ranging from 20 to 30 in a 3-month interval. The collected data were

**Table 1.** Main characteristics of patients included in the study.

| | Patients |
|---|---|
| Number of patients | 27 |
| Sex, n (%) | |
| Male | 19 (70) |
| Female | 8 (30) |
| Age, y, median (range) | 68 (34–78) |
| Level of education, n (%) | |
| Median/primary school | 9 (33) |
| High school | 16 (59) |
| University | 2 (8) |
| Type of tumor, n (%) | |
| Mesothelioma | 10 (37) |
| Melanoma | 9 (33) |
| Sarcoma | 8 (30) |
| Type of treatment, n (%) | |
| Chemotherapy | 18 (67) |
| Carboplatin + pemetrexed | 8 |
| Vinorelbine | 1 |
| Gemcitabine | 3 |
| Trabectedin | 2 |
| Anthracyclines + ifosfamide/dacarbazine | 4 |
| Immunotherapy | 9 (33) |
| Nivolumab | 2 |
| Pembrolizumab | 7 |
| Setting, n (%) | |
| First-line treatment | 15 (56) |
| Second-line treatment | 5 (18) |
| Third- or further-line treatment | 7 (26) |
| Comorbidities, n (%) | |
| Hypertension | 12 (44) |
| Heart disease | 4 (15) |
| Diabetes and metabolic disease | 5 (18) |
| Other | 13 (48) |

analyzed using IBM SPSS for Windows version 25.0. All the recorded variables were summarized and reported through descriptive analysis.

### *Ethical aspects*

PROsEXPLOR was run according to Good Clinical Practice by Helsinki Declaration and subsequent revisions (D. Lgs n. 211 del 24.06.03). The study protocol was approved by the Comitato Etico Interaziendale AO SS. Antonio e Biagio e Cesare Arrigo of Alessandria.

## Results

From June to August 2018, the study was proposed to 27 consecutive patients and all of them agreed to participate. Patient characteristics and treatment data are summarized in Table 1. All the patients but one filled in all 4 required sPQs; 1 patient filled in the basal and the 2 subsequent sPQs, then treatment was interrupted due to worsening of general condition. A total of 107 sPQs were analyzed and the number of monitored courses was 80. For each item, the weighted value was calculated at t0 and the following assessments (t1, t2, t3). The items that were reported as worsening during treatment through the subsequent assessments were, in descending order, fatigue, nausea, decrease in appetite, mouth and sore problems, difficulties in swallowing, burning in urination, pins and needles in arms and legs, itching, dyspnea, and vomiting. Items not significantly changed during treatment were constipation, diarrhea, and pain. Items improving during treatment were headache, cough, and peripheral edema. The weighted values for each item at the different assessments are reported in Table 2. The weighted values at each assessment of items worsening during treatment are represented in Figure 2. The only additional toxicities reported in the free field ("other") of the sPQ were sweating, indicated by 1 patient, and alopecia, indicated by 2 patients.

**Table 2.** Weighted values for each item at different assessments.

| Items | Weighted values | | | |
|---|---|---|---|---|
| | t0 | t1 | t2 | t3 |
| Difficulties in swallowing | 2 | 7 | 3 | 11 |
| Mouth or sore problems | 1 | 5 | 7 | 6 |
| Decrease in appetite | 4 | 9 | 12 | 11 |
| Nausea | 8 | 16 | 24 | 18 |
| Vomiting | 1 | 0 | 4 | 5 |
| Constipation | 17 | 20 | 15 | 16 |
| Diarrhea | 15 | 19 | 15 | 11 |
| Dyspnea | 15 | 15 | 18 | 17 |
| Cough | 8 | 6 | 4 | 9 |
| Edema | 16 | 13 | 15 | 18 |
| Itching | 7 | 16 | 5 | 5 |
| Pins and needles in arms and legs | 10 | 13 | 11 | 11 |
| Pain | 30 | 27 | 36 | 28 |
| Headache | 6 | 2 | 3 | 4 |
| Fatigue | 23 | 31 | 34 | 39 |
| Burning in urination | 4 | 10 | 7 | 7 |

Eleven patients had worsening in fatigue ("much" or "very much") and asked to be contacted by the study nurse: behavioral advice was given and in none of these cases was therapy changed. Nausea was reported "often" or "almost always" in 5 sPQs: in all these cases, the specialized nurse called the patients and suggested adding antiemetic drugs according to internal guidelines. Three patients complained of severe decrease in appetite ("very much"): all these patients were addressed to the general practitioner, who prescribed food integrators. One patient complaining of severe decrease in appetite and vomiting ("very much") had been hospitalized for intravenous rehydration and parental nutrition; this patient was diagnosed with acute pancreatitis likely related to chemotherapy and stopped treatment. One patient

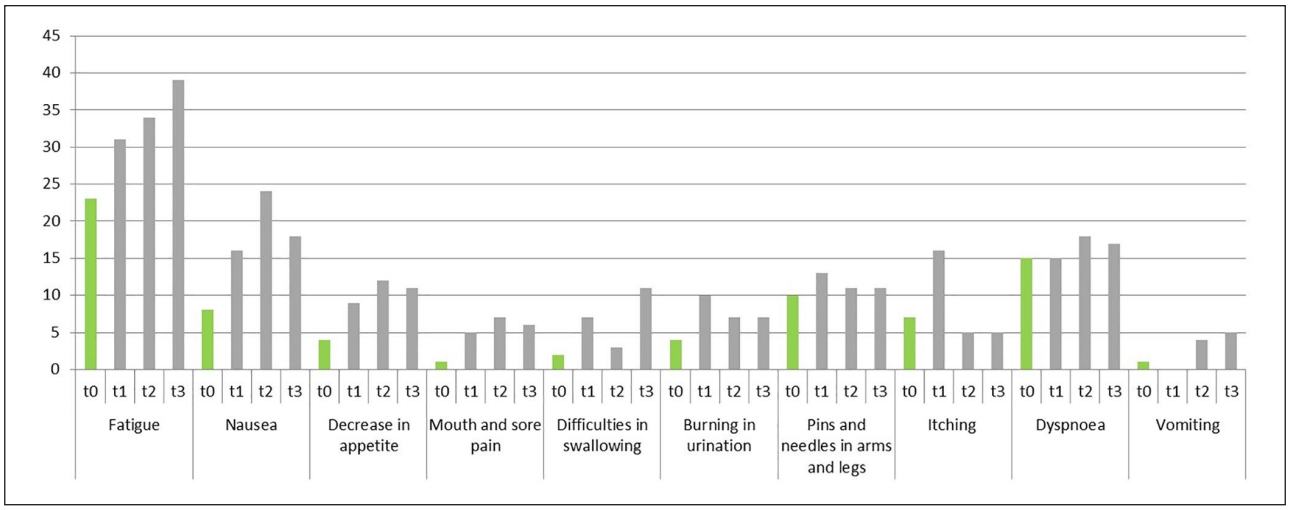


**Figure 2.** Weighted values of worsening items.

**Table 3.** Action undertaken as a consequence of a difference in replies in the questionnaire.

| Item | Phone call by nurse | Therapy modification by referral nurse | Therapy modification by the referral oncologist | General practitioner visit | Specialist visit | Hospitalization |
|---|---|---|---|---|---|---|
| Nausea | 5 | 5 | — | — | — | — |
| Fatigue | 11 | — | — | — | — | — |
| Decrease in appetite | 3 | — | — | 3 | — | — |
| Vomiting and decrease in appetite | 1 | — | 1 | — | 1 | 1 |
| Pain | 10 | 8 | 1 | — | 1 | — |
| Itching | 2 | — | 1 | — | 1 | — |
| Pins and needles in legs | 1 | — | 1 | — | — | — |
| Mouth and sore problems | 3 | 1 | — | — | — | — |
| Total | 36 | 14 | 4 | 3 | 3 | 1 |

developed pins and needles in his legs and the oncologist prescribed symptomatic drugs. During the study, the referral nurse contacted patients 10 times due to worsening pain: in 8 cases, therapy was added according to internal guidelines; in 1 case, the patient was referred to the palliative care physician; and in 1 case, the patient was visited by the oncologist, who varied the antalgic therapy. One patient complained of severe itching and was contacted by the oncologist, who prescribed symptomatic therapy. Another patient complaining of severe itching was referred to a dermatologist. In 3 cases, mouth and sore problems were reported as changed from the previous sPQ, and in all these cases the nurse called the patients to verify that symptoms did not interfere with the capability of eating and drinking adequately. In 1 case, food integrators were suggested in addition to symptomatic treatment according to internal guidelines. The actions undertaken as a consequence of a difference in replies are summarized in Table 3.

The dose intensity of therapy was maintained in 24 patients. Two patients interrupted the treatment, 1 due to worsening of general condition and 1 due to pancreatitis, and 1 patient delayed a course of chemotherapy due to persisting nausea. None of the patients included in the study had unplanned hospital or emergency department visits during the study period.

All 107 sPQs were completed in an interval of less than 10 minutes. Six patients were helped by a caregiver in filling out the sPQs. All patients but one completed the final SQ. Twenty-five patients had no difficulty in filling out the sPQ and 1 had “some” difficulty. Eighteen patients considered the sPQs very useful for their health, 7 sufficiently useful, and 1 not useful. Eighteen patients suggested implementing the protocol in routine practice, considering it very useful; 8 considered its use in clinical practice sufficiently useful. Fourteen patients did not have any difficulty understanding the items and considered the sPQ very easy to fill out and 12 reported some difficulty in understanding some items. The time required to complete the sPQ was considered acceptable by 25 patients and 1 patient stated that the time required was too long.

## Discussion

This study shows the feasibility of adopting an sPQ in routine oncologic clinical practice to monitor toxicities and adverse events. All patients asked to participate in the study agreed to be included and completed the sPQs. Overall the vast majority of patients enrolled in the study considered the sPQ acceptable and useful and therefore the study met its primary and secondary aims. The dose intensity of therapy was maintained in all but 3 cases, and no urgent or unplanned emergency or hospital visits were registered, suggesting that this approach could improve the management of toxicity, thus increasing compliance with therapy and reducing urgent medical interventions. This study was designed as an exploratory experience, with a small sample size and without a control group, to assess the feasibility of introducing a simplified method to use PROs in clinical routine. We enrolled patients with sarcoma, melanoma, or mesothelioma receiving systemic therapies because the unit in which the study was conceived and performed is specialized in caring for patients with these cancers.

The data manager and the oncologic nurse were the cornerstones of this program, allowing interception and prompt management of symptoms to prevent worsening.[8,9]

Several trials aimed at analyzing the usefulness of PROs have directly involved nurses but their roles mainly consisted of receiving alerts from the patients.[5] In contrast, in the present study, nurses called patients and in many cases were able to suggest therapy modifications to solve the patients' problems.

Without prompt intervention, some symptoms can worsen, causing severe complications that can affect the dose intensity of treatments, decreasing their efficacy.

The relevance of dedicated nurses in interactions with patients has been highlighted in the study of Baratelli et al.,[10] demonstrating that with an active role of nurses, the introduction of PROs in clinical practice was feasible and produced high patient satisfaction compared to the traditional modality of visits. In common clinical practice, the oncologist acquires information about symptoms and toxicities during visits. Usually the interview performed by the physician to collect toxicities information is unstructured and can result in underreporting of some symptoms that have already resolved or underestimate their severity.[1,10,11] Using PROs in the interval between 2 courses can limit or avoid this problem and improve the management of toxicities especially in the outpatient setting.[12–15] The mentioned Italian study draws the conclusion that the introduction of PROs in clinical practice had a significant impact in improving quality of life, as measured by European Organization for Research and Treatment of Cancer QLQC30.[10,16]

In our experience, the sPQs were considered acceptable and useful by the vast majority of patients, who suggested extending its use beyond the present study.

Of note, none of the patients had unplanned emergency department or hospital visits, and all additional visits required were scheduled by the referral nurse or the data manager, allowing efficient organization within the multidisciplinary team.

One of the most innovative aspects of our study was the collection and analysis of PROs in the interval between 2 courses performed by a dedicated data manager that allowed us to intercept toxicities when they were at their worst, according to the specific disease as well as the specific therapy. We therefore succeeded in limiting the consequences of the different toxicities. In the majority of cases, a phone call by a specialized nurse was sufficient to overcome the problem; only in a few cases were the oncologist or other specialists involved in the management of adverse events. The general practitioner had an active role in solving the patients' problems and supporting the oncologic team.

In our model, the patient was at the center of a multiprofessional team, in which the data manager and the nurse were easily reachable by the patient and wholly informed about the patient's condition owing to sPQ reports. On the contrary, in common practice, the patient often is lost in a series of phone calls trying to reach the oncologist or other specialists directly.

Based on these findings and considerations, we decided to define a new protocol that will include a greater number of patients, with all types of solid cancers, to validate the simplified questionnaire tested in the present study and the new modality of collecting and analyzing PROs not during the scheduled visits but in the interval when they usually reach their peak. Besides dedicated oncologic nurses, other nurses will also be included in the study team after appropriate training and the role of general practitioners will be reinforced. In selected patients, we plan to use electronic devices to collect the information.

## Conclusion

Using PROs was feasible in our clinical practice, owing to an active role of data managers and nurses collaborating with the oncologic team and serving as referral sources for patients. The new modality tested in this study could be advantageous and deserves to be investigated further in a larger cohort.

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