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# Patterned Surface Energy in Elastomeric Molds as a Generalized Approach to Polymer Particle Fabrication

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 ABSTRACT: We present a generic fabrication scheme to produce
 Cure and release

**ABSTRACT:** We present a generic fabrication scheme to produce polymer microparticles with engineerable, complex shapes. The polymer particles are made from polyethylene glycol based hydrogels using a poly(dimethylsiloxane) (PDMS) molding technique. A simple surface treatment is used to pattern the surface energy of the PDMS molds, engendering the recessed wells in the molds with a higher surface energy than that of the surface. The contrast in surface energy causes hydrogel precursor to wet only the inside of the molds, creating isolated particles after curing with UV light. This eliminates the formation of an interconnecting "scum" layer and allows for fabrication of well-defined, independent particles. We discuss resolution limits for the approach and present a simple strategy for releasing the particles.



Finally, to show how the fabrication technique is inherently compatible with further particle modifications, we also demonstrate magnetic functionalization of particles.

KEYWORDS: hydrogels, soft lithography, microparticles, PDMS, surface energy

# 1. INTRODUCTION

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Polymeric microparticles have been used across a diverse range of fields-from self-assembly<sup>1-3</sup> to drug delivery<sup>4</sup> and biomaterials.<sup>5</sup> The functionality of colloidal systems is often correlated with their shape. To fully realize advanced functionalities of microparticles, it is often desirable to produce particles with shapes that are more complex than the common spherical geometry. For instance, particle shape can play an important role in interaction with biological systems through parameters such as curvature, surface to volume ratio and variable surface functionality.<sup>6</sup> Tuning these interactions in biosystems requires control over the shape of particles across relevant biological length scales. Particle size can be adjusted to increase the probability of cellular intake.7 The shape of particles also has a strong impact on their self-assembly properties. Shape complexity can be used to expand the ways through which microparticles can assemble. For instance, aspherical particles can be tuned to reversibly assemble using engineerable convexity of "dimple-shaped" colloidal particles.

In this manuscript, we describe a generalizable approach for fabricating nonspherical polymeric particles from hydrogel precursors. Hydrogels are an increasingly important class of biomaterials that are being studied for applications in drug delivery and biosensing.<sup>9–12</sup> The gels are especially attractive for biomaterial applications because they can be engineered to be both biocompatible and environmentally responsive. That is, the shape and material properties of hydrogels can be tuned

so that they are reconfigurable based on interaction with biologically relevant conditions and analytes, such as pH,<sup>13,14</sup> temperature,<sup>15,16</sup> enzymes<sup>17</sup> and glucose.<sup>18–20</sup> The environmental response of these so-called "smart particles" makes them excellent candidates for biosensing.

A variety of approaches to hydrogel microparticle fabrication have been explored with the ultimate goal of creating a scalable, parallelized, batch production technique that also allows for engineered control over size, shape, functionality, and material properties. Reverse emulsion techniques can create batch-sized amounts of monodispersed particles but are limited, often to creating spherical or elliptical shapes.<sup>10,21</sup> Microfluidic flow lithography can create monodispersed particles with tunable geometry and subcomponents made of different phases but is limited to serial production of particles.<sup>22,23</sup> Techniques using photolithography and electron beam lithography can create polymeric particles with different shapes and sizes,<sup>24,25</sup> but necessitate a cleanroom and costly equipment, which limits the flexibility of the approach. Some of the most promising approaches for meeting all of the demands of versatile microparticle fabrication have spawned

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from soft-lithography.<sup>26–30</sup> One popular top-down, soft-lithographic approach to particle fabrication uses an elastomeric mold, typically made of poly(dimethylsiloxane) (PDMS), to confine hydrogel monomer to desired shapes before curing them in place, often with UV-irradiation.<sup>31</sup> Because the mold is "soft," the cured polymeric particles can be removed from the mold and released without damage. The benefits of this approach include batch-level scalability and control of size, shape and composition of the final particles. However, the technique is highly sensitive to the wetting properties of the polymeric monomer and surface energy of the elastomeric mold.

In practice, it is quite difficult to mold the particles without an interconnecting "scum" or "flash" layer that joins the particles together via an unwanted base layer after release.<sup>32</sup> The presence of an interconnecting layer can hamper selfassembly or distort particle sensing through agglomeration, so it is desirable to eliminate the "scum" layer. To address this challenge, the DeSimone group has developed an innovative approach to micromolding fabrication of polymeric particles called PRINT (particle replication in nonwetting templates).<sup>33-37</sup> The PRINT process uses photocurable molds made of perfluoropolyether (PFPE) which have low surface energy and are therefore nonwetting to inorganic and organic materials. When precursor hydrogel solution is compressed between the mold and a nonwetting substrate, the solution preferentially fills the recessed regions of the mold ensuring no residual interconnecting layer. While this approach creates isolated polymeric particles with controlled shape, size and composition, PFPE is not commonly used in research laboratories. PDMS, on the other hand, is used quite widely as an inexpensive elastomer for soft lithography. Although of higher surface energy than PFPE, in certain situations, micropatterned polymer features with no residual layer can also be fabricated using PDMS via a technique known as discontinuous wetting. Liquid precursor solution is drawn across a patterned, elastomeric substrate and capillary forces pull the liquid preferentially into molded regions.<sup>38</sup> Discontinuous wetting has been used to generate a variety of nano- and microstructures,  $^{39-41}$  and it is adaptable for roll-toroll industrial scale fabrication.<sup>42,43</sup> This method does use materials that are accessible to most research laboratories, but it is only compatible with liquid/substrate pairs whose receding contact angle falls below a certain critical value,  $\theta_{crit}^{38}$  which can limit applicability.

Here, we describe a micromolding approach where patterned surface energy on templated substrates assists in uniform filling across molds. The contrast in surface energy between templated wells and the PDMS surface drives hydrogel monomer to wet the wells instead of the PDMS surface, which eliminates a "scum" or "flash" layer. The modification of the PDMS surface energy is achieved through a simple "inking" step in combination with exposure to an oxygen plasma. We also demonstrate that the particles can be removed from molds by submerging the PDMS/cured microparticle substrate into a bath of deionized water and isopropyl alcohol (IPA). In the bath, the PDMS mold expands slightly from absorption of IPA, which allows controlled release of the cured particles using sonication. Currently, the simple inking approach can be used to faithfully pattern microparticles down to 2  $\mu$ m, although the resolution may be increased with additional refinement of the technique, discussed herein. While the approach described here does not yet match the resolution

of established PRINT techniques, which have been shown to pattern down to 100 nm, the simplicity of the technique makes it useful for researchers. Each step of the approach outlined here uses common research materials (PDMS, IPA) already employed for a variety of applications in many biomaterial research laboratories, making the technique particularly accessible to researchers interested in microparticle fabrication. Rather than depending solely on discontinuous wetting, we assist the process through a quick and easy surface patterning step. We show that the technique is compatible with an evaporation assisted, discontinuous wetting-type filling of molds, but also with a much quicker, spin coating approach. The technique will enable researchers to prototype polymeric microparticles cheaply and quickly in even a basic laboratory type environment. As one example of possible added functionality, we also show that the particles can be made magnetic for remote manipulation.

## 2. MATERIALS AND METHODS

**2.1. Materials.** 2,2-Dimethoxy-2-phenylacetophone, polyethylene glycol (PEGDA) diacrylate 700, acrylic acid, sodium hydroxide, ammonium hydroxide and iron chloride tetrahydrate and iron chloride hexahydrate were purchased from Sigma-Aldrich Chemicals. Sylgard 184 elastomer and curing agent was purchased from Ellsworth Incorporated. Polyethylene glycol dimethacrylate (PEGDMA) 200 and 1000 were purchased from Polysciences, Inc.

2.2. Silicon Master Mold Fabrication. A silicon wafer was spincleaned with acetone and isopropyl alcohol. HMDS photoresist adhesive was spun onto the wafer at 4000 rpm. Then AZ nLOF 2020 negative photoresist was spun on the wafer at 4000 rpm. Afterward, the wafer was prebaked at 110 °C for 60 s and exposed at 120 mJ/cm<sup>2</sup> in an ASML 5500/100 D wafer stepper with a prepatterned reticle. The wafer was postbaked at 110 °C for 60 s, then developed using Micro Chem MF 26a with a double puddle (5-20 s each, depending on the pattern) development. Following development, the wafer was etched in an STS Pegasus DRIE (deep reactive ion etching) system to form silicon features of a desired height. After etching, the photoresist was removed using gentle sonication in an acetone bath. Following photoresist removal, the wafer was loaded into the STS Pegasus DRIE for application of a single passivation layer of Teflon-like C<sub>4</sub>F<sub>8</sub>. The application of a passivation layer ensures high fidelity pattern transfer between the silicon master and PDMS by eliminating adhesion of the PDMS to the silicon.

**2.3. Fabrication of PDMS Micromolds.** Elastomer base and curing agent from Sylgard 184 were mixed together in a 10:1 ratio and poured on top of the silicon master mold. The edges of the silicon mold were wrapped with Kapton tape to create a well, so that the elastomer base cures on top of the silicon. The silicon mold with uncured PDMS was transferred to a hot plate, where the PDMS cured at 110  $^{\circ}$ C for 60 min. After curing, the Kapton tape was removed, and the PDMS was peeled off of the silicon master.

**2.4. Surface Modification of PDMS with Inking.** SPR 220-3 photoresist was spun on a silicon wafer at 2500 rpm. Then, the PDMS mold was pressed against the photoresist layer, mold side facing the photoresist, with moderate force (hand pressure). When the PDMS was removed, a thin photoresist layer coated the PDMS surface, but not the recessed molds. The PDMS micromold was then subjected to a brief oxygen plasma (60 W, 50 sccm, 40 s) with a Technics PE-IIA Plasma System. Following the O<sub>2</sub> plasma, the inking layer on the PDMS micromold was removed using acetone while spinning the mold at 2500 rpm.

**2.5. Micromolding Fabrication of Hydrogel Microparticles.** A 1.5% (by weight) solution of photoinitiator (2,2-dimethoxy-2-phenylacetophone) dissolved in PEGDA 700 or PEGDMA 1000 was prepared as a photocurable precursor. For magnetic particles, a 3:1 ratio of PEGDA 700 (with photoinitiator) to acrylic acid was used as a precursor. Since PEGDA 700 is a liquid at room temperature, we were able to fill molds through spin coating. In this process, 3 mL of



**Figure 1.** Fabrication procedure for producing hydrogel microparticles. (a) PDMS is cured on top of silicon master mold. (b) PDMS is peeled off the Si mold, creating a templated surface for patterning hydrogel microparticles. (c) The templated surface of the PDMS is pressed against a wet photoresist layer, inking the surface of the PDMS but not the inside of the templates. The PDMS is then subjected to an oxygen plasma which increases the surface energy inside of the molds. (d) The inked surface is rinsed with acetone, removing the photoresist. This leaves a PDMS mold with variable surface energy (e) The molds are filled with PEGDMA and (f) cured with UV at a wavelength of 365 nm. (g) The mold with cured hydrogel particles is placed in a bath with a mixture of IPA/DI water and sonicated, which (h) releases the particles into solution.

precursor was statically dispensed on top of a 76 mm wide PDMS mold. The mold was then spun at 200 rpm for 10 s and then 5000 rpm for 240 s.

PEGDMA 1000 is a solid at room temperature and could not be spun into the molds. Filling via evaporative dewetting was used instead. For this process, a 0.0005-0.005 mass fraction of PEGDMA/ photoinitiator solution in DI water was added dropwise to the surface of the PDMS mold while it sat on a hot plate at 90 °C. After ~1 h, the water had evaporated, leaving PEGDMA in the molded regions. In some situations, excess polymer left a "coffee ring" residue around the region with filled molds. The coffee ring residue could be cured and peeled away before particle release. To eliminate the coffee ring, we also explored filling the particle molds by heating the PDMS with a glass coverslip placed on top. The coverslip adheres to the PDMS mold surface through capillary forces and water in the precursor system evaporates away from the edge of the glass. This process takes longer (~4 h) but eliminates a coffee ring and produces a more homogeneous degree of particle filling.

After filling (either by spinning or evaporation) molds were then placed in a sealed curing chamber under constant flow of  $N_2$  gas. The mold was exposed to UV irradiation (365 nm) for 5 min for photopolymerization of the PEGDMA/PEGDA.

**2.6.** Harvesting and Release of Hydrogel Particles. Particles were released into a 1:1 mix of DI water and IPA. The mold with cured particles was placed in the solution for 2-4 h, the solution was sonicated for 5 min and particles were released into solution. Particles were collected using centrifugal filters with a 0.22  $\mu$ m mesh size.

**2.7. Magnetic Functionalization of Microparticles.** The microparticles were made magnetic using *in situ* coprecipitation, which grows  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>/ Fe<sub>3</sub>O<sub>4</sub> nanoparticles throughout the cross-linked hydrogel. We followed the procedure outlined by Suh et al.,<sup>44</sup> whereby cross-linked particles are soaked in iron chloride (II, III) salt solutions and then transferred to ammonium hydroxide to initiate nanoparticle nucleation and growth. Particles were made with a 3:1 mixture of PEGDA and acrylic acid as a precursor. They were released in a bath of NaOH, which deprotonates carboxyl groups to COO<sup>-</sup> and encourages uptake of Fe<sup>3+</sup> and Fe<sup>2+</sup> within the hydrogel network. Then, particles were soaked in a mixture of 2 M FeCl<sub>3</sub> and 1 M FeCl<sub>2</sub> for 1.5 h. Excess iron chloride solution was removed using centrifugal filters and the particles were then soaked in ammonium hydroxide for 1.5 h. These steps were repeated three times until particles responded strongly to a permanent magnet. Particles were washed three times

with oleic acid (100  $\mu \rm L)$  and ethanol to remove excess iron oxide nanoparticles.

**2.8. Scanning Electron Microscopy (SEM).** SEM images were taken using either a FEI Sirion 400 or a Zeiss Sigma 300 instrument. Images were taking using accelerating voltages ranging from 2 to 10 kV. Energy dispersive X-ray spectroscopy was performed using the Zeiss 300 instrument at an accelerating voltage of 10 kV and an aperture size of 120  $\mu$ m.

**2.9. Optical Microscopy.** Optical micrographs were taken using a Leica DM8000 M instrument operating in bright field mode.

# 3. RESULTS AND DISCUSSION

The fabrication process is outlined in Figure 1. A silicon master mold is first created using photolithography and deep reactive ion etching. PDMS (10:1 ratio of elastomer to curing agent) is cured on top of the silicon wafer and removed, creating a negative mold of the silicon features. The PDMS mold is then "inked" with wet photoresist, covering the surface of the PDMS with photoresist but not the insides of the templates. This is achieved by spinning photoresist on a separate silicon wafer and then pressing the templated surface of the PDMS on to the spin-coated wafer. The PDMS is then briefly treated with an oxygen plasma. The oxygen plasma modifies the surface of the PDMS inside of the wells, but not on the top surface because the inked photoresist layer protects the top surface of the PDMS from the oxygen plasma. The oxygen plasma increases the surface energy of the bare PDMS, thus making the patterned regions more susceptible to wetting.<sup>4</sup> The efficacy of the protective photoresist layer was confirmed by inking, then exposing a flat PDMS surface to an oxygen plasma. Following removal of the inked layer, the surface remained hydrophobic (Figure S1 in the Supporting Information). After the inking and surface treatment, the photoresist is removed with acetone.

We explored filling the templates with both polyethylene glycol dimethacrylate (PEGDMA 1000) and polyethylene glycol diacrylate (PEGDA 700), which are two common hydrogel precursors. Both the PEGDA and PEGDMA were mixed with a photoinitiator (2,2-dimethoxy-2-phenylaceto-phone) to make the hydrogel precursors photocurable using



Figure 2. Schematic illustrating the effect of the inking/oxygen plasma surface treatment: (a) untreated surface with low surface energy, hydrogel dewets from templates and fills variably; (b) entire surface treated with oxygen plasma, surface energy of PDMS is increased uniformly, and the PEGDMA totally wets the surface, leading to "flash" layer formation; (c) contrast in surface energy (high in templates, low on surface) leads to selective wetting of PEGDMA within the templates, creating uniform microparticles.



Figure 3. (a) High resolution SEM image of 10  $\mu$ m cube-shaped PEGDMA microparticles. (b) Lower magnification SEM image showing many microparticles dispersed on silicon substrate.

ultraviolet light. PEGDA 700 is a liquid at room temperature and could be spin-coated into PDMS molds using high angular velocity (5000 rpm). PEGDMA 1000, however, is a waxy solid at room temperature and had to be dissolved in water to form a liquid phase precursor. To ensure the PEGDMA stayed in a liquid phase before curing, we filled the molds using an evaporatively driven process at elevated temperature. A 0.0005–0.005 mass fraction of PEGDMA/photoinitiator solution in DI water was added dropwise to the PDMS surface on a 90  $^{\circ}$ C hot plate. The water evaporated but the PEGDMA did not, leaving PEGDMA inside of the molds

We filled the molds with PEGDA/PEGDMA immediately after the oxygen plasma because the effect of the surface treatment degrades with time, restoring the PDMS to its native surface energy state.<sup>48</sup> After filling, the PEGDA/PEGDMA is cured using UV irradiation and placed in a bath of DI water and IPA. The PDMS absorbs a fraction of the IPA, causing the whole mold to expand by a factor of 1.09.<sup>49</sup> While the mold expands with IPA, the particles swell with water and become more flexible. This allows for easy liberation of the hydrogel microparticles with gentle sonication.

The production of isolated hydrogel particles is enabled by the patterned variation in surface energy in the patterned templates, versus the surface of the PDMS. The PEGDA/ PEGDMA precursor dewets from untreated surfaces, leading to variable filling of PDMS molds (Figure 2a). On the other hand, if the whole surface is treated with an oxygen plasma, the surface energy and hydrophilicity of the PDMS is increased uniformly. This causes the PEGDA/PEGDMA precursor to wet evenly across the surface. The recessed templates are joined by thin (less than 1  $\mu$ m) liquid bridges, creating a "flash" layer after curing (Figure 2b). In the situation where the templates have relatively higher surface energy than the PDMS surface, the PEGDA/PEGDMA fills only the patterned regions (Figure 2c). The degree of wetting was confirmed by inspecting the molds with and without the surface treatment with dyed PEGDMA 200 solution (Figure S2 in the Supporting Information).

The process described here is capable of making large quantities (10<sup>7</sup>) of monodispersed, hydrogel microparticles with variable shape, size, and complexity. Figure 3 shows an example of 10  $\mu$ m wide, cubical PEGDMA 1000 particles. The particles were collected via centrifugation and pipetted onto a silicon wafer for inspection with SEM. In addition to cubical particles (Figure 4a), the process has also been used to make triangular prisms (Figure 4b), cylinders (Figure 4c), cylindrical shells (Figure 4d) and even letters and words (Figure 4e). In principle, the approach should be able to pattern down to submicrometer lengths scales, since PDMS can transfer patterns down to tens of nanometers.<sup>27</sup> However, resolution is currently limited at the inking step, where incomplete adhesion of the PDMS mold with the photoresist ink causes incongruent pattern transfer from molds to particles. Incomplete adhesion, which can be caused by trapped air between the mold and photoresist, or partial swelling of the PDMS mold when in contact with photoresist, leaves a small uninked region around the recessed mold (Figure 5a). This unprotected region is rendered hydrophilic during the subsequent oxygen plasma. The hydrogel precursor readily wets both the interior of the mold as well as the uninked satellite area. Following UV cure and particle release, the wetting around the particle manifests itself as tapered edges or "feet" surrounding the base of the particle (Figure 5b). With the simple materials described here and manual adhesion of molds to inked substrates, the technique is limited by these "feet" to  $\sim 2 \,\mu$ m resolution. While this is an order of magnitude higher than established techniques, like PRINT,<sup>36</sup> we believe that the approach described here can be used by researchers to cheaply and quickly prototype polymer particles for research applications. Moreover, it is possible that resolution can be



**Figure 4.** PEGDMA particles shaped like (a) cubes, (b) triangular prisms, (c) cylinders, and (d) cylindrical shells and (e) forming letters that comprise a NIST logo.



**Figure 5.** (a) Schematic showing the effect of mold stiffness on adhesion between PDMS molds and the silicon substrate used for applying photoresist ink. (b) 2  $\mu$ m sized cylinders with tapered edges from nonconformal contact of mold with ink. (c) 2  $\mu$ m sized cylinders with much smaller feet created by using a stiffer PDMS mold.

further improved through modification of mold composition and chemistry of the inking layer. We explored the elimination of incomplete adhesion by changing the stiffness of the PDMS

molds. Increased stiffness or compound stamp/mold designs have been used effectively in microcontact printing to increase pattern fidelity and resolution to submicrometer regimes.<sup>50,51</sup> The Young modulus of PDMS can be modified easily by changing the ratio of curing agent to elastomer base. We created two molds with 2  $\mu$ m diameter, 2  $\mu$ m tall cylinders using PDMS with different ratios of curing agent to base, 10:1 and 4:1. The literature suggests that the change in stiffness between the two molds is a 33% increase beyond the standard 10:1 ratio (~1.5 MPa).<sup>52</sup> The increase in stiffness significantly reduced the "feet" caused by incomplete contact between the molds and the ink layer (Figure 5c). Further increases in resolution can likely be achieved by considering in more quantitative detail the impact of dewetting on mold filling. Filling via discontinuous dewetting has been shown to have a complex dependence on critical capillary number, aspect ratio of molds, and azimuthal angle between principal axes of shaped molds and dewetting direction.<sup>42</sup>

We also explored the compatibility of our technique with additional particle functionalization by adding material within the hydrogels. One simple example is adding magnetic functionality to the particles. Magnetic hydrogels are attractive, multifunctional materials because they can be remotely manipulated and actuated using external magnetic fields.53,54 Magnetic material was added to the particles by growing iron oxide nanoparticles within the cross-linked hydrogel network using in situ coprecipitation. Suh et al. showed that the magnetization of PEGDA 700 particles could be increased in stepwise manner through successive coprecipitation reactions.<sup>44</sup> We first fabricated 25  $\mu$ m × 25  $\mu$ m × 75  $\mu$ m rectangular prisms using a 3:1 ratio of PEGDA 700 to acrylic acid. Following three cycles of coprecipitation, the microparticles showed a clear color change from the loading of iron oxide nanoparticles (Figures 6, parts a and b). SEM and EDS



**Figure 6.** (a) Optical image of 25  $\mu$ m × 25  $\mu$ m × 75  $\mu$ m PEGDA rectangular prism. (b) Optical image of PEGDA rectangular prism after three coprecipitation cycles of iron oxide growth, brown color change is due to nanoparticles grown through hydrogel network. (c) SEM image of two PEGDA rectangular prisms with iron oxide. (d) EDS image showing Fe distributed uniformly across the magnetically functionalized PEGDA particles. (e) The magnetic microparticles are easily collected to the side of a vial using a permanent magnet.

images show uniform iron oxide nanoparticle growth across the rectangular microparticles (Figures 6, parts c and d). The microparticles could be easily collected using a small permanent magnet, suggesting they could be effectively used for magnetic separation or magnetophoresis (Figure 6e). In addition to magnetic functionalization, it should be possible to multiplex the functionality of the particles by adding fluorescent tags or biomaterials prior to the curing step. Moreover, because of the simple release strategy, the particles can easily be functionalized in solution after they have been liberated from their templates.

In conclusion, we have presented a fabrication protocol for generating micrometer-sized, hydrogel particles with engineered shape and size. PEGDMA and PEGDA were chosen as representative hydrogels for the study because of their biocompatibility<sup>45</sup> and use in biomedical applications,<sup>55</sup> but the technique should be compatible with other UV curable hydrogels. The process relies on patterning the surface energy of a PDMS mold so that hydrogel precursor selectively wets the template wells. This allows for fabrication of isolated particles and eliminates the problem of interconnecting surface "scum" and "flash" layers. Particles in the molds can also be easily and controllably released through expansion of PDMS in a water/IPA bath. Finally, we show that the particles can be easily functionalized by incorporating other materials into the hydrogel, such as for magnetic manipulation.

# ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsapm.9b01109.

Contact angle of two flat pieces of PDMS and wetting in logo pattern observed by optical microscope (PDF)

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## Notes

The authors declare no competing financial interest.

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