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# 2D monolithic silicon-diode array detectors in megavoltage photon beams: does the fabrication technology matter? A medical physicist's perspective

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# 2D monolithic silicon-diode array detectors in megavoltage photon beams: does the fabrication technology matter? A medical physicist's perspective

# Abstract

A family of prototype 2D monolithic silicon-diode array detectors (MP512, Duo, Octa) has been proposed by the Centre for Medical Radiation Physics, University of Wollongong (Australia) for relative dosimetry in small megavoltage photon beams. These detectors, which differ in the topology of their 512 sensitive volumes, were originally fabricated on bulk p-type substrates. More recently, they have also been fabricated on epitaxial p-type substrates. In the literature, their performance has been individually characterized for quality assurance (QA) applications. The present study directly assessed and compared that of a MP512-bulk and that of a MP512-epitaxial in terms of radiation hardness, long-term stability, response linearity with dose, dose per pulse and angular dependence. Their measurements of output factors, off-axis ratios and percentage depth doses in square radiation fields collimated by the jaws and produced by 6 MV and 10 MV flattened photon beams were then benchmarked against those by commercially available detectors. The present investigation was aimed at establishing, from a medical physicist's perspective, how the bulk and epitaxial fabrication technologies would affect the implementation of the MP512s into a QA protocol. Based on results, the MP512-epitaxial would offer superior radiation hardness, long-term stability and achievable uniformity and reproducibility of the response across the 2D active area.

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# **2D** monolithic silicon-diode array detectors in megavoltage photon beams: does the fabrication technology matter? A medical physicist's perspective

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18 A family of prototype 2D monolithic silicon-diode array detectors (MP512, Duo, Octa) has been proposed by the Centre for 19 Medical Radiation Physics, University of Wollongong (Australia) for relative dosimetry in small megavoltage photon beams. 20 These detectors, which differ in the topology of their 512 sensitive volumes, were originally fabricated on bulk p-type substrates. More recently, they have also been fabricated on epitaxial p-type substrates. In the literature, their performance has been 21 individually characterized for quality assurance applications. The present study directly assessed and compared that of a MP512-22 23 bulk and that of a MP512-epitaxial in terms of radiation hardness, long-term stability, response linearity with dose, dose per 24 pulse and angular dependence. Their measurements of output factors, off-axis ratios and percentage depth doses in square 25 radiation fields collimated by the jaws and produced by 6 MV and 10 MV flattened photon beams were then benchmarked against those by commercially available detectors. The present investigation was aimed at establishing, from a medical physicist's 26 27 perspective, how the bulk and epitaxial fabrication technologies would affect the implementation of the MP512s into a quality assurance protocol. Based on results, the MP512-epitaxial would offer superior radiation hardness, long-term stability and 28 achievable uniformity and reproducibility of the response across the 2D active area. 29

Key words: dosimetry, 2D monolithic silicon-diode array detector, epitaxial silicon, megavoltage photon beam

## 33 **1. Introduction**

The Centre for Medical Radiation Physics (CMRP), University of Wollongong (Australia) has designed a range of silicondetector prototypes dedicated to quality assurance (QA) applications in megavoltage (MV) photon beams delivered with medical linear accelerators (linacs) [1], [2]. Among these, it has proposed and characterized three 2D monolithic silicon-diode arrays (the MP512, the Duo and the Octa), different in the topology of their 512 diode-sensitive volumes (SVs) (Figure 1).



Figure 1. 2D monolithic silicondiode array detectors proposed by the CMRP for QA in MV photon beams: (a) the MP512, (b) the Duo and (c) the Octa.

<sup>39</sup> 



These devices, operated in passive mode (no external bias applied), have a high temporal resolution of the read-out electronics (pulse-by-pulse acquisition) [3] which makes them attractive for applications in dynamic stereotactic treatment modalities. They were devised for in-phantom measurements. As such, they are sandwiched between two 5 mm thick PMMA slabs, with the

upper one having a small recess or air gap [4] on top of the SVs to minimize [5] the corrections required to account for the field
 size-dependent response of these silicon-based detectors in small MV photon beams [6].

51 The detectors were originally fabricated on a bulk p-type silicon-wafer Czochralski [7] substrate (resistivity of  $10 \ \Omega cm$ ) and 52 pre-irradiated to stabilize their response with accumulated dose [8]. More recently, the same devices have also been fabricated on 53 a radiation-hard p-type epitaxial [9] layer (resistivity of  $100 \ \Omega cm$ ), grown onto a thick heavily-doped silicon substrate (resistivity 54 of  $0.001 \ \Omega cm$ ). The thin active epitaxial layer has the required mechanical strength over large areas. These epitaxial devices may 55 have improved radiation hardness and may not require pre-irradiation for sensitivity stabilization [10], [11].

In the literature, the performances of the MP512-bulk [12], [13], the MP512-epitaxial [14], the Duo-bulk [15], the Duoepitaxial [16] and the Octa-epitaxial [17], [18] have been individually characterized for machine-specific and patient-specific QA. Machine QA describes procedures intended to verify the dosimetric parameters of a linac, such as its output factor. Patient QA, also referred to as pre-treatment QA, describes procedures to verify clinical plans. There is, however, a lack of a direct and thorough comparison of how the bulk and epitaxial fabrication technologies would affect the implementation of these devices into a QA protocol. Aiming at answering this question, the present study evaluated and compared, from a medical physicist's perspective, the performance of a MP512-bulk and of a MP512-epitaxial.

## 64 2. Materials and methods

## 2.1. Dosimeters and participating facilities

Along with the MP512-bulk and the MP512-epitaxial prototypes, the present study considered as benchmark measurements,
 under the same experimental conditions, by multiple alternative detectors: Gafchromic<sup>TM</sup> EBT3 films (Ashland Inc., USA),
 MOSkin<sup>TM</sup> detectors and three different ionization chambers (Table 1).

Films were scanned with a Microtrex ScanMaker i800 flatbed scanner using a 48-bit RGB and a resolution of 72 dpi. All
 films were pre- and post-scanned six times using only the last three optical density maps, maintaining a consistent orientation.
 The film analysis methodology was the same as that used by Aldosari et al. [12].

MOSkin<sup>TM</sup> are metal-oxide-semiconductor field-effect transistor (MOSFET) -based devices developed for real-time *in vivo* dose measurements. Their SV consists of a 0.55  $\mu$ m thick SiO<sub>2</sub> layer, on top of a silicon substrate, mounted underneath a thin plastic layer with a uniform thickness of 0.07 mm. As such, they provide a skin-equivalent depth-dose when placed on a surface [19], [20].

The ionization chambers used were a CC13 (IBA Dosimetry, Germany), a Farmer chamber type NE2571A used with a UNIDOS electrometer (PTW, Germany) with a supply voltage of +300 V, and a Markus chamber model N23343 (PTW, Germany).

80 Table 1. Description of benchmarking detectors considered for each test in the present study.

Benchmarking detectors	Test
films	Angular dependence, output factors, off-axis ratios
MOSkin™	Output factors
CC13 chamber	Percentage depth dose
Farmer chamber	Dose per pulse dependence
Markus chamber	Percentage depth dose

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Experimental measurements for radiation hardness investigation were performed at the Gamma Technology Research Irradiator (GATRI) facility at the Australian Nuclear Science and Technology Organisation (ANSTO, Lucas Heights, NSW, Australia). Investigations of long-term stability, response linearity with dose, dose per pulse dependence, angular dependence and measurements described in the clinical application section were performed at the Illawarra Cancer Care Centre (ICCC, Wollongong, NSW, Australia) using a Varian Clinac® iX (Varian Medical System, Palo Alto, CA, USA) medical linac. The linac operated with a pulse frequency of 360 Hz and was calibrated to deliver 1 cGy/MU at d<sub>max</sub> in water at 100 cm source-tosurface distance (SSD).

## 2.2. Radiation hardness, long-term stability and response linearity with dose

Investigation of radiation hardness was performed by irradiating the MP512s with a dose rate 2.28 kGy/hr using a Co-60 gamma source. The MP512-bulk was irradiated with a total water-equivalent dose of 80 kGy, with response stability assessed after dose increments of 10 kGy. The MP512-epi was irradiated with a total water-equivalent dose of 140 kGy, with response stability assessed after dose increments of 20 kGy or 40 kGy. Response stability assessments were performed by irradiating the devices, at 1.5 cm depth in solid water phantom, 100 cm SSD, with a 10 cm side square field collimated by the jaws and produced by a 6 MV photon beam. Each measurement was repeated 5 times to minimize random uncertainties, and only the average response of the 4 central SVs was considered.

97 Investigation of long-term stability after pre-irradiation was performed by considering the response variation of the MP512s 98 over 12 months. Assessments, made at 1 month intervals, were done by irradiating the devices, at 1.5 cm depth in solid water 99 phantom, 100 cm SSD, with a 10 cm side square field collimated by the jaws and produced by a 6 MV photon beam. Accumulated total dose was 500 Gy, while each measurement had a delivered dose of 100 monitor units (MU) at 600 MU/min. 100 101 Only the average response of the 4 central SVs was considered.

Investigation of response linearity was done in the range from 1 MU to 500 MU. The test was performed by irradiating the 102 MP512s, at 1.5 cm depth in solid water phantom, 100 cm SSD, with a 10 cm side square field collimated by the jaws and 103 104 produced by 6 MV and by 10 MV photon beams.

#### 105 2.3. Dose per pulse dependence

106 Investigation of the dose per pulse dependence of the response of the MP512s was performed by irradiating the devices, at 1.5 cm depth in solid water phantom, with a 10 cm side square field collimated by the jaws and produced by a 6 MV photon 107 108 beam. The devices were irradiated by a fixed number of MU, changing the SSD in the range of 100 cm to 370 cm to change the 109 dose per pulse at the detector location [12], [21]. Doses per pulse in the range from 0.01 mGy/pulse to 0.34 mGy/pulse were considered. Each measurement was repeated 5 times to minimize random uncertainties. 110

111 The relative sensitivity S<sub>SSD</sub> of the MP512s at any given SSD was defined as:

112 
$$S_{SSD} = \frac{Q}{Q_{IC}}$$
(1)

with Q the average charge collected by their 4 central SVs and  $Q_{IC}$  the charge collected by the ionization chamber used as reference, at the same SSD (i.e. for the same dose per pulse). The dose per pulse dependence of the MP512s was defined as: 113 114

- $DPP_{dep} = \frac{S_{SSD}}{S_{SSD=ref}}$ with S<sub>SSD=ref</sub> the sensitivity S<sub>SSD</sub> at the reference dose per pulse of 0.278 mGy/pulse. (2)115
- 116

#### 117 2.4. Angular dependence

118 Investigation of the angularly-dependent response was performed by irradiating the MP512s, lodged into a cylindrical PMMA 119 phantom, with a 10 cm side square field collimated by the jaws and produced by 6 MV and 10 MV photon beams. The radiation-120 beam incidence angle  $\theta$  was changed in the range from 0° to 180° in 10° steps, irradiating the MP512s at each step 5 times with 121 100 MU at 600 MU/min. Films were used as reference assuming their response is angular independent [22], although this has 122 recently been disputed [23].

123 The investigation procedure, described also by Stansook et al. [24], starts with defining, for each SV of the MP512s, a 124 calibration factor A as the ratio of their response, MP( $\theta$ ), to the response of the film, EBT3( $\theta$ ), in the same location: MD(A)

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127

$$A(\theta) = \frac{MP(\theta)}{EBT3(\theta)}$$
(3)

3

126 The angular response of each SV was then defined as:

$$C(\theta) = \frac{A(\theta)}{A(\theta = 0^{\circ})}$$
(4)

with  $\theta = 0^{\circ}$  the incidence angle for which the beam was perpendicular to the 2D active surface of the MP512s. Only the average 128 response of the 4 central SVs was considered. 129

130 2.5. Clinical application

131 As a clinical application, we considered measurements relevant to machine-specific QA, such as output factors (OFs), off-axis 132 ratios (OARs) and percentage depth doses (PDDs).

133 Prior to all measurements, the MP512s were aligned with respect to the machine central axis (CAX) by maximizing the 134 response of their central SVs using the smallest available square field (0.5 cm side). Each measurement was repeated 3 times to 135 minimize random uncertainties.

136 For OFs, the MP512s, at 10 cm depth in solid water phantom, 90 cm SSD, were irradiated with square fields in the range 137 from 0.5 cm to 10 cm side collimated by the jaws and produced by 6 MV and 10 MV photon beams.

138 For OARs, the MP512s, at 10 cm depth in solid water phantom, 90 cm SSD, were irradiated with square fields in the range 139 from 1 cm to 4 cm side collimated with the jaws and produced by a 6 MV photon beam. For a quantitative estimation of full-140 width half-maximum (FWHM) and penumbra width (taken as the distance between the 80% and the 20% isodose levels), all 141 OARs were analysed with MATLAB® (MathWorks, Inc., Natick, MA, USA) using a shape-preserving interpolant function.

142 For PDDs, the MP512s were irradiated in a solid water phantom at depths in the range from 0.5 cm to 30 cm, 100 cm SSD, 143 by a square field 10 cm side collimated by the jaws and produced by 6 MV and 10 MV photon beams. PDDs by the MP512s 144 were benchmarked against those by a CC13 chamber for depths in the range from 1.5 cm to 30 cm and those by a Markus 145 chamber for depths in the range from 0.5 cm to 10 cm. The known dose over-estimation by the Markus chamber was corrected 146 for by following the Velkley and Rawlinson method [25][26].

## 148 **3. Results**

149 3.1. Radiation hardness, long-term stability and response linearity with dose

Radiation hardness in terms of sensitivity degradation with accumulated dose is in Figure 2 for both MP512s. Sensitivity is shown normalized to that at zero accumulated dose. Error bars, calculated as 1 standard deviation, did not exceed the symbol size. Sensitivity of the MP512-bulk was reduced to about 75% of the initial value after 10 kGy, that of the MP512-epitaxial was approximately 85% of the initial value after 80 kGy.

In terms of long-term stability, the variation in sensitivity was  $\pm 10\%$  for the MP512-bulk, after up to 500 Gy delivered by a 6 MV photon beam over 12 months. It was within  $\pm 0.9\%$ , with 2 standard deviations being  $\pm 0.03\%$ , for the MP512-epitaxial.

The response of the MP512s was linear in the investigated dose range from 10 to 500 MU (adjusted regression coefficient  $R^2 = 1.000 \pm 0.001$ ).

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Figure 2. Sensitivity degradation with accumulated dose of the MP512s. Response is shown normalized to that at zero dose. Sensitivity of the MP512-bulk was reduced to  $\sim$ 75% of the initial value after 10 kGy. Sensitivity of the MP512-epitaxial was reduced to  $\sim$ 85% of the initial value after 80 kGy.

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159 *3.2. Dose per pulse dependence* 

The dose per pulse-dependence of the MP512s is in Figure 3. Error bars are 1 standard deviation. Maximum dose per pulsedependence was approximately 6% at 0.01 mGy/pulse, relative to 0.278 mGy/pulse, for the MP512-bulk. It was 8% at 0.02 mGy/pulse, relative to 0.278 mGy/pulse, for the MP512-epitaxial.

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Figure 3. Dose per pulse dependence of the MP512s. Response is shown normalized to that at 0.278 mGy/pulse. Maximum dose per pulse-dependence was  $\sim 6\%$  at 0.01 mGy/pulse for the MP512-bulk. It was  $\sim 8\%$  at 0.02 mGy/pulse for the MP512-epitaxial.

164 *3.3. Angular dependence* 

The angularly-dependent response of the MP512s is in Figure 4 (6 MV beam) and in Figure 5 (10 MV beam). Error bars, calculated as 2 standard deviations, did not exceed the symbol size.



Figure 4. 6 MV beam: angularly-dependent response of the MP512s. 0° refers to incident-beam direction perpendicular to the 2D detector plane. Maximum sensitivity degradation was reached at incident-beam angle of 90°, i.e. beam direction parallel to the 2D detector plane.

Figure 5. 10 MV photon beam: angularly-dependent response of the MP512s. Differences seen by comparing the angular dependence in a 6 MV and in a 10 MV beam are explained by beam quality-dependent perturbations to particle spectra introduced by SV and packaging.

### 168 *3.4. Clinical application*

169 OFs by the MP512s, films and MOSkin<sup>TM</sup> are in Figure 6 (6 MV beam) and in Figure 7 (10 MV beam). Percentage differences 170 are shown in the lower panels.

A cross-plane OAR by the MP512-epitaxial and by film in a square field jaws-defined of 1 cm side is shown in Figure 8 (6 MV beam). In all investigated fields, FWHMs of cross-plane OARs measured by the MP512-epitaxial agreed with those by films to within 1% in a 6 MV beam and to within 1.5% in a 10 MV beam. All penumbra widths agreed within 0.6 mm.

174PDDs by the MP512s, Markus and CC13 chambers are in Figure 9 (6 MV beam) and in Figure 10 (10 MV beam). Differences175between measurements by the MP512s and the chambers were within  $\pm 2\%$  at all depths, for both beam energies investigated.176Error bars, calculated as 2 standard deviations, do not exceed the symbol size.





Figure 6. 6 MV beam: OFs by the MP512s, films and MOSkin<sup>TM</sup>. Percentage differences are shown in the lower panel.



Figure 7. 10 MV beam: OFs by the MP512s, films and MOSkin<sup>TM</sup>. Percentage differences are shown in the lower panel.



Figure 8. 6 MV beam: cross plane OAR in a 1 cm side square field by the MP512-epitaxial and by film.



Figure 9. 6 MV beam: PDDs by the MP512s, Markus and CC13 chambers. Percentage differences are shown in the lower panel.



Figure 10. 10 MV beam: PDDs by the MP512s, Markus and CC13 chambers. Percentage differences are shown in the lower panel.

## 178 **4. Discussion**

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## 4.1. Radiation hardness, long-term stability and response linearity with dose

180 For a bulk device, pre-irradiation is required to stabilize its response with accumulated dose, at the cost of a reduced sensitivity 181 [8]. In the present work, the sensitivity of the MP512-bulk was heavily reduced to close to 75% of the initial value and stabilized 182 after irradiation with 20 kGy by a Co-60 gamma photon source, but with a residual sensitivity variation of approximately  $\pm 5\%$ 183 which would call for frequent recalibrations. The sensitivity of the MP512-epitaxial was stabilized within  $\pm 3\%$  after 40 kGy and 184 within  $\pm 0.3\%$  after 80 kGy, demonstrating its superior radiation-hardness and making frequent recalibrations optional. Residual 185 sensitivity was close to 85% of the initial value. These results can be complemented by those on the investigation of the long-186 term stability of the MP512s after pre-irradiation, adding to the superior performance of the MP512-epitaxial over the MP512-187 bulk.

The linear response of the MP512s in the investigated dose range from 10 to 500 MU agrees with previous investigations which have demonstrated that the MP512-bulk [12], the Octa-bulk and the Octa-epitaxial [27] were linear in the dose range 50 to 500 MU. These results suggest that both a bulk and an epitaxial substrate would in principle offer an equivalent performance in terms of response linearity with delivered dose.

## 192 *4.2. Dose per pulse dependence*

The dose per pulse of the order of  $10^2$  Gy/s under which the detector is operated is much different than the average dose to water delivered by medical linacs of the order of 4 Gy/min at d<sub>max</sub> [1], [28]. For QA applications, the dose per pulse varies with depth in water, across the radiation field, due to introduction of beam attenuators [29] and, if flattening filter free photon beams are used, also in the central axis region of a radiation field [30]. The dose per pulse dependence of the response of silicon-based detectors is well-known, with a decrease in sensitivity expected with decreased dose per pulse, as first reported by Rikner and Grusell [31]. This dependence affects measurement accuracy and would call for a correction.

Previous studies have investigated the dose per pulse dependence of the MP512, Duo and Octa in a 6 MV beam. The MP512bulk had a maximum sensitivity degradation of approximately 5% in the range from 0.009 mGy/pulse to 0.34 mGy/pulse with respect to 0.278 mGy/pulse [12]. The Duo-bulk had sensitivity degradation within 23% at 0.021 mGy/pulse with respect to 0.278 mGy/pulse [15]. The non-preirradiated Octa-epitaxial had a maximum sensitivity degradation of close to 26% at 0.021 mGy/pulse relative to 0.278 mGy/pulse [32].

In the present study, the maximum sensitivity degradations of approximately 6%, MP512-bulk, and 8%, MP512-epitaxial, found was of the same order of magnitude between the two devices. The degradation was however significantly smaller than that reported by investigations on the Duo and on the Octa, a result which would merit further investigation. The larger relative sensitivity degradation of the MP512-epitaxial over the MP512-bulk can be explained by the fact that the dose per pulse dependence decreases by decreasing the resistivity of the silicon active substrate, or by reducing the minority carrier lifetime by pre-irradiation [11], [33].

## 210 *4.3.* Angular dependence

The angularly-dependent response of a silicon detector is mainly explained in terms of anisotropy in its materials and assembly [34].

In a previous investigation [32], the Octa-bulk had a maximum angular dependence of 30% in the case of a 6 MV beam. The Octa-epitaxial had a maximum angular dependence of 23% in the case of a 6 MV beam and of 20% in the case of a 10 MV beam. It was also reported that the MP512-bulk [24] had a maximum angular dependence of  $18.5\% \pm 0.5\%$  in the case of a 6 MV beam and of  $15.5\% \pm 0.5\%$  in the case of a 10 MV beam.

In the present study, results for the MP512-epitaxial were within  $\pm 2\%$  of those for the MP512-bulk [24] at all angles. In all cases, maxima were reached at incident beam angle of 90° i.e. when the beam direction was parallel to the 2D detector plane. In the range from 0° to 90°, angular dependence increases owing to increasing beam attenuation by the silicon. From 90° to 180°, angular dependence decreases for the opposite reason. In this case, lower relative values are explained by additional attenuation owing to the detector packaging. The differences seen by comparing the angular dependence in a 6 MV beam with that in a 10 MV beam are explained by beam quality-dependent perturbations to the particle spectra introduced by the SV and its packaging [6].

For application in arc radiotherapy QA, the angularly-dependent response of a detector such as the MP512 can be mitigated by corrections [14], [24], provided the radiation-beam incidence angle is known at any time. Alternatively, the 2D active surface could be maintained always perpendicular to the incident beam by using a suitable rotating phantom.

These results, supported by those of a previous investigation [32], suggest that the MP512-bulk and the MP512-epitaxial are affected by a comparable angularly-dependent response. To minimize uncertainties in the reported dose measurements, however, the devices would call for correction factors to be measured individually, for each field size and beam quality considered.

230 4.4. Clinical application

OFs by the MP512s agreed within  $\pm 2\%$  with those by films and MOSkin<sup>TM</sup>, for all square fields investigated in the range 0.5 cm to 10 cm side, for both 6 MV and 10 MV beams.

Considered cross-plane OARs in square fields defined by the jaws in the range 1 cm to 4 cm with a 6 MV beam, it was found that FWHMs by the MP512-epitaxial agreed within  $\pm 1\%$  with those by films, while penumbra widths agreed within 0.6 mm. These results were consistent with those by the MP512-bulk reported in a previous investigation, in which discrepancies with respect to results by films were within  $\pm 1.2\%$  [12]. In the same radiation fields with a 10 MV beam, FWHMs by the MP512epitaxial agreed within  $\pm 1.6\%$  with those by films, and penumbra widths agreed within 0.6 mm.

Considering PDDs, differences between measurements by the MP512s and the chambers were within  $\pm 2\%$  at all depths, for both beam energies investigated. Difference between measurements by the MP512-bulk and the MP512-epitaxial were always within  $\pm 2\%$ .

## 241

## 242 **5.** Conclusions

The present study assessed and compared the performance of two prototype detectors, a MP512-bulk and a MP512-epitaxial, in the context of quality assurance applications in megavoltage photon beams delivered by medical linear accelerators.

Experimentally, both MP512s showed good linearity with delivered dose. However, the MP512-epitaxial demonstrated a superior radiation hardness and long-term stability of the response, suggesting pre-irradiation may not be necessary and frequent recalibrations would be redundant. It was then highlighted that both the MP512s were affected by a dose per pulse and angular dependence of a similar magnitude, requiring suitable corrections to be assessed individually. Their performance in terms of typical machine-specific quality assurance measurements, such as output factors, off-axis ratios and percentage depth dose, were also of comparable accuracy when benchmarked with commercially available detectors.

Based on these results, supported by those reported by previous investigations [27], [32], [35], our conclusion is that, from a medical physicist's perspective, the MP512-epitaxial would be the candidate of choice as a quality assurance tool owing to superior radiation hardness, long-term stability and achievable uniformity and reproducibility of the response of the SVs across a large 2D active area. We also expect the same conclusion to apply to similar devices (Duo-bulk, Duo-epitaxial and Octa-bulk, Octa-epitaxial), which differ from the MP512 only in the topology of the sensitive volumes.

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## 261 Compliance with ethical standards

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265 **Conflicts of interest** The authors declare they have no conflicts of interest.

Research involving human and animal participants This article does not contain any studies with human participants or animals performed
 by any of the authors.

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