INFORMATION BRIEF (RAPID REVIEW)

Artificial Intelligence [redacted] in Auto-Segmentation for Radiotherapy.

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TITLE: Artificial Intelligence [redacted] in auto-segmentation for Radiotherapy.

PURPOSE

To provide evidence of the effectiveness, safety and cost-effectiveness of artificial intelligence [redacted] in assisting with radiotherapy treatment planning. This report has been prepared to offer value-based input to the Ministerial Office following proposal from a company to introduce and integrate [redacted] suite in Malaysia healthcare.

BACKGROUND

In recent years, the intersection of artificial intelligence (AI) and healthcare has given rise to transformative advancements across various medical disciplines. One such domain where AI is making significant strides is in the field of radiotherapy. Radiotherapy, a cornerstone in the treatment of cancer, involves the precise delivery of targeted radiation to destroy cancer cells or inhibit their growth. The integration of AI into radiotherapy processes has been anticipated as a game-changer, revolutionizing treatment planning, delivery, and outcome prediction.[1]

The treatment of cancer using radiotherapy, involves a complex and meticulous processes involving enormous amount of information (e.g. clinical, dosimetry, imaging, and biologics), human-machine interaction, optimization and decision making. Thus, artificial intelligence can play a role in automation many of these processes and information while allowing for personalization of treatment via application of its predictive analytics.[2] Figure 1 below highlighting possible artificial intelligence role in radiation oncology.[3]

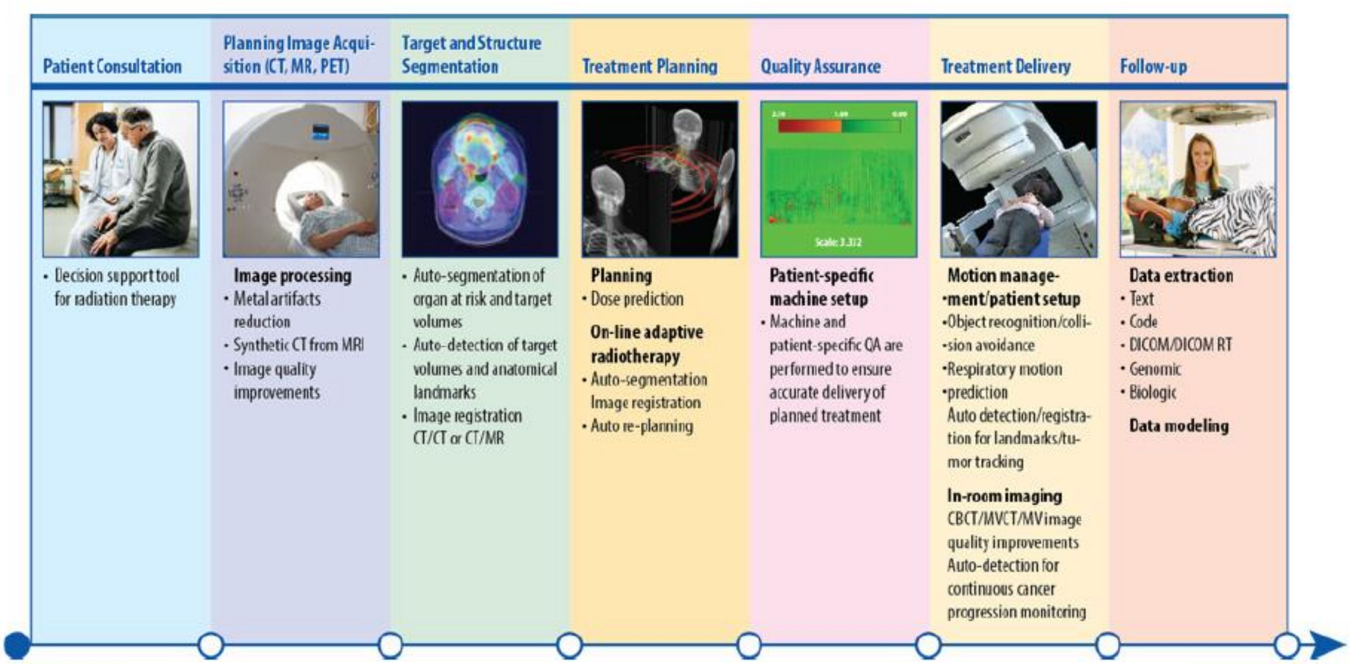

Figure 1: The schematics highlights AI role in radiation oncology. Source from Meyer et al. (2018)

One among many prominent applications of artificial intelligent in radiotherapy treatment planning is auto-contouring (segmentation) of organs, tissues and the targeted tumor. Contouring involves outlining the critical structures, organs at risk (OAR) and target volumes within a patient's anatomy on medical imaging data to guide radiotherapy treatment. Artificial Intelligence (AI) algorithms are trained on large datasets of medical images, encompassing a variety of anatomical variations and pathologies. These algorithms learn to identify and differentiate between different structures, such as organs at risk (OARs) and the target tumor volume, within the imaging data.[4]

Accurate segmentation of organs-at-risk (OARs) is critical for minimizing radiation toxicities to the normal structures during radiotherapy. Manual delineation of the target volume and OARs regions by the clinician is considered the gold standard in current clinical practice. However, contouring has been a time-consuming and labor-intensive.[5] Artificial intelligent auto-contouring is believed to be valuable in fastening radiotherapy treatment planning pathway and shorten time to treatments to patients. Furthermore, increased in efficiency from using AI auto-contouring will increase capacity, allowing clinician to focus more on patient-facing tasks and reduce waiting list. Automation of contouring hold potential to minimize the variability introduced by manual contouring, promoting consistency across different planners and institutions.[6]

Technical Features

According to the company submitted documents, [redacted] leveraging artificial intelligence to optimize radiotherapy process. It encompasses multiple software such as [redacted], [redacted], [redacted], [redacted], [redacted] and [redacted]. [redacted] is designed to target full-spectrum automation in radiotherapy, incorporating automated target delineation, process management, dose verification, scientific research platform, adaptive radiotherapy, telecollaboration, and AI-facilitated educational systems into a singular, all- inclusive solution. It is aimed to enhances target volume delineation, treatment planning, and quality assurance, optimizing treatment uniformity and addressing healthcare resources shortages.

Figure 2: Various artificial intelligence-based software incorporated in [redacted].

Among of the included software in [redacted], only [redacted] has been approved by U.S. Food and Drug Administration (FDA) and registered as class III by China National Medical Products Administration (NMPA). [redacted] registered with US FDA under company of [redacted] based in Shanghai, China in 2021.[7]

[redacted], is a standalone software which used by radiation oncology department to segment (non-contrast) CT images, to generate needed information for treatment planning, treatment evaluation and treatment adaptation.[7]

According to US FDA website, the software main function includes; 1) deep learning contouring – automatic segment on desktop and on the Web, and 2) manual segment – adjust the segment results after automatic segment. Others general functions includes preset region of interest (ROI), preset templates, transmit DICOM data, desktop patient management, review images, ROI management, web-based patient management and open and save of files. [redacted] can contour organ-at-risk (OAR) in anatomic region of head & neck, thorax, abdomen and pelvis.[7]

EVIDENCE SUMMARY

A total of 1107 titles were retrieved from the scientific databases such as Medline via OVID, and PubMed, using the search term; *radiotherapy, radiotherapy planning, computer assisted,* [redacted]*,* [redacted]*, artificial intelligence, and deep learning*. Search were limited to *English, Human and clinical study*. The last search was run on 10 January 2023. After reading tittles and abstract there is no evidence mentioning the effectiveness, safety or cost-effectiveness of [redacted] or [redacted] specifically. However, 10 studies submitted by the company, that were relevant to the topic has been chosen and included in this review.

EFFECTIVENESS

The role of artificial intelligence in auto-segmentation has been extensively discussed by scholars in recent years.[2] The included studies have proposed models based on convolutional neural networks (CNNs) within deep learning methods for segmentation of organ-at-risk (OAR) and clinical tumor volume (CTV) for head and neck tumor, lung cancer, breast cancer, prostate cancer, rectal cancer, and cervical cancer.[4]

The National Institute for Health and Care Excellence (NICE) published a health technology evaluation in September 2023 titled "Artificial Intelligence Technologies to Aid Contouring for Radiotherapy Treatment Planning: Early Value Assessment." In this technology evaluation, nine identified artificial intelligence technologies have been assessed for use in the NHS, namely: [redacted] [redacted], [redacted]), [redacted]), [redacted]), [redacted]), [redacted]), [redacted]), [redacted] and [redacted] This evaluation included 15 studies, comprising 8 prospective studies, 4 retrospective studies, 1 mixed retrospective and prospective study, and 2 conference abstracts. Although the level of evidence varied across technologies, all technologies assessed had some evidence showing the potential benefit of AI auto-contouring. Overall, the clinical evidence showed that AI autocontours were generally similar to manual contours, with most rated as clinically acceptable and ready to use or needing only minor edits. Artificial intelligence (AI) auto-contouring was consistently shown to be quicker than manual contouring, even when including time for healthcare professional review and edits. NICE concluded that AI auto-contouring with healthcare professional review and edits was likely to be clinically equivalent to manual contouring and quicker to perform. However, NICE has stated that technology developers must confirm agreements to generate more evidence in areas such as the clinical acceptability of contours and the amount of edits needed, the impact of AI autocontouring on radiation dose to organs at risk (OAR) and the tumor, time-saving including time for healthcare professional review and edits, resource use defined by healthcare professionals, and time and contouring errors and adverse events associated with AI autocontouring.[8]

Geng J et al. (2023) have published a blind randomized validation study to assess a proposed deep learning (DL)-based model in auto-segmentation of clinical target volume (CTV) and gross tumor volume (GTV) delineation for rectal cancer neoadjuvant radiotherapy. The proposed model is based on the DpnUnet architecture. Data were collected from 141 patients with stage II-III rectal cancer who received neoadjuvant chemotherapy at Peking University Cancer Hospital between March 2020 and May 2022. The cohort was divided into a training group (121/141) and a testing group (20/141) by random sampling (Fisher-Yates shuffle). Clinical tumor volume (CTV) and GTV contoured by two senior physicians were used as the "ground truth" (GT). The Dice Similarity Coefficient (DSC) values of the proposed model for CTV segmentation ranged from 0.69 to 0.97, with a mean ± SD of 0.85±0.06. The 95HD values ranged from 1.37 to 32.71, with a mean ± SD of 7.75±6.42. When excluding outliers (patients with perirectal lymph node invasion (LNI)), the 95HD values ranged from 1.37 to 8.1, with a mean ± SD of 5.93±1.55. For DL-based GTV segmentation, the DSC values ranged from 0.64 to 0.94, with a mean ± SD of 0.87±0.07, and the 95HD values ranged from 2.38 to 8.70, with a mean ± SD of 4.07 ± 1.67. Blind and randomized assessment of the CTV contour by an expert clinician showed that 96.4% in the GT group and 95.7% in the DL group were deemed clinically viable (Score $\geqslant$ 2) (p-value = 0.180). Over the testing GTV contours, contours that were considered clinically accepted were 100% in the GT group and 99.5% in the DL group (p-value = 0.012). The proposed DL model passed a head-to-head Turing test (>30%) for both CTV and GTV segmentation. In this study, it was not mentioned how long it took for DL to auto-segment one case when compared to manual segmentation[9]

Shen J et al. (2023) conducted a study to assess a convolutional neural network for automatic and accurate CTV and OARs segmentation in prostate cancer. Computed Tomography (CT) data from 217 patients with locally advanced prostate cancer requiring radiotherapy were retrospectively collected from January 2013 to January 2019 at The Peking Union Medical College Hospital. Clinical tumor volume (CTV) and OARs were manually contoured by a radiation oncologist prior to irradiation and served as the segmentation ground truth (GT). The patient dataset was then randomly assigned to a training-validation set (195 patients) and a test set (28 patients). The proposed model in this study is based on the CUNet architecture. The mean DSC and 95HD values for the defined CTVs were (0.84 ± 0.05) and (5.04 ± 2.15) mm, respectively. The mean DSC and 95HD values for the OARs were as follows: 0.913 ± 0.078 and 2.462 ± 3.984 mm for the bladder, 0.850 ± 0.051 and 1.973 ± 0.924 mm for the bone marrow, 0.899 ± 0.027 and 1.424 ± 0.329 for the femoral head left, 0.897 ± 0.023 and 1.547 ± 0.421 for the femoral head right, 0.783 ± 0.032 and 6.278 ± 2.275 for the rectum, 0.822 ± 0.035 and 5.369 ± 2.294 for the small intestine, and 0.824 ± 0.056 and 3.345 ± 3.431 for the spinal cord. In the Turing Imitation test, the AI contour scored 53.15% and 54.05% positive when evaluated by clinicians A and B, respectively. The average delineation time was less than 15 seconds for the CT scan of one patient.[10]

Shen J et al. (2022) conducted a study analyzing the accuracy of a proposed model (DiUNet) in segmenting the clinical target volume for lung cancer with bulky lymph nodes. Computed Tomography (CT) data from 200 patients with stage III-IV small cell lung cancer (SCLC) were collected at Peking Union Medical College Hospital from November 2010 to January 2021, with a total slice number of 16,676. The CT image dataset was randomly divided into training-validation (180 patients) and test (20 patients). The DSC values of the AI contour for the lymph node stations ranged from 0.65 to 0.92, and the 95HD values ranged from 1.61 to 4.68. When evaluated by the oncologist, 98.87% of AI contours were deemed clinically acceptable (Score ⩾ 2). The average scores were 2.914 and 2.899 for AI and GT, respectively, showing no significant difference ($p > 0.05$). The proposed method took approximately 5 minutes per test case to generate a contour compared to more than 80 minutes if completely delineated by the oncologist.[11]

Liu Z et al. (2021) conducted a study to test the accuracy and effectiveness of a new CNN model based on the 2D U-Net model (U-ResNet) in segmenting the CTV and OARs in breast cancer patients who underwent breast-conserving surgery (BCS) and were treated with radiotherapy. In this study, CT scans from 160 patients were obtained at Peking Union Medical College Hospital from January 2019 to December 2019, totaling 12,640 CT slices. Manual segmentation of the CTV and OARs (contralateral breast, lungs, heart, and spinal cord) by trained radiation oncologists was used as the 'ground truth.' For CTV segmentation, the average DSC and 95HD values of U-ResNet were 0.94 ± 0.019 and 4.31 mm ± 1.76, respectively. For OARs segmentation, the mean DSC and 95HD values were 0.94 ± 0.016 and 3.59 ± 1.56 for the contralateral breast, 0.93 ± 0.024 and 4.37 mm ± 2.13 for the spinal cord, 0.94 ± 0.023 and 4.86 mm ± 1.48 for the heart, 0.96 ± 0.017 and 3.18 mm ± 1.64 for the right lung, and 0.96 ± 0.025 and 2.79 mm ± 1.62 for the left lung, respectively. Evaluation by two independent oncologists, A and B, showed that CTV contours generated by AI were deemed clinically acceptable in 99.4% of cases. The Wilcoxon matched-pairs test was performed for the evaluation of the two oncologists for AI and GT contours separately. The results indicated that the average score of oncologist A was higher than that of oncologist B in AI contours, with a significant statistical difference ($P = 0.009$ for AI contours and $P = 0.314$

for GT contours). The time for auto-segmentation of CTV and OARs with the U-ResNet model was 10.03 seconds compared with 20-30 minutes when done manually by an experienced oncologist.[12]

Liu Z et al. (2021) conducted a study to evaluate a deep-learning-based auto-segmentation model for CTV delineation in cervical cancer, comparing it to manual delineation by radiation oncologists. The proposed model is based on DpnUnet and was trained and tested using sets of CT scan data from 237 patients with locally advanced cervical cancer at Peking Union Medical College Hospital. In order to evaluate the model, another 20 new validation patients with locally advanced cervical cancer undergoing intensity-modulated radiation therapy (IMRT) were collected from November 2018 to December 2018. Clinical tumor volume contours delineated manually by radiation oncologists served as the 'ground truth' (GT). The DSC and 95HD values of the proposed model were 0.88 $\pm$ 0.03 and 3.46 $\pm$ 1.88 mm, respectively. When evaluated by the oncologist, 97.4% of the AI contours were deemed suitable for clinical application (score $\geqslant$2). The overall average scores for AI and GT were 2.68 vs. 2.71 in week 0 ($P = .206$) and 2.62 vs. 2.63 in week 2 ($P = .552$), respectively. In the Turing imitation test, the AI contour received a 54% positive rate in both week 0 and week 2 when compared to the GT contour. This test demonstrated that the proposed deep learning machine model performed equally well or even better than human delineation. However, in this study, there was no mention of time-cost analysis for AI to segment a model compared to manual delineation.[13]

Wu Y et al. (2021) have published a blind randomised validation study assessing a novel convolutional neural network (CNN)-based model for auto-segmentation of CTV in rectal cancer patients receiving neoadjuvant radiotherapy. The proposed model was based on the U-Net architecture and was trained using CT images from 122 rectal cancer patients receiving neoadjuvant radiotherapy at Peking Union Medical College Hospital between July 2018 and August 2019. All patients' ground truth (GT) CTVs were manually delineated by a radiation oncologist with more than 10 years of experience. Thirteen cases were used as the test set. The mean DSC values of the two randomly validated groups for clinicians' evaluation and Turing test were 0.91 ± 0.02 and 0.89 ± 0.02 ($p = 0.113$), while the mean 95HD values were 8.59 ± 1.98 and 8.97 ± 1.86 ($p = 0.284$), respectively. According to the evaluation by clinicians in Week 0, 94.6% of AI contours and 94.0% of GT contours were deemed clinically acceptable (score $\geqslant$ 2). The AI group's mean scores were better than the GTs, though there was no significant difference (Week 0: 2.59 vs. 2.52, $p = 0.086$; Week 2: 2.55 vs. 2.47, $p = 0.11$). In the Turing test, nearly half of the slices were scored $\geqslant$ 0.5, indicating clinicians cannot distinguish between AI and GT contours in these slices. The average time for automatic segmentation in the validation groups was 15 seconds per patient, compared with about 45–60 minutes for manual work in clinical practice."[14]

Liu Z et al. (2020) conducted a study evaluating the accuracy of a segmentation method in locally advanced cervical cancer patients who had been treated with radiotherapy. The proposed method was based on the U-net architecture. One hundred five patients' CT scans were collected at Peking Union Medical College Hospital, Beijing, China, from November 2012 to January 2015. The training set contained 77 patients, the validation set contained 14 patients, and the testing set also contained 14 patients. Seven organs, including the bladder, bone marrow, femoral head left, femoral head right, rectum, small intestine, and spinal cord, were defined as cervical cancer OARs. Organ at risk (OARs) segmented by the models were compared to segmentation delineated manually by trained radiation oncologists. The mean DSC values of the proposed model were 0.924 ± 0.046, 0.854 ± 0.054, 0.906 ± 0.031, 0.900 ± 0.023, 0.791 ± 0.032, 0.833 ± 0.030, and 0.827 ± 0.063 for the bladder, bone marrow, femoral head left, femoral head right, rectum, small intestine, and spinal cord, respectively. The mean Hausdorff Distance (HD) values were 5.098 ± 11.84, 1.993 ± 1.153, 1.390 ± 0.380, 1.435 ± 0.413, 5.949 ± 3.781, 5.281 ± 2.294, and 3.269 ± 3.756 for the respective OARs. The segmentations were then evaluated by an oncologist with more than 15 years of experience. The mean percentage of 'acceptable' or 'requiring minor revision' segmentation was 90.34%. This proposed model can segment OARs on one slice in 0.06 seconds when running on GTX 1080 GPU compared to more than 30 seconds when being done manually by an experienced oncologist.[15]

In another study by Liu Z et al. (2020), the accuracy of a novel 2.5D CNN network-based method called DpnUNet in segmenting the CTV and OARs in cervical cancer patients was evaluated. The study was conducted at Peking Union Medical College Hospital, Beijing, China, where CT data from 237 patients with locally advanced cervical cancer were collected from November 2012 to January 2018. The CTV and OARs segmented manually by trained radiation oncologists were used as comparators and ground truth. The mean DSC and 95HD values for delineated CTV were 0.86 and 5.34 mm, respectively. For OARs segmentation, the mean DSC and 95HD values for the bladder, bone marrow, left femoral head, right femoral head, rectum, bowel bag, and spinal cord were 0.91 and 4.05 mm, 0.85 and 2.16 mm, 0.90 and 1.27 mm, 0.90 and 1.51 mm, 0.82 and 4.29 mm, 0.85 and 4.35 mm, and 0.82 and 4.96 mm, respectively. When evaluated by a professional radiation oncologist with more than 15 years of experience, more than 90% of the slices predicted from DpnUNet were evaluated as 'No revision' or requiring 'Minor revision.' The average delineation time for one patient's CT images was about 15 seconds. The average time for manually revising the produced segmentation was 10.37 ± 3.42 minutes per test case.[16]

Liu Z et al. (2020) conducted another study aiming to construct and validate a model that can auto-segment CTVs of breast cancer patients for radiotherapy. In this study, CT scans of 110 patients who underwent modified radical mastectomies were collected. The data were taken from female patients at Peking Union Medical College Hospital, Beijing, China, from March 2019 to July 2019. A total of 9130 CT slices were collected from those patients. Manually generated segmentation by a radiation oncologist was used as 'ground truth (GT).' The mean DSC and 95HD values of the proposed model in this study were 0.90 ± 0.02 and 5.65 ± 1.29 mm, respectively. The segmented CTV by both AI and manual segmentation were then evaluated anonymously by two experienced clinicians, A and B. The results given by clinician A showed that 99.3% of the chest wall CTV slices from the AI group, and all the chest wall CTV slices from the GT group, can be accepted. Meanwhile, clinician B showed that 98.9% of the chest wall CTV slices from the AI group, and all the chest wall CTV slices from the GT group, can be accepted. The score differences between the AI group and the GT group showed no statistically significant differences for either clinician (P = 0.075 and P = 0.444). The proposed model took 3.45 seconds to finish segmentation compared to 20 minutes when being done manually.[17]

SAFETY

From the evidence search, there is no evidence retrieved on the safety, adverse events or errors reported due to AI segmentation. However, in the health technology evaluation published by NICE, they stated that AI auto-segmentation must always be reviewed by trained healthcare professionals and edited as needed before being used. NICE also considers that the risk of AI auto-contouring with healthcare professional review and edit is likely to be low.[8]

According to the NICE technology evaluation, healthcare professionals were advised although AI auto-contouring can segment most organs at risk (OAR) and clinical target volumes (CTV), there were some structures that needed major edits or were unusable. These were typically smaller structures such as the cochlea, optic chiasm, optic nerve, penile bulb, and pituitary gland. Furthermore, AI technologies sometimes have difficulties contouring very small or irregularly shaped organs. Artifical Intelligence (AI) autocontours may also be less accurate for people with atypical anatomy, i.e., previous surgery or with less familiar positioning during imaging. Artifical Intelligence (AI) models also can contain algorithmic bias depending on the population used in training, which may not be representative of populations in clinical practice. There might be populations that were underrepresented in the training set, such as the female pelvis, breast cancer in men, children, and young patients. In these specific populations, manual segmentation might be more appropriate and accurate[8]

COST-EFFECTIVENESS

There was no evidence found on the cost-effectiveness of artificial intelligence use in auto-segmentation for radiotherapy. The exact price of *RT-Solution* software including the cost for implementation and training were unable to be found. In UK, commercially produced AI-based auto-contouring software cost ranged from [redacted] plan[8]. NICE concluded in the technology evaluation that although there were uncertainties in the cost analysis, AI technologies were likely to be cost-saving or cost-neutral, but it largely depended on the technology costs and time saving.[8]

ORGANIZATIONAL

Artificial intelligence software for auto-segmentation in radiotherapy treatment planning needs to be compatible with local existing hospital ecosystem. Technology providers also need to include training packages for healthcare professionals to develop and adapt their skills to the system. Artificial intelligence software may be exposed to the risk of bias depending on its training set data, which may not be representative of the local population. In any case, AI models should ideally be trained on a representative national population. If the training set was not based locally, technology providers should be able to provide information on the training dataset as part of their product information pack, including demographics of the population dataset. Patients should be informed and explained whenever artificial intelligence software is used in their radiotherapy treatment planning.[8]

CONCLUSION

There was no evidence retrieved on [redacted] or [redacted] for radiotherapy treatment planning. However, there was fair amount of evidence retrieved on of use of artificial intelligence in auto-segmentation, demonstrating its potential in shortening time for segmenting organ-at-risk and target volume. Organizational issue when considering integration of AI-based software for radiotherapy includes but not limited to, compatibility of the software to existing local infrastructures and system, and training to the providers on the usage of the software. More studies are needed to explore and evaluate the safety of AI software in a longer term.

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