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An Assistive Electronic Patient-Reported Outcome Monitoring Intervention for Management of Immune-Related Toxic Effects—Moving Toward Efficiency and Scale

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In *JAMA Network Open*, Zhang et al[1] report the results of a multicenter, randomized clinical trial evaluating an electronic patient-reported outcome (ePRO) intervention to monitor immune-related adverse events (irAEs) among patients receiving immunotherapy. The intervention consisted of a smartphone application through which patients completed weekly structured symptom assessments and uploaded laboratory results to monitor common toxic effects of immunotherapy. Symptom assessments included severity of rash, diarrhea, shortness of breath, and chest pain/palpitations and interference with daily life functions related to eye discomfort and joint pain. Patients were also prompted to report other symptoms such as mood, appetite change, thirst and/or excessive urination, and headache. In response to reported symptoms and uploaded laboratory results, the ePRO intervention automatically sent patients standardized self-management advice for low-grade irAEs or alerted health care teams for severe irAEs. Among 278 patients across 28 tertiary care hospitals at 6 months of follow-up, those randomized to the ePRO intervention compared with usual care had decreased incidence of serious irAEs (29 of 141 [20.6%] vs 46 of 137 [33.6%]), fewer emergency department visits (23 of 141 [16.3%] vs 23 of 141 [29.9%]), and lower rates of treatment discontinuation (5 of 141 [3.5%] vs 15 of 137 [10.9%]). Moreover, the intervention was associated with higher aggregate quality of life scores and decreased time spent on health care compared with usual care. These findings extend the evidence base for PRO monitoring to a new patient population and raise several important considerations for PRO research and implementation.

First, to our knowledge, Zhang et al[1] are the first to report a significant benefit of ePRO monitoring among patients receiving immunotherapy for cancer treatment. Given the potential for rare but serious irAEs for which early recognition is critical, there is strong rationale for remote PRO monitoring among patients receiving immunotherapy. However,

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the seminal interventional PRO trials[2,3] that established an evidence base for routine symptom monitoring in oncology either were conducted largely in the preimmunotherapy era or focused on patients in the surveillance setting. Patient-reported outcome monitoring specific to patients receiving immunotherapy is a current area of active investigation. Recently, a single-site pilot randomized trial[4] of 146 patients with metastatic melanoma receiving immunotherapy failed to show a reduction in grade 3 or 4 or overall irAEs with ePRO monitoring compared with standard monitoring of toxic effects. The study was conducted at an academic hospital in Denmark with an oncology team experienced with irAE monitoring, and most patients received immune monotherapy (67%) and had a low incidence of severe irAEs (13%). In contrast, Zhang et al[1] predominantly enrolled patients with gastrointestinal malignant neoplasms (190 of 278 [68.3%]) and allowed patients to receive combination regimens with chemotherapy or targeted therapies (183 of 278 [65.8%], immune monotherapy; 95 of 278 [34.2%], combination regimen), and patients reported high levels of toxic effects (228 of 278 [82.0%], any irAE; 75 of 278 [27.0%], severe irAE). The observed benefit in a more symptomatic population underscores the hypothesis that PRO monitoring may be most effective in highly symptomatic patients owing to treatment, disease type, or limited access to symptom management. In addition, the high rate of severe irAEs in the study by Zhang et al[1] included severe laboratory alerts flagged for clinicians. Standardized monitoring and early recognition of abnormal laboratory findings before patients become symptomatic is critical for management of irAEs and may have contributed to the efficacy of their intervention. It remains unknown whether ePRO monitoring alone provides benefit in this patient population. In the US, we await results from a large, multisite study of prospective PRO monitoring that includes patients receiving chemotherapy, targeted therapy, or immunotherapy, which will hopefully shed further light on which patient populations benefit from more intensive symptom monitoring.[5]

Second, the intervention tested by Zhang et al[1] included several key innovations that expand on previous models. The ePRO remote monitoring program used by participants of this trial exhibited several best practice elements, such as use of a digital interface accessible by mobile phone or computer, weekly prompts (with reminders) to complete a parsimonious questionnaire of common actionable symptoms, and automated electronic alerts to the care team to inform potential interventions. Novel elements included the integration of symptom management pathways to promote algorithmic self-management of low-grade symptoms and integrated laboratory monitoring with care team alerts. Although the intervention moves the needle toward automation of symptom monitoring, it is important to note that it was designed to augment—not supplant—human decisions and actions. For example, each site was required to have a designated team to manage PRO alerts that consisted of 1 oncology specialist and 2 nurses with expertise in irAE management. The digital application informed rapid triage to this clinical team, thereby providing an assistive technology to optimize and scale the human-delivered clinical intervention.[6] These innovative elements may have contributed to the success of the program and underscore the importance of incorporating both automated and human effectors into PRO monitoring systems.

Third, ePRO monitoring provides a health technology infrastructure to support system-level efficiency and reduce time spent on health care. The intervention developed by Zhang et al[1] focused on optimizing efficiency by automatically sending follow-up tasks, providing

standardized advice, and using automated symptom and laboratory result recognition. The authors note that only a small group of patients with grade 3 or 4 irAEs required contact by telephone, because lesser-grade symptoms were automatically recognized by the platform and responded to with standardized advice. In addition, total time per follow-up visit was shorter in the intervention vs control group (mean [SD], 8.2 [3.9] vs 36.1 [15.3] minutes). An important future direction in the field is to study how PRO monitoring can improve efficiency and burden for clinicians while facilitating high-quality care. This is critical to the long-term success of PRO implementation, especially as we face an epidemic of clinician burnout in health care. Another high-priority area for future research should be studying care efficiency from the patient perspective. Patient time spent on health care is a highly valuable entity, especially among patients with advanced cancer who have limited life expectancy. As a field, we should be working to understand how interventions impact patient time spent on health care and incorporating such patient-centered outcomes into clinical trials.

In summary, we commend Zhang et al[1] for their contribution to the mounting literature supporting routine PRO monitoring for patients with cancer across diverse settings, now to include patients receiving immunotherapy. Robust PRO monitoring programs have the potential to improve quality of life and survival for patients, as well as system efficiency. They are an evidence-based practice and cornerstone of high-quality, patient-centered cancer care. In addition, standardized system-level PRO monitoring may have the potential to reduce disparities in health care outcomes by overcoming bias and structural inequities that result in lesser quality care for vulnerable groups. Still, most centers lack routine PRO monitoring systems and even when such systems exist, challenges remain with respect to patient adherence and clinician engagement. Increasingly, the central challenge facing the field is one of optimal and equitable implementation.[7]

Conflict of Interest Disclosures:

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REFERENCES

1. Zhang L, Zhang X, Shen L, Zhu D, Ma S, Cong L. Efficiency of electronic health record assessment of patient-reported outcomes after cancer immunotherapy: a randomized clinical trial. JAMA Netw Open. 2022;5(3):e224427. doi:10.1001/jamanetworkopen.2022.4427 [PubMed: 35357459]
2. Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. J Clin Oncol. 2016;34(6):557–565. doi:10.1200/JCO.2015.63.0830 [PubMed: 26644527]
3. Denis F, Basch E,Septans AL, et al. Two-year survival comparing web-based symptom monitoring vs routine surveillance following treatment for lung cancer. JAMA. 2019;321(3):306–307 doi:10.1001/jama.2018.18085 [PubMed: 30667494]
4. Tolstrup LK, Bastholt L, Dieperink KB, Möller S, Zwisler AD, Pappot H. The use of patient-reported outcomes to detect adverse events in metastatic melanoma patients receiving immunotherapy: a randomized controlled pilot trial. J Patient Rep Outcomes. 2020;4(1):88. doi:10.1186/s41687-020-00255-0 [PubMed: 33125537]
5. Electronic patient reporting of symptoms during cancer treatment (PRO-TECT). ClinicalTrials.gov identifier: NCT03249090. Updated December 8, 2021. Accessed February 2, 2022. https://clinicaltrials.gov/ct2/show/NCT03249090

6. Hermes ED, Lyon AR, Schueller SM, Glass JE. Measuring the implementation of behavioral intervention technologies: recharacterization of established outcomes. J Med Internet Res. 2019;21(1):e11752. doi:10.2196/11752 [PubMed: 30681966]

7. Kaufmann TL, Rocque GB. Pathway to precision patient-reported outcomes. J Clin Oncol. 2021;39(34):3770–3772. doi:10.1200/JCO.21.02163 [PubMed: 34597155]