Polyomavirus BK and prostate cancer: a complex interaction of potential clinical relevance

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SUMMARY

Several studies associating BK polyomavirus (BKPyV) and prostate cancer (PCa) suggested that this virus may exert its oncogenic activity at early stages of cancer development. The BKPyV oncogene, the large T antigen (LTag), has frequently been detected in areas of proliferative inflammatory atrophy, which is considered a precursor lesion leading to prostatic intraepithelial neoplasia and overt PCa. In a recently updated systematic review, the presence of BKPyV was significantly higher in PCa tissues than in healthy control tissues, providing an indication for a link between BKPyV infection and cancer risk. In addition, recent original investigations highlighted an association between expression of the virus and the clinical course of PCa. For example, by studying immune responses elicited against BKPyV LTag, a significant association between LTag positive cancer lesions and a peculiar regulatory profiling has been observed in PCa patients with evidence of disease recurrence after surgical radical prostatectomy. Lastly, a study carried out in a larger cohort of patients undergoing radical prostatectomy revealed the IgG response against LTag as an independent predictor of disease recurrence. Although a full picture of the mechanisms potentially responsible for the involvement of BKPyV in PCa is not available yet, continuing work on this topic should help to refine the potential role of BKPyV in PCa patients, perhaps revealing unsuspected associations with the clinical course of this disease. Copyright © 2015 John Wiley & Sons, Ltd.

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INTRODUCTION

Human polyomaviruses (HPyVs) are small, non-enveloped viruses with a circular double-stranded DNA genome of about 5000 base pairs that encode for about six main proteins. Of these, two are functional: large T antigen (LTag) and small T antigen; three are structural: viral capsid protein (VP) 1, 2, or 3, although Merkel cell polyomavirus (MCPyV) lacks VP3 [1]; one is a small non-structural protein, the agnoprotein, which is only detected in BK polyomavirus (BKPyV) and JC polyomavirus (JCPyV), whose function remains to be confirmed [2]. Among the 13 HPyVs discovered so far [3,4], only MCPyV has been clearly identified as neither "passenger" nor "bystander" virus but as an infectious agent having a putative role in the onset of an aggressive primary cutaneous neuroendocrine carcinoma, the Merkel cell carcinoma (MCC). Indeed, about 80% of MCC-bearing patients show MCPyV DNA clonally integrated into the genome of infected cells [5]. In addition, the MCC LTag sequences harbor signature mutations that abort

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Abbreviations used
APOBEC, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like; BAZ2A, bromodomain adjacent to zinc finger domain, 2A; BKPyV, BK polyomavirus; HPyV, human polyomaviruses; JCPyV, JC polyomavirus; KT, kidney transplant; LTag, Large T antigen; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; mRNA, microRNA; MPM, malignant pleural mesothelioma; PCa, prostate cancer; PIN, proliferative inflammatory atrophy; PIA, proliferative inflammatory atrophy; SV40, simian virus 40; VP, viral capsid protein.
(i) viral DNA replication (i.e. generation of a truncated LTag lacking the region required for binding to the MCPyV viral origin of replication); (ii) helicase activity; and (iii) ability to bind to p53. These mutations do not affect the oncogenic potential of MCPyV LTag, because the LXCXE binding motif required for binding the retinoblastoma tumor suppressor protein is maintained [6]. Although MCPyV-related carcinogenesis has been experimentally proved in vitro [7,8], new techniques, such as the fluorescence in situ hybridization, are employed to improve the quality of the molecular-based testing for MCPyV detection with the aim to elucidate MCPyV-related carcinogenesis in humans [9].

The oncogenic potential reported in vitro [10] and/or in vivo in animals [11] for both the human BKPyV and JCPyV does not provide satisfactory evidence to address their association with human cancers [12,13]. Nevertheless, at a recent World Health Organization (International Agency for Research on Cancer) meeting with 26 scientists from 11 different countries, BKPyV and JCPyV were classified as “possibly” carcinogenic to human (group 2B) because of the sufficient evidence in experimental animals for their carcinogenicity, while MCPyV as “probably” carcinogenic to human (group 2A; http://monographs.iarc.fr/ENG/Monographs/vol104/mono104.pdf) [14]. The gap between the experimental findings observed in animals and the difficulty to reproduce them in humans leads to the conclusion that there is insufficient information to prove their specific role in human cancers, particularly prostate cancer (PCa) [15]. However, two recent studies that employed a high-throughput sequencing method (RNA-seq) to investigate the presence of viral sequences in different malignancies failed to detect BKPyV in 140 [16] and 53 prostate cancers [17] and in 39 normal prostate tissues [16]. Therefore, the disparity between the negative to moderate to high BKPyV detection at molecular level and the negligible to rare BKPyV protein expression in cancer specimens, is considered a paradox. An exception is the presence of the virus at both levels in some cases reports of urogenital-tract malignancies, particularly where immune suppression represents a strong risk factor for BKPyV-associated human malignancies [18–23].

Prostate cancer is the third cause of morbidity and the fourth cause of cancer death in western countries, but it is becoming more relevant worldwide because of higher life-expectancy and refined diagnostic procedures [24,25]. In addition to several risk factors that are known to be important for PCa onset, infectious agents such as viruses, should be included in the equation. Owing to its anatomic location and configuration, the prostate is prone to infections, and there is no reason or evidence for excluding a role of infectious agents, such as BKPyV, in the development of PCa [26]. We are aware of the artifacts that occurred in several laboratories while testing the expression of the xenotropic murine-related virus in human PCa by PCR (i.e. the contamination of DNA specimens with viral plasmid DNA) [27] and, previously, when testing patients affected by chronic fatigue syndrome [28]. Notwithstanding these technical artifacts, recent findings on the potential viral etiology of PCa should not be mistrusted because of general skepticism but, on the contrary, should strongly encourage new investigations [29].

HUMAN BKPyV AND PROSTATE CANCER: THE PROPOSED MECHANISM OF ACTION

Despite recent evidence for viral gene expression in the early stage PCa areas [30–32], the question concerning the role of BKPyV in the etiology of this disease is still ruling the scientific discussion. Not only single reports but also systematic reviews consider investigations on BKPyV expression in PCa development a fruitless endeavor [33]. Recently, however, after focusing on inflammatory areas, such as proliferative inflammatory atrophy (PIA), where BKPyV is more likely to be detected [34,35], an increased PCa risk with the presence of BKPyV infection has been observed when precancerous lesions were included as “case” in a case–control study [36].

Inflammation has been defined as the seventh hallmark of cancer [37]. For PCa, there are at least three reasons to contemplate an involvement of inflammation in the development of the malignancy: (i) the PCa incidence/mortality in low-risk populations increases after migration to high-risk countries (such as Japanese migrating to the USA), which is to be attributed to environmental factors—such as diet or endemic infections—rather than genetic predispositions [38,39]; (ii) acute or chronic inflammatory infiltrates in prostatic lesions associated with atrophic areas, particularly PIA, and are to be found predominantly in the peripheral area of the organ,
coinciding with the location of 80% of all diagnosed PCa [26]; and (iii) non-steroidal anti-inflammatory drugs provide a certain degree of protection against PCa [40]. The growing amount of evidence for a link between inflammation and PCa is also reflected by the recent work by Gurel et al. In this study, it has been observed that individuals bearing benign areas with marked inflammation in the organ prostate have a higher risk to develop PCa than those without evidence of inflammation. This increased odd was more pronounced for high-grade than low-grade PCa [41].

Because of the preeminent detection of BKPyV-DNA in prostatic areas where histological transitions between inflammation and premalignant/malignant lesions occur (Figure 1(A1)) [34], the “hit-and-run” mechanism of action, which to a great extent is considered a plausible hypothesis for carcinogens, has repeatedly been proposed to apply also for the oncogenic potential of BKPyV in early stage PCa (Figure 1(B2)) [35]. The “hit-and-run” mechanism is based on the fact that environmental factors, occupational exposures, life habits, and several oncogenic compounds are able to pave the way for tumorigenic transformation, such as chromosomal instability and point mutations. Hence, after genetic alterations are acquired by the infected cells and the oncogenic process is started, the presence of the virus is no longer required for the progression of disease and may disappear immediately afterwards. To corroborate the applicability of this mechanism to viruses, a group of scientists at the University of Cambridge has highlighted that the link between viruses and cancer is not necessarily straightforward [42]. This hypothesis also gains relevance when trying to explain the association between MCPyV and MCC in patients when the virus is no longer evident in tumor specimens and cells [43]. Similarly, because of the detection of human BKPyV in PIA, but not in early stages of PCa, such as the prostatic intraepithelial neoplasia (PIN), this virus has been proposed as an important pathogen involved in the transition of normal prostate glands towards an overt malignancy [44] (Figure 1(A1)). Particularly, the virus could play a dual role: first acting as a “driver” in the initial phase of PCa development (Figure 1(B3)) and, subsequently, disappearing (“hit and run”; Figure 1(B4)) or acting as an “innocent bystander,” explaining the sporadic detection of BKPyV in PCa tissue with higher pathologic stages than PIN [31,36] (Figure 1(B5)).

In our opinion, the BKPyV “hit-and-run” mechanism of PCa induction can also be supported by the new quest put forward by Moens [45]. Because of the co-existence of BKPyV with other oncogenic viruses in cancer lesions, particularly in the genito-urinary tract, the virus might contribute greatly to cancer onset as a co-factor by transactivating promoters of other oncoviruses, advancing an oncovirus superinfection by inhibiting immune responses, and possibly producing oncoproteins with bystander functions. Although the qualification of BKPyV as a co-factor has been strongly rooted since being proposed by Imperiale [35], the viral etiology of PCa has not been experimentally confirmed so far [33]. However, the identification of the ribonuclease L (RNaseL) gene in the hereditary prostate carcinoma 1 predisposition locus on chromosomal region ch1q25 strongly suggests viral involvement in this disease [46]. The RNaseL gene is an essential component of the IFN-driven antiviral response with antiviral and apoptotic activity [47]. The prevention of its activation by infecting viruses leads to a diminished antiviral activity in response to type I and type II IFNs [48].

Hence, although correlations between several oncogenic viruses and human malignancies have already been established [49], many additional investigations are required to refine the molecular mechanism underlying viral oncogenic activities. For instance, it remains to be explained how the virus interferes with proapoptotic and antiproliferative pathways of infected cells intracellularly and how the virus orchestrates both the tumor microenvironment and the tumor immune escape extracellularly [50–52].

**LARGE T ANTIGEN: AN INFORMATIVE ANTIGENIC DETERMINANT**

The simplicity of polyomaviruses turned them into prototypes for *in vitro* analysis of molecular mechanisms of cell biology and for the cell cycle in particular. Indeed, LTag was relevant for the discovery of the cellular tumor suppressor p53 [53,54], because of its ability to interfere with the strategic checkpoints of the cell cycle of infected cells by binding to p53 and thereby inactivating its tumor suppressor functions. This inactivation allows the infected cells to activate an oncogenic transformation [12,55]. In contrast to the human papillomavirus E6 that induces a p53 ubiquitination-mediated degradation [56] or the adenovirus E1B that
interferes with p53 transcription functions in infected cells by binding the amino-terminus domain of p53 [57], the peculiarity of the LTag is to bind the protein within its core DNA-binding domain in its wild-type form (wt-p53) and then sequestering it as protein complex (LTag-p53 complex) without interfering with p53 transcriptional activity [58]. The LTag-p53 complex has also been observed in the cytoplasm of infected [59] and transformed [60] cells. However, cytoplasmic sequestration is not required for inhibition of p53 transactivation [57] but could abolish p53 functions because its accumulation in the cytoplasm of infected cells correlates with an increased rate of genomic mutations of LTag-expressing cells [61]. Rather, the binding stabilizes the LTag-p53 complex, rendering the viral antigen a suitable immunogenic determinant in transformed infected cells against which a specific...
immunologic potential caused by the antigenicity of simian virus 40 (SV40) in human. Ever since SV40 was suggested as an etiological factor for human tumors, and in particular for malignant pleural mesothelioma (MPM) [72,73], no convincing epidemiological and serological evidences have linked this simian virus to human malignancies [74,75]. Any possible association was merely attributed to the inadvertent contamination of polio vaccines, which occurred more than 50 years ago [76]. Nonetheless, recent investigations suggest that SV40 might have a human tropism, because 15% of healthy individuals and 26% of MPM patients, presumably not infected with contaminated polio vaccines, showed a positive IgG response to SV40 capsid protein mimotopes, without cross-reactivity with phylogenetically related human BKPyV and JCPyV [77,78]. In addition, the significantly higher prevalence of IgG responses against VPs in MPM patients, together with a similarly higher prevalence of SV40 genomic sequences in these patients, suggests an etiological role for this virus in the disease. This corresponds also to observations made for MCPyV in MCC [79] and is in line with the finding that strains differing in four amino acid positions in the VP1 sequence, because of point mutations occurring among isolates from Europe and USA [80], react differently in terms of IgG activity against the capsid antigens. In addition, responsive sequences confer antibody specificity for MCPyV
among HPyVs [81]. Nonetheless, MCPyV VP1 specific IgG elevation in MCC patients cannot be attributed to a strong immune response elicited by tumor cells, because they do not express the VP1 protein [79]. Therefore, the significant correlation between high levels of such antibodies and the better progression-free survival reported in all MCC patients with MCPyV-positive tumors [82] is still subject to interpretation. This would also exclude the attribution of anti-MCPyV IgG levels to MCC patients bearing negative lesions, because this seroprevalence is similar to the one observed in the general population [83].

In the case of BKPyV VP1, the capsid protein is extensively exposed to the immune system upon lytic productive infection, and seroprevalence rates of up to 80% have been reported in adult humans [71]. BKPyV is endemic worldwide, establishing subclinical persistent infections in the genitourinary tract, where in the absence of competent immune surveillance, it can induce a hemorrhagic cystitis after bone marrow transplantation [84] or a nephropathy in kidney allograft [85,86]. Indeed, in kidney transplant (KT) patients, after high-level virus replications characterized by high viral load first in urine (viruria) and then in plasma (viremia) of infected patients [87,88], a high anti-VP1 antibody response and a cell-mediated immune activity are promptly elicited [89,90]. The latter event is documented by the detection of a peculiar polyfunctional BKPyV VP1-specific T-cell population with a resting memory phenotype, which patrols virus activity in immune-competent subjects, ready to be switched into an effector phenotype when specifically reactivated [91]. In our own series of PCa patients undergoing surgical radical prostatectomy at first diagnosis, no statistically significant serological disease recurrence-free survival differences were observed between BKPyV VP1 seronegative and seropositive patients [70], even though antigenically distinct serotypes might have represented a limitation in this study [92]. Hence, although the measurement of antibodies generated against capsid proteins represents a method of choice for the assessment of the individual exposure to given HPyVs and while it represents an indication for viral etiology, VP1 IgG activity should not count for support for HPyV causality in tumor development [31] nor be taken as evidence with prognostic potential [70]. Alternatively, this antibody activity might be the consequence of a strong reactivation of cell-mediated VP1-specific immune response [93] and indicates the presence of sufficient viral progeny to infect noncanonical targets in which HPyV-related malignancies could develop.

In contrast, LTag expression is necessary for in vitro oncogenic features at any stage [94], and the magnitude of immune responses against this antigen might associate with the clinical course of HPyV-related malignancies. Indeed, high-IgG activity levels against LTag reflected increasing estimates of serological recurrence-free survival in PCa patients [70] or progressive disease in MCC patients [95]. However, owing to the low LTag-specific T-cell precursor frequency, which is not measurable after productive infections [96,97], there is no support for a T cell-mediated IgG elevation, unless LTag-specific memory cells are artificially expanded [97,98]. In fact, in KT patients, virus replication is not followed by a strong immune response against LTag [89,90], but an ex vivo induction of lymphocytes of KT patients by synthetic LTag peptides generates T cell-specific responses, which are able to counteract BKPyV reactivation [89]. Hence, the boosting of a LTag-specific B-cell and T-cell immunological memory in cancer patients could be the result of continuous LTag presentation in the tumor microenvironment, in specific settings such as dying cells in cancer tissues (Figure 1(B4) and (B5)).

**BKPyV LTag EXERTS TOLEROGENIC SIGNATURES IN PCa**

Recent investigations have devoted much effort in supporting a co-factorial role for BKPyV in the onset of PCa by characterizing the cellular immune response against its main regulatory protein LTag in both seropositive healthy donors and patients and in assessing the clinical relevance of these findings. A significant association between a peculiar regulatory profiling elicited by LTag peptide-pool stimulation, markedly observed in PCa patients with BKPyV positive cancer lesions and evidence of biochemical recurrence has been documented [31]. In particular, two T-cell epitopes, LTag<sub>406-414</sub> (VIFDFLHCl) and LTag<sub>579-587</sub> (LLLIWFPRPV), nested in the p53-binding regions of LTag and previously reported to induce pro-inflammatory responses in BKPyV [96,97], JCPyV [96], and SV40 [99] seropositive healthy donors, triggered an immune regulatory response with suppressive
properties in this disease [100] (Figure 2). Our findings reconcile with that observed in MCC, namely, that MCC-targeting T cells are mostly CD4 and/or CD8 T cells with either regulatory or exhausted phenotype, both with a local [101] and a systemic [102] impact on tumor immune evasion.

The LTag-specific immunological pattern observed in PCa patients cannot be merely attributed to a physiological decline in immune fitness, which frequently occurs in elderly individuals, but most likely to a determinant immunodominance hierarchy in LTag peptide processing, resulting in the promotion of a definite immune responsiveness that characterizes peculiar clinical settings [67]. Indeed, we found novel epidemiological evidence to support an association between BKPyV infection and the clinical course of PCa in patients undergoing radical prostatectomy by measuring preoperative IgG responses [70] against the N-terminal 133aa LTag subdominant 1 [90], a region encoding for the immunogenic peptide LTag27–35 (LPLMRKAYL) [103] (Figure 2).

Although this finding is in its infancy, it proposes that strategic regions of BKPyV LTag, appointed to carry out oncogenic activities, might influence cellular immune responses so far as to generate a regulatory environment favoring PCa progression (Figure 1(B5)). Possibly, the established regulatory microenvironment observed in PCa [104], which is characterized by infiltrating regulatory [105] and functionally exhausted [106,107] T cells, might support the LTag tolerogenic activity in orchestrating PCa development. Thus, the clinical implementation of immunogenic tools that are able to boost LTag-specific T-cell activities in PCa patients with a BKPyV-driven tolerogenic signature could represent a treatment option in PCa [108].

Undoubtedly, the characterization of humoral and cellular immune responses against portions of viral proteins that are relevant for oncogenic activities, such as the p53-binding regions of polyomaviruses LTag, could unravel the ways BKPyV becomes one of the major protagonists in PCa immunoediting, controlling cancer immune surveillance, and strengthening tumor immune escape. Therefore, further investigation of the systemic adaptive immune response to BKPyV LTag could clarify its role as a key target of cancer immune surveillance, which might also lead to an LTag-targeted therapy, as already set by using target proteins such as the prostate-specific antigen [109] or the prostatic acid phosphatase [110] for antigen-specific immunotherapy [111].

**CONCLUSION AND FUTURE DIRECTIONS**

On account of the discussed peculiarities of BKPyV in PCa development, the conservative Henle–Koch postulate—stipulating that a pathogen is closely related to the induced disease and that it cannot occur as a fortuitous and nonpathogenic agent in a different disease—would exclude a role for BKPyV as a causative agent in human cancer in the first place. As a matter of fact, Henle–Koch’s postulate is not applicable to most pathogens, as outlined by a review on the causal role of viruses in human cancer [112]. Rather, causal inference for a viral pathogen in human cancer should rely on revised and adapted Hill’s criteria [113], which

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*[Figure 2. Functional domains of BKPyV nesting LTag-specific peptides. The figure illustrates the linear sequence of the 708 amino acid (aa) BKPyV LTag. The domains required for BKPyV-induced oncogenic transformation, which are the region binding pRb (102–115; LXCXE) and the two regions binding p53 (351–450 and 533–626), are depicted in orange. The two p53 binding regions nest the two tolerogenic peptides LTag406–414 (VIFDFLHCI) and LTag579–587 (LLLIWFRPV), respectively (in gray). In addition to the pRb binding region, the N-terminal LTag subdominant 1 (LTD1, 1–133) contains regions not specifically required for BKPyV-induced oncogenic transformation, in particular the DnaJ domain (1–80) that contains the HPDK motif required for binding the chaperone heat shock protein 70 (green), in which the immunogenic peptide LTag27–35 (LPLMRKAYL; red) is nested.]*
would be “useful to challenge any etiological hypothesis when the epidemiological studies are inconsistent or when only weak associations are reported” [114]. Indeed, criteria like dose–response or biological gradient (estimates of viral load), which imply a relationship between the magnitude of the exposure and the risk of disease, are operational for the role of BKPyV in the onset of polyomavirus-associated nephropathy in immunocompromised patients [115]. Conversely, they do not assume any significance in cancer development, because neither virus reactivation nor sustained productive infections occur in immunocompetent cancer subjects (PCa patients at early diagnosis and not undergoing chemotherapy treatments should be considered as such). Therefore, it would be advisable to establish a model of multifactorial etiology by integrating other factors that might favor and potentiate the oncogenicity of the virus. It has been recently seen that functional alterations of the epigenetic factor bromodomain adjacent to zinc finger domain, 2A (BAZ2A) promote cell growth in PCa and that its overexpression correlates with the metastatic potential of the PCa [116]. Because both early and late transcriptions of JCPyV are regulated by epigenetic mechanisms [117,118], any disruption of the epigenetic pathways involved in the replicative fitness of BKPyV might contribute to its role in PCa development. In addition, the discovery of viral microRNAs (miRNAs) has revolutionized the concept of viral replication and virus protein expression [119]. In particular, HPyV miRNAs may function as regulators of LTag expression [120] and modulators of innate immunity [52]. Accordingly, studying the expression and the activity of BKPyV miRNAs in PCa patients could unravel whether they play a role in human oncogenesis by interfering with LTag expression and, consequently, LTag immunogenicity [121]. In conclusion, recent findings indicate that the antiviral role of the apolipoprotein B mRNA editing enzyme catalytic polypeptide-like (APOBEC) in restricting retrovirus replication [122] can be extended to DNA viruses, including oncogenic viruses [123]. The latter information, together with the finding of APOBEC-mediated mutagenesis operative in 19 human cancers [124], may be relevant in the development of virally driven cancers [125]. These features might justify the applicability of the “hit-and-run” mechanism of action proposed for BKPyV involvement in PCa (Table 1).

So far, BKPyV LTag expression at early events in PCa may be considered a risk factor for the development of this malignancy and the BKPyV LTag-specific antibody immune response as a clinically valuable prognostic factor for this disease. However, these findings do not provide any evidence for a causal relationship between BKPyV

| Table 1. Factors possibly favoring and potentiating the BKPyV oncogenic activity |
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| Factor | Function | Target | Outcome | Citation |
| BAZ2A | Heterochromatin formation (epigenetic control of rDNA locus) | Viral genome | —Replicating fitness controlled by acetylation/deacetylation of viral genome associated histones | [117,118] |
| miRNA | Regulator of viral replication and virus protein expression (degradation of mRNA from LTag ORF) | LTag | —Regulation of LTag production/expression —Modulation of LTag-specific immune activity | [120] [52,121] |
| APOBEC | Restriction of viral replication (cytidin-to-uracil mutation of the viral DNA) | viral DNA | —APOBEC-dependent innate antiviral immunity —APOBEC-mediated mutagenesis in virus-related cancers | [124,125] |

BKPyV, BK polyomavirus; BAZ2A, bromodomain adjacent to zinc finger domain, 2A; LTag, Large T antigen; APOBEC, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like.
and PCa development. Rather, they suggest the existence of an interaction of potential clinical relevance, which might serve as a learning model to understand the contribution of putative oncogenic viruses to the development of cancers. In that sense, harnessing both BKPyV interactions with the tumor microenvironment and the cellular immune response against the oncogenic LTag would allow integration of BKPyV in prognostic and therapeutic approaches for PCa [126]. This complex interaction would undoubtedly set a milestone in the assessment of the role of BKPyV in PCa and offer an opportunity for further research.

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CONFLICT OF INTEREST
The authors have no competing interest.

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