

made of the need to mitigate risks of exploitation when healthy volunteers receive financial compensation for their participation, a crucial feature that differentiates them from patients. Finally, the revised Declaration of Helsinki states: "Medical research with some particularly vulnerable individuals, groups, or communities is only justified if it is responsive to their health needs or priorities; they stand to benefit from the resulting knowledge, practices, or interventions." Such a statement ignores the sociofinancial vulnerabilities experienced by many volunteers who, by definition, have no specific health needs or priorities and thus do not stand to derive any benefit other than financial gains from their participation.<sup>3,4</sup>

The Declaration of Helsinki is a fundamental text for medical research. Although we wish its revision process resulted in specific provisions for healthy volunteers, we appreciate that its broad principles must apply to all medical research fields in a fast-changing world in which new and complex ethical issues continuously arise. Unlike patients, whose voices are increasingly heard in care and research, healthy volunteers are largely invisible in public fora. In an attempt to change this, in 2024, we released the first *Global Ethics Charter for the Protection of Healthy Volunteers in Clinical Trials*,<sup>5</sup> which we propose as a complement to the revised Declaration of Helsinki to better protect this specific group of participants in human research.

We declare no competing interests.

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<sup>1</sup> World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**: 2191–94.

- 2 Fisher JA, Bompart F, Montrasio L, et al. A global ethics charter to protect healthy volunteers. *Lancet* 2024; **404**: 651.
- 3 Mwale S. Healthy volunteers in commercial clinical drug trials: when human beings become guinea pigs. London: Palgrave MacMillan, 2017.
- 4 Fisher JA. Adverse events: race, inequality, and the testing of new pharmaceuticals. New York: New York University Press, 2020.
- 5 The VolREthics initiative. The Global Ethics Charter for the protection of healthy volunteers in clinical trials. Inserm, 2024. <https://www.inserm.fr/en/ethics/volrethics/#the-global-ethics-charter-for-the-protection-of-healthy-volunteers-in-clinical-trials> (accessed Oct 23, 2024).

## AI ethics in medical research: the 2024 Declaration of Helsinki

The recent update to the World Medical Association's Declaration of Helsinki,<sup>1</sup> adopted at the 75th World Medical Association General Assembly in October, 2024, signals yet another milestone in the ongoing effort to safeguard ethical standards in medical research involving human participants. As with previous revisions, this update aims to reflect contemporary challenges, but it raises questions about the extent of its novelty and efficacy in addressing the evolving landscape of medical research.

On reviewing the latest changes, some aspects of the Declaration have undergone noteworthy improvements. The inclusion of environmental sustainability in medical research (article 11) is a progressive step, acknowledging the growing concern for the environmental impact of scientific pursuits. Moreover, enhanced emphasis on the inclusion of underrepresented groups (article 13) and the focus on minimising disparities by weighing the risks of inclusion versus exclusion in research (article 19) are commendable advancements towards equity. Another substantial addition is the call for meaningful engagement with communities and participants throughout the research process (article 6). This engagement reinforces

the ethical obligation to involve participants in decision making, enhancing the collaborative nature of medical research. However, although these advancements are positive, the 2024 revision does not radically transform the Declaration.

Many of the core ethical principles remain unchanged from previous iterations, whereas some essential areas still require further development. For example, despite the growing prominence of artificial intelligence (AI) and digital health in research,<sup>2</sup> the Declaration remains largely silent on the unique ethical challenges posed by these technologies. Additionally, although post-trial provisions (article 34) have been reinforced, their practical implementation remains an area of concern. Without a robust mechanism for enforcing these provisions globally, vulnerable populations might still be left unprotected in regions with weaker regulatory frameworks.

Finally, although the 2024 revision of the Declaration of Helsinki offers incremental improvements, it does not constitute a radical overhaul. The ethical challenges of modern medical research, particularly in the digital era, necessitate continued updates and increased specificity to remain relevant and protective of all participants. Will the current version of the Declaration adequately address the ethical complexities introduced by AI in research? Unfortunately, no. The absence of detailed guidance on AI, including issues of data privacy, algorithmic bias, and the role of machine learning in clinical decision making, suggests that more robust updates are necessary to fully confront these emerging ethical dilemmas.

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- 1 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human participants. *JAMA* 2024; published online Oct 19. <https://www.doi.org/10.1001/jama.2024.21972>.
- 2 Jeyaraman M, Balaji S, Jeyaraman N, Yadav S. Unraveling the ethical enigma: artificial intelligence in healthcare. *Cureus* 2023; **15**: e43262.

## Pembrolizumab for locally advanced cervical cancer

We read with great interest the results from the ENGOT-cx11/GOG-3047/KEYNOTE-A18 trial reported by Domenica Lorusso and colleagues.<sup>1</sup> The improvement in progression-free survival is exciting but difficult to interpret without additional radiation details and sites of progression. The total equivalent dose in 2 Gy fractions is reported as 87 Gy (IQR 83–92), which suggests that 25% of patients received less than 83 Gy. Data from EMBRACE-1 show that the minimum dose that covers 90% of the target volume of 85 Gy is required to offer a 95% chance of local control at 3 years for squamous cell cancers, and an even higher dose is needed for adenocarcinomas.<sup>2</sup> Additional information on volume and dose received by the high-risk cervix target and the technique of brachytherapy would be helpful. In addition, the protocol suggested a total dose of 60 Gy (equivalent dose in 2 Gy fractions) to enlarged lymph nodes;<sup>1</sup> however, the total dose delivered to nodes and their size was not reported, which is important as more than 80% of participants were node-positive. The overall imaging response rate of 76–79% in both treatment groups and complete response rate of about 50% are lower than the response rates reported in most modern series

with advanced radiation techniques. Clarification regarding some of the radiation details would be helpful to aid interpretation of the results, especially regarding whether the effect of adding pembrolizumab is local, regional, or distant (or a combination). Given EMBRACE-II<sup>3</sup> is investigating the effect of modern radiotherapy techniques, including intensity-modulated radiation therapy, image-guided radiation therapy, prophylactic para-aortic region radiation therapy for disease with more than two positive nodes, integrated boost to nodes, and adaptive brachytherapy, it is important to try to understand the results of ENGOT-cx11/GOG-3047/KEYNOTE-A18 in the context of the highest standard of chemoradiation treatment.

MK reports consulting fees from Theragenics, Pfizer, and Adaptiliv; reports being a member of the data and safety monitoring board for Alessa and GT Medical; reports receiving book royalties from Springer; and is the Vice President of the American Brachytherapy Society. SB reports being an employee of Varian, receiving fees for consulting from Elsevier, and being a member of the data and safety monitoring board for Xoft.

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- 1 Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial. *Lancet* 2024; **403**: 1341–50.
- 2 Schmid MP, Lindegaard JC, Mahanshetty U, et al. Risk factors for local failure following chemoradiation and magnetic resonance image-guided brachytherapy in locally advanced cervical cancer: results from the EMBRACE-I study. *J Clin Oncol* 2023; **41**: 1933–42.
- 3 Pötter R, Tanderup K, Kirisits C, et al. The EMBRACE II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018; **9**: 48–60.

We read with interest the Article by Domenica Lorusso and colleagues about the ENGOT-cx11/GOG-3047/

KEYNOTE-A18 trial.<sup>1</sup> This phase 3 study showed that pembrolizumab, when administered in combination with chemoradiotherapy, resulted in a statistically significant improvement in progression-free survival, compared with chemoradiotherapy alone, for patients with locally advanced cervical cancer. However, the results are difficult to interpret.

Although the total physical dose received by the cervix was provided in the Article, no information was provided regarding the minimal dose received by 90% of the high-risk clinical target volume, which is strongly associated with local control rate and progression-free survival.<sup>2</sup> Currently, it is inconceivable to compose a study on image-guided brachytherapy for cervical cancer without incorporating such dose information. The EMBRACE-I study has already shown that if an adequate dose of more than 85 Gy is delivered to 90% of the high-risk clinical target volume, a local control rate of 90% can be expected.<sup>2</sup> Therefore, it is possible that the poor quality of brachytherapy in this study led to a local control rate far inferior to that of the EMBRACE-I trial. Had high-quality brachytherapy been conducted and better local control achieved, it is likely that no statistically significant additional effect of pembrolizumab would have been observed. If this is the case, it would be challenging to consider the combination of pembrolizumab and chemoradiotherapy as a new standard of care. These points should be addressed by the authors.

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