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REVIEW

# The subcortical maternal complex: multiple functions for one biological structure?

**D. Bebbere**[1] · **L. Masala**[1] · **D. F. Albertini**[2,3] · **S. Ledda**[1]

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**Abstract** The subcortical maternal complex (SCMC) is a multiprotein complex uniquely expressed in mammalian oocytes and early embryos, essential for zygote progression beyond the first embryonic cell divisions. Similiar to other factors encoded by maternal effect genes, the physiological role of SCMC remains unclear, although recent evidence has provided important molecular insights into different possible functions. Its potential involvement in human fertility is attracting increasing attention; however, the complete story is far from being told. The present mini review provides an overview of recent findings related to the SCMC and discusses its potential physiological role/s with the aim of inspiring new directions for future research.

**Keywords** OOEP/FLOPED · NLRP5/MATER · TLE6 · KHDC3/FILIA · Oocyte · Developmental competence

## Introduction

Infertility is nowadays an ongoing global challenge, being estimated to affect as many as 186 million people worldwide [1] and having significant medical, social, and financial implications. Human assisted reproductive technologies (ART) considerably contribute to relieve fertility problems; however, a significant fraction of infertility cases still finds no solution, despite the fast progression in reproductive medicine.

Male and female infertility account for about a third of cases, respectively, whereas the other third is due to problems in both partners or to unknown reasons [2]. Genetic abnormalities, mitochondrial and epigenetic disturbances, hormonal disorders, and exposure to environmental toxicants/endocrine disruptors often underlie impaired fertility in both genders. When the cause of infertility is not identified in either the woman or the man, the diagnosis is of unexplained (or idiopathic) infertility. Despite the substantial research effort invested worldwide, the incidence of unexplained infertility remains unchanged since 2003 (11–13 %) [2].

Recent evidence has raised the possibility that part of idiopathic infertility may be caused by very early forms of embryonic lethality that escape nonspecific molecular analysis [3]. Such early lethality would not show an obvious phenotype, and consequently, it would not trigger an appropriate investigation.

The earliest phases of embryo development are uncoupled from new transcription and rely exclusively on maternal macromolecules deposited during oocyte growth. Although the zygote is formed by the fusion of the maternal and paternal pronuclei, early mammalian development is therefore essentially under "maternal command" from factors deposited in the ooplasm. The gradual transition from maternal to embryo control (embryo genome activation, EGA) that occurs during early development is a crucial step during embryonic ontogeny and coincides with the developmental block often observed within mammalian embryos cultured in vitro, which is likely to occur in vivo as well.

*Capsule* The present mini review provides an overview of recent findings related to the SCMC and discusses its potential physiological role/s with the aim of inspiring new directions for future research.

✉ D. Bebbere
dbebbere@uniss.it

[1] Department of Veterinary Medicine, University of Sassari, via Vienna 2, 07100 Sassari, Italy

[2] The Center for Human Reproduction, New York, NY, USA

[3] Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, USA

Maternal effect genes (MEGs) code for a special type of maternal transcripts expressed exclusively in oocytes and early embryos. Functional studies in mice [4, 5] have demonstrated that these unique transcripts are fundamental for early cleavage events post fertilization [6, 7], and have been suggested to play roles in developmental processes, including epigenetic reprogramming, EGA, and cell specification [8]. Despite the proven importance, the molecular mechanisms responsible for the lethal phenotypes are not well understood, with few recent exceptions [9]. The key role of MEG during early development suggests a potential implication in human fertility. Unfortunately, the causes of infertility specific to zygote formation and early zygote cleavage are difficult to detect during in vitro procedures.

Recently, the earliest known human embryonic lethal phenotype was identified and associated with a mutation in transducin-like enhancer of split 6 gene (*TLE6*; [3]). *TLE6* is a member of the subcortical maternal complex (SCMC), a multiprotein complex uniquely expressed in mammalian oocytes and early embryos, whose components are all encoded by MEGs [10].

Similar to other factors encoded by MEGs, the complex is essential for early embryo development [10, 11]; its physiological role remains unclear, although recent evidence has provided important molecular insights into different possible functions. Its involvement in human fertility has renewed interest in understanding the role of MEGs during early human development.

The present mini review provides an overview of recent findings related to the SCMC and discusses its potential physiological role with the aim of inspiring new directions for future research.

## Role of the SCMC in meiotic spindle formation and positioning

The subcortical maternal complex (SCMC) is a multiprotein complex uniquely expressed in mammalian oocytes and early embryos [10] composed of at least four proteins: oocyte expressed protein [OOEP; also known as factor located in oocytes permitting embryonic development (FLOPED)]; NLR family, pyrin domain containing 5 [NLRP5; also known as maternal antigen that embryo requires (MATER)]; transducin-like enhancer of split 6 (TLE6); and KH domain containing protein 3 [KHDC3; also known as FILIA].

The SCMC shows a peculiar localization: it is situated in the subcortex of murine and human eggs and preimplantation embryos and is excluded from regions of cell-cell contact in the cleavage-stage embryo [10, 12]; it segregates to the outer cells of morulae and blastocysts, being therefore completely absent in the embryo inner cell mass [13]. Despite being essential for murine zygote progression beyond the first embryonic cell divisions [10, 11], its structure, composition, and specific functions are yet to be completely clarified.

The proteins that contribute to the SCMC are encoded by maternal effect genes (MEGs) [4, 10, 14, 15]. MEGs code for a special class of maternal transcripts required for early cleavage events post fertilization [6, 15]. They are expressed exclusively in oocytes and early embryos and are usually degraded by the time of EGA without compensation by embryonic transcription. Functional studies in mice have indeed demonstrated that MEG knockout results in the inability of the embryo to develop beyond the first cleavage stage [4, 5]. Nevertheless, to date, the molecular mechanisms responsible for the lethal phenotypes are largely unknown.

The genes encoding the four SCMC components are expressed during oogenesis, and the transcripts are rapidly degraded after EGA; their proteins accumulate already in growing oocytes and persist in cleavage-stage embryos up to the blastocyst stage [10, 13, 16, 17]. *Mater*, *Floped*, and *Tle6* expression was observed in oocytes as early as the primary follicle stage [10, 17, 18]. Comparative studies showed the expression of the genes in several mammalian species, with a moderate degree of sequence conservation, suggesting the potential existence of the complex in all mammals (Table 1) [19–22].

Null mutations of the single-copy genes encoding MATER, FLOPED, or TLE6 result in cleavage-stage embryonic arrest and female sterility [4, 10, 14]. The absence of Filia has a more subtle phenotype with delayed preimplantation development and decreased fecundity [15]. The presence of MATER, FLOPED, or TLE6 (but not FILIA) is required for the formation of the SCMC [10, 14, 15].

The analysis of the *TLE6* null phenotype [14] led to the identification of the first and unique demonstrated function of the SCMC. Indeed, the absence of TLE6 prevents the formation of the cytoplasmic F-actin fine meshwork in the murine zygote subcortex and leads to asymmetric cell division and cleavage-stage embryonic death. The interaction of TLE6 with the F-actin meshwork occurs through Cofilin [14], a known regulator of actin cytoskeleton that centrally positions the spindle in mouse zygotes [23]. Together, these findings show that the SCMC controls spindle formation and positioning through the cytoplasmic F-actin meshwork in mouse zygotes and clarify why its presence is required for proper symmetric cell division.

**Table 1** Identification of the SCMC or its component transcripts or proteins in different mammalian species

| Species | SCMC | *KHDC3* | *NLRP5* | *OOEP* | *TLE6* | Reference |
|---|---|---|---|---|---|---|
| Mouse | Yes | T P | T P | T P | T P | [10, 13] |
| Human | Yes | T P | T P | T P | T P | [12] |
| Ovine | n.a. | T | T | T | T | [19] |
| Bovine | n.a. | n.a. | T | n.a. | n.a. | [20, 21] |
| Swine | n.a. | n.a. | T | n.a. | n.a. | [22] |

*T* demonstrated existence of the transcript, *P* demonstrated existence of the protein, *yes* the SCMC was visualized in oocytes or embryos, *n.a.* data not available

The identified function of the SCMC comprises spindle positioning through regulation of subcortical F-actin, focusing the investigation on the complex role towards a structural function. Nevertheless, the complex functions are most probably not limited to this, as suggested by its persistence in embryos up to the blastocyst stage. In accordance, SCMC components were seen to be important for both meiotic spindle migration [24] and embryo survival [15].

Expression analysis in sheep, where EGA occurs later in development compared to mouse (8–16-cell stage vs. 1–2-cell embryo), evidenced the persistence of transcripts up to the 16-cell stage and allowed identifying the specific time points of messenger RNA (mRNA) decrease [19]. Significant abundance reductions take place over oocyte maturation, fertilization, and around EGA. As most probably the transcript decreases are due to protein synthesis, such pattern of expression suggests the specific need for the complex during different phases of preimplantation development. In accordance, the SCMC analyzed by proximity ligation assays, a highly specific and sensitive in situ method for detection of protein interactions within a complex [25], is more abundant and concentrated in mouse eggs, zygotes, and morulae than in two-cell embryos [11]. The dynamic changes of SCMC abundance raise the possibility that its function varies depending on the embryonic stage and suggest additional roles beyond the positioning of the spindle.

## Potential involvement of the SCMC in regulation of translation

New inputs on additional functions of the SCMC come from the analysis of the SCMC structure. Experiments of coimmunoprecipitation [10] originally identified the physical interactions among the SCMC components: FLOPED, the smallest one (18 kDa, 164 amino acids), interacts with TLE6 (65 kDa, 581 amino acids) and with the largest element, MATER (125 kDa, 1163 amino acids), while FILIA (38 kDa, 346 amino acids) interacts only with MATER (Fig. 1). Analysis of the complex by fast protein liquid chromatography (FPLC) gel filtration followed by immunoblotting indicated a molecular mass between 669 and 2000 kDa [10], which is considerably in excess of the total mass (~250 kDa) of the four identified proteins. Hence, more proteins are expected to be part of the complex.

Despite a considerable effort by different research groups, the identification of additional members of the SCMC has not been straightforward. So far, the only valid candidate is protein PADI6, an oocyte-specific, 77-kDa peptidylarginine deiminase that is preferentially located in the cortex of eggs and preimplantation embryos [26]. It was identified as a potential SCMC component by tandem mass spectrometry after immunoprecipitation with anti-FLOPED antibodies [10]. Moreover, loss of *Padi6* function [27] resembled *Mater* and *Floped* null mutations (cleavage-stage embryonic arrest and female sterility) [4, 10], strongly suggesting PADI6 as a fifth member of the SCMC.

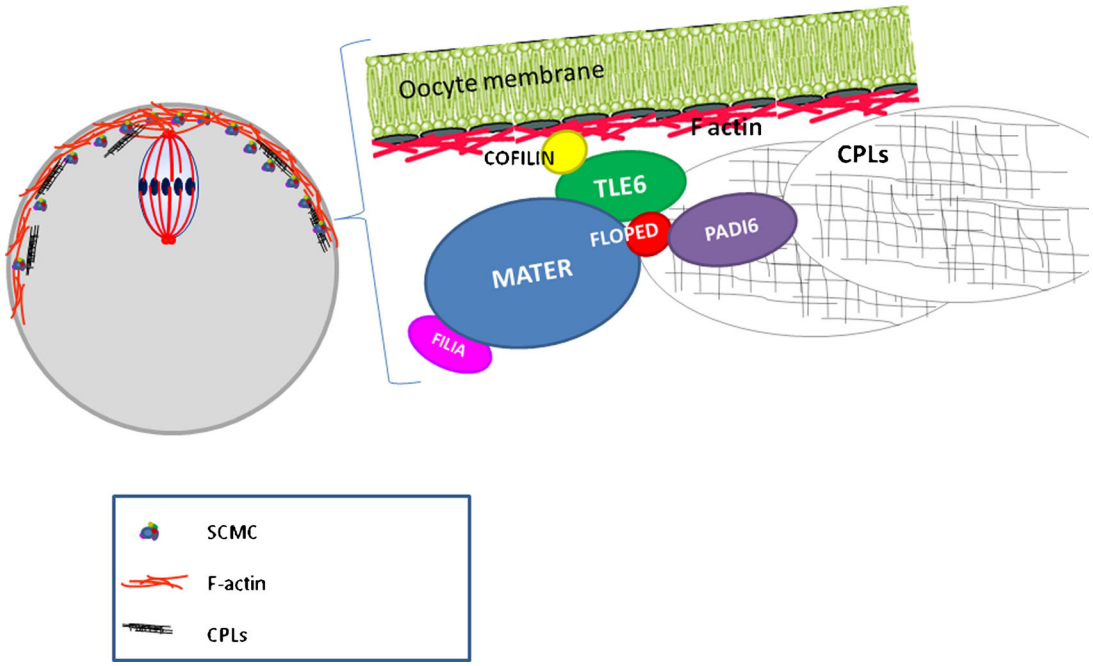


**Fig. 1** Schematic representation of the hypothesized structure of the SCMC and localization within the MII oocyte

Interestingly, PADI6 was seen to localize to [26] and be essential for the formation of the oocyte cytoplasmic lattices (CPLs), a fibrillar matrix composed of a proteinaceous component and RNA [27, 28]. The CLPs contain five to seven parallel fibers with repeating units of about 20 nm [29]. The bundled fibers are first observed at early stages of oocyte growth (30–40 μm) [30] and persist in the early embryo until the blastocyst stage [31].

CPLs are highly abundant in the oocytes and have long been predicted to function as a storage form for the maternal contribution of ribosomes to the early embryo [29]. Additional work confirmed their involvement in ribosomal storage in oocytes [28] and showed that PADI6, NLRP5/MATER [32], and FLOPED/OOEP co-localize at the CPLs and are required for their formation. These studies unexpectedly raised the possibility of a physical association and a potential interaction between CPLs and the SCMC, which indeed share localization, pattern of expression during oocyte growth, and embryo development and null phenotype of their components.

CPLs are thought to play a role in organizing and regulating the translational machinery, as suggested by functional studies showing impaired embryonic transcription, reduced ribosomal component levels, and dysregulated de novo protein synthesis in *PADI6* null two-cell embryos [28]. In parallel, *MATER* null embryos arrest at the two-cell stage and show decreased transcription and translation. The similar null phenotypes and the potential interaction of the SCMC with CPLs suggest a role for the complex in regulation of translation.

In somatic cells, a translational compartmentalization has long been proved, with the two main compartments being the cytoplasm and the endoplasmic reticulum (ER) (reviewed in [33]). Ribosomes are freely dispersed through the cytoplasm or bound to the ER surface. The compartmentalization regulates translation by exposing distinct pools of transcripts to specific regulatory factors and translational components, affecting protein production. Such spatial organization is a form of post-transcriptional regulation that shows specific patterns, depending on cell specialization.

Messenger RNA stabilization and translation are crucial for oocyte and early embryo gene regulation, as transcription is silent until EGA. Beyond the canonical regulatory steps, oocyte-specific mechanisms have been described, such as regulation of mRNA poly (A) tail length [34–36]. The SCMC and CPLs may play a role in an oocyte-specific translational compartmentalization, where the oocyte subcortex acts as a distinct translational environment. Indeed, CPLs were seen to function as a storage form for the maternal contribution of ribosomes and mRNA to the early embryo [37]. In addition, *OOEP/FLOPED* and *KHDC3/FILIA* belong to a family of genes with several members, located in a single syntenic region, that encode structurally related proteins with an atypical RNA-binding N-terminal KH domain, named FILIA N Like [38] that binds polynucleotides and endogenous RNA in vitro [39]. Wang and collaborators [39] suggested an involvement of KHDC3 and OOEP in RNA degradation during oocyte maturation or early embryogenesis. Alternatively, we propose that the two SCMC components may be involved in binding the mRNAs and localizing them to the subcortical region, where they would be exposed to distinct pools of regulatory factors and translational components (possibly part of the SCMC). Further studies should be performed to test this hypothesis.

In accordance with the oocyte spatial translational control, it has been recently demonstrated that the oocyte nucleus contains an RNA population retained during the transcriptionally active phase [40]. The observed nuclear localization of RNAs is proposed as a mechanism to ensure temporal and spatial translation of mRNAs important for the onset and progression of the dynamic processes of meiosis, especially spindle assembly.

## Molecular upstream regulators of the SCMC

Besides the null phenotype and the physical association, *PADI6* and *MATER* share, at least to some extent, a mechanism of regulation of expression. In fact, the expression of both maternal genes is regulated by the transcription factors factor in the germ line, alpha (FIGLA) [41] and SEBOX homeobox [42], whose expressions are in turn interdependent.

FIGLA is a germ cell-specific, basic helix-loop-helix transcription factor [43]. It was reported to be a key regulatory molecule in coordinating the expression of the NALP family of genes and of oocyte-specific genes that play roles in folliculogenesis, fertilization, and early development [41].

SEBOX is a regulatory transcription factor that controls the expression of other MEGs during preimplantation embryonic development in mice, mainly by regulating the process of maternal factor degradation [42]. *Sebox* is a MEG itself, as knockdown of Sebox mRNA and protein does not affect the meiotic cell cycle of the oocytes but causes arrest of the embryos at the 2C stage. *Sebox*-knockdown GV oocytes develop to normal MII in appearance, but show aberrant (upregulated) expression of several MEGs, including *MATER* and *PADI6* [42]. Interestingly, Sebox was seen to affect also *Figla* expression, as it increased 11.7-fold in *Sebox*-knockdown MII oocytes compared to that of controls [42]. These findings strongly suggest that Sebox, Figla, SCMC components, and possibly CPLs are linked.

## SCMC participation in mitochondria redistribution during maturation and after fertilization

A relationship between the SCMC and mitochondria was demonstrated by an interesting work carried out by Fernandes and collaborators [44] that showed that *NLRP5* mediates mitochondrial function in mouse oocytes and embryos. They observed that ovulated oocytes

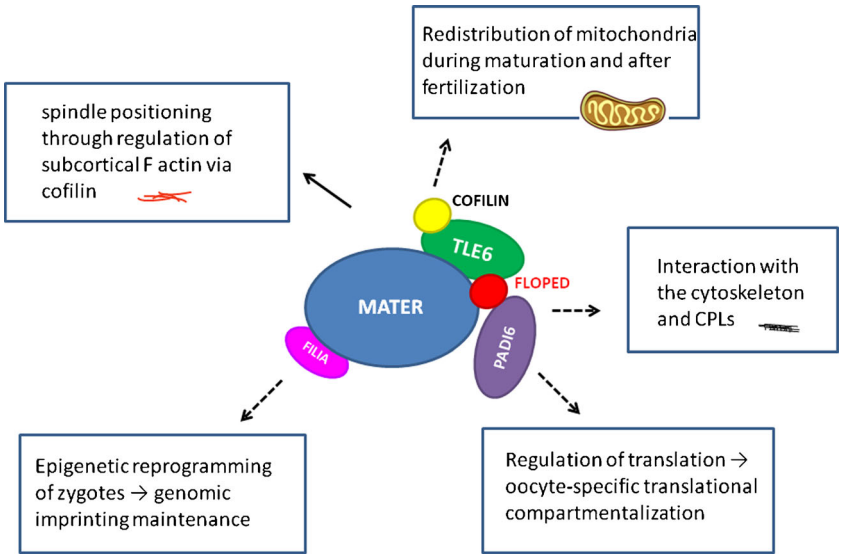


**Fig. 2** Proven (*continuous line*) and hypothesized (*dotted line*) functions of the SCMC

lacking Nlrp5 have altered localization of mitochondria: they are scattered throughout the cytoplasm, rather than concentrated in the subcortical layer, and show increased activity in order to sustain the oocyte physiological ATP requirement. Proper mitochondrial localization in oocytes and embryos is fundamental for signaling events associated with fertilization and developmental competence [45]. Indeed, anomalous mitochondrial aggregation patterns were previously identified in preimplantation embryos undergoing arrest [46]. The SCMC may be involved in translocating mitochondria (and possibly other organelles) to the subcortical region of the oocyte at appropriate times during embryo development, probably through its functional interaction with F-actin meshwork via Cofilin. Accordingly, studies in hamster two-cell embryos suggested that the translocation of mitochondria to the subcortical regions of the cells, and especially to areas of cell-to-cell contact, is mediated by actin microfilaments [47].

## SCMC involvement in epigenetic reprogramming of zygotes

Unexpectedly, the SCMC may be also involved in the epigenetic reprogramming of the nascent embryo, as suggested by strong evidence that individually associates two of its components, *NLRP5* [48] and *KHDC3L* [49], with imprinting disruptions in humans.

On fertilization, the genome undergoes genome-wide epigenetic reprogramming to substitute the developmental programs of the differentiated gamete nuclei with that of the developing totipotent embryo. A small number of gametic epigenetic marks escape this reprogramming and survive in the organism as genomic imprints; such marks regulate the expression of certain genes according to their parent of origin [50]. Disturbance of imprinting affects metabolism, growth, and behavior [51] and is involved in the etiology of severe developmental disorders in humans including Beckwith-Wiedemann and Angelman syndromes [52, 53].

Recently, mutations in *NLRP5* were associated with reproductive wastage and multilocus imprinting disorders in humans [48]. Multilocus imprinting disturbances (MLID) are human imprinting disorders caused by *trans*-acting mutations that affect establishment or maintenance of multiple imprinting marks across the genome. They exert a wider impact on development compared to *cis*-acting mutations, which affect one imprint and the gene(s) controlled by it, and they are often less clinically defined. Mutations in *NLRP5* were identified by whole-exome sequencing in mothers of individuals affected by MLID. Mothers with mutated *NLRP5* suffered from periods of infertility and reproductive wastage including miscarriage and reported molar pregnancy, while patients exposed to maternal *NLRP5* variants showed regions of methylation disturbance at known imprinted loci, with variable distribution and severity [48]. Remarkably, the epigenetic reprogramming and development of the embryo was disturbed by *NLRP5* variants predicted to disrupt its ligand-binding and consequent SCMC oligomerization.

Aberrant methylation was observed also in human molar tissues from patients with *NLRP7* or *KHDC3L* mutations. Both genes were repeatedly seen to be responsible for recurrent hydatidiform moles (RHMs) [54–61]. Despite being diploid biparental, therefore with a normal biparental contribution to their genomes, RHM tissues lack maternal methylation marks on several maternally imprinted genes. This has led to the suggestion that also NLRP7 and KHDC3L play roles in establishing or maintaining maternal epigenetic marks during oogenesis or post-zygotic development [55, 56, 62, 63]. Moreover, a

recent work [49] localized both maternal effect proteins to the oocyte cytoskeleton and more abundantly to the cortical region of the ovulated human oocyte and early preimplantation embryo, with absence of the two proteins in cell-to-cell contact regions. The shared clinical phenotype of *NLRP7* and *KHDC3L* and the overlapping protein localization suggest a potential involvement of NLRP7 with the SCMC or CPLs.

The finding of *NLRP5* and *KHDC3L* mutations in association with imprinting disturbance suggests a potential involvement of the SCMC in epigenetic and developmental reprogramming of zygotes, and raises the possibility of a link with maternal reproductive fitness and reproductive outcomes.

## SCMC involvement in fertility

Abundant evidence now associates the expression of the different SCMC components to oocyte developmental competence. Aberrant expression of SCMC members was observed in different animal models of differential competence [19, 64, 65], while MATER abundance was repeatedly associated with maternal ageing in mice [66–70] suggesting that a decrease or absence of NLRP5 may result in compromised fertility in women of advanced reproductive age. Moreover, *NLRP5* altered expression in abnormal human embryos and developmentally arrested two-cell embryos strongly suggests a role in preimplantation embryo development [71, 72].

As anticipated above, defects in the human SCMC were proved to be responsible for the earliest known human embryonic lethal phenotype [3], confirming with genetic and molecular evidence that the SCMC components are essential for human preimplantation development.

## Concluding remarks

The SCMC has now been linked to several important functions that involve crucial phases of embryonic ontogeny (Fig. 2). The composite biological function of the complex and the early lethal phenotypes hinder the identification of the specific molecular mechanisms and the association with sterility in humans. However, its role in fertility and the possibility of a link with maternal reproductive fitness and reproductive outcomes seem now more than plausible, while waiting for further clarification of the involved molecular mechanisms.

Clarification of the SCMC specific functions is a milestone for the comprehension of the maternal effect gene network, whose great importance during early embryogenesis is now generally accepted. Extensive research is currently performed in model organisms and will likely reveal additional novel genes and molecular mechanisms, contributing to the understanding of the fundamental biological processes that control early development in mammals, including humans.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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