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Increasing incidence of melanoma after solid organ transplantation: a retrospective epidemiological study

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SUMMARY

The risk of melanoma in organ transplant recipients (OTR) is increased compared with the general population. This retrospective study registered all cases of post-transplant melanoma in kidney, heart, lung, and liver transplant recipients followed in our specialized post-transplant Dermatology Clinic since 1991. The yearly prevalence of melanoma and skin carcinoma between 2000 and 2015 was computed and compared in this population. Based on another cohort of kidney transplant recipients grafted since 2005, adjusted age- and sex-standardized incidence ratio (SIR) was calculated using a renal transplantation registry. In our overall OTR cohort, between 1991 and 2000, five melanomas occurred in 1800 OTRs (0.28%), whereas between 1991 and 2015, 53 melanomas were diagnosed in 49 of 4510 OTR (1.09%), representing a 3.9-fold increase in prevalence after 2000. Remarkably, the prevalence of nonmelanoma skin cancers remained unchanged over this period. Two deaths related to melanoma were recorded with an overall follow-up of 62 months. In our cohort of 1102 renal transplant recipients, the SIR of melanoma was 4.52. Our data suggest that contrasting with nonmelanoma skin cancer, the risk of post-transplant melanoma has considerably increased over the last decade.

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immunosuppression, incidence, melanoma, organ transplantation, skin cancer

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Introduction

The increased incidence of skin cancer following organ transplantation is well established, particularly for squamous-cell carcinomas, which occur 65–250 times more frequently compared with the general population [1]. While most studies have highlighted the excess risk of nonmelanoma skin cancer, data on melanoma in organ transplant recipients (OTR) are more limited and somewhat controversial [2]. Two recent reviews concluded that compared with the general population, the risk for melanoma in OTR is increased 2.4–2.71-fold [3,4]. On the other hand, the incidence of melanoma in the general population has been steadily rising [5]. In France, it increased from 5.4 per 100 000 person-years in 1990 to 8 in 2000 and 10.9 in 2012 [6]. The prognosis of melanoma in OTR has also been a matter of debate. Some studies suggested a worse outcome in patients with thick melanomas compared with the general population [7].

The increasing number of *de novo* post-transplant melanomas diagnosed in our center prompted us to study the demographic and clinicopathological features of melanoma

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in OTR followed in our specialized outpatient transplant Dermatology Clinic from 1991 to 2015. We conducted a retrospective cohort study using a post-transplant skin cancer registry. To estimate the relative risk of melanoma compared with the general population, we analyzed another cohort of 1102 kidney transplant recipients grafted from 2005 to 2015, based on a renal transplantation registry.

Patients and methods

Patients

The majority of patients transplanted in our hospital consulted our Dermatology Clinic. All kidney, heart, lung and liver transplant patients with skin carcinomas and/or melanoma followed in our clinic from 1991 to March 2015 were recorded. Classical cutaneous melanoma-associated features were collected from the medical files; they included skin type, sun exposure, presence of atypical nevi or atypical nevus syndrome, family history of melanoma and history of squamous- or basal-cell carcinoma. The age of patients at transplantation and at melanoma diagnosis was recorded. The following clinical and histological features were noted: site of occurrence, histological subtype, Breslow thickness (in mm), presence of ulceration and regression, and presence of a pre-existing nevus. The American Joint Committee on Cancer (AJCC) staging was used, stages I and II corresponding to localized melanoma, stage III to regional metastatic melanoma, and stage IV to distant metastatic melanoma [8]. Details on the transplanted organ, history of acute graft rejection, and immunosuppressive treatments were documented, including the use of T-cell depleting agents for induction immunosuppression or for treatment of acute graft rejection. For patients with more than one transplantation, the duration of immunosuppression was calculated by summing the number of months of immunosuppressive treatment after the first transplantation and subtracting the intervening time period(s) of dialysis. Management, changes of immunosuppressive treatment, and outcomes were also recorded.

Statistical analysis

Overall OTR cohort—prevalence of melanoma and comparison of clinicopathological features

The yearly prevalence of melanoma and skin carcinomas in our OTR cohort followed in the Dermatology Clinic between 2000 and 2015 was computed, and the p-value for comparison was approximated using the formula of Altman and Bland [9] based on the logs of relative risks and their confidence intervals. Because of missing data on follow-up of some patients registered in our department, we were unable to estimate the incidence of melanoma in this cohort. Azathioprine was the main immunosuppressive treatment used until 2000 and was thereafter replaced by mycophenolate mofetil (MMF). We then compared the clinicopathological features of patients with melanoma who had been grafted before and after 2000.

Cohort of renal transplant recipients—standardized incidence ratio of melanoma

Considering that almost all kidney transplant patients (kidney, kidney–pancreas and pancreas) grafted in our hospital were referred to our Dermatology Clinic for a systematic cutaneous follow-up, we used the renal transplant registry provided by our transplantation center with follow-up data to compute the standardized incidence ratio (SIR). Reliable data were only available for patients transplanted since January 1, 2005. The at-risk cohort was defined by all patients who received a kidney, kidney–pancreas, or pancreas transplant since 2005 in our hospital and who had a functional graft during at least 6 months. The period of risk was calculated from the date of the first transplantation to the date of the latest medical consultation or the date of death. The SIR was calculated as the ratio between the observed and the expected cases of melanoma. The observed number of melanoma was defined as the number of patients included in our dermatological registry who developed melanoma (they were also part of the at-risk cohort of kidney transplant patients). The expected number of melanoma was calculated by multiplying the number of patients in each gender and age group for each year of observation by the corresponding melanoma incidence rate in the general population in France, given that the incidence of melanoma in our region is not different from the incidence in the rest of the country [6]. These reference population data were obtained by 5-year age groups for each gender for 2005 and 2012 from the National Institute for Public Health Surveillance [6,10]. All statistical analyses were performed using Statistical Analysis Software SAS 9.2 and Microsoft Excel.

Results

Melanoma SIR

The at-risk cohort of kidney transplant recipients included 1102 patients with a mean age at

transplantation of 49.2 years and a mean follow-up of 54 months (4972 person-years). Among them, melanoma occurred in six patients, yielding an age- and sex-adjusted SIR of 4.52 (95% CI: 1.65–9.83).

Prevalence of melanoma and skin carcinoma between 1991 and 2000 and 1991 and 2015

Between 1991 and 2015, 4510 OTR were followed in our Dermatology Department (Fig. 1). Among them, 49 patients (1.09%) developed melanoma, when between 1991 and 2000 only five melanomas had been diagnosed among 1800 OTR (0.28%). This represents a 3.9-fold increased prevalence since 2000. The prevalence of squamous- and basal-cell carcinomas in the same OTR cohort remained almost unchanged between the two periods: 13.55 in the first and 14.12% in the second one, representing a 1.04-fold increase. Therefore, considering both periods, the prevalence of melanoma increased significantly more than that of skin carcinomas (3.9 vs. 1.04, $P = 0.005$).

Characteristics of OTR with melanoma

Fifty-three melanomas were diagnosed in 41 men and eight women, who had been transplanted between 1971 and 2012 (Table 1). The mean age at first transplantation and at diagnosis of the first melanoma was 49.9 (range 9–75) and 60.1 (range 19–80) years, respectively. The mean duration of immunosuppression before the first melanoma was 9.8 years (median 8.4 years, range 3 months–31.4 years). Three patients had been transplanted during childhood; one of them developed melanoma 5 years later, the two others 29 years later. Patients transplanted after 2000 were older at transplantation than those transplanted before (54.7 vs. 45.6 years, $P = 0.0097$), and the duration of immunosuppression before the diagnosis of melanoma was shorter (39 vs. 186 months, $P < 0.0001$). The clinical risk factors for melanoma were comparable during the two periods. Two patients developed a second melanoma (one during the same year, the other 5 years later), and one patient developed three melanomas during the same year. None of them had a family history of melanoma. A history of squamous- and/or basal-cell carcinoma was found in 21 patients with melanoma (43%), as compared to 14% of patients without melanoma ($P < 0.0001$); furthermore, 11 of the 49 patients with melanoma developed nonskin cancers after transplantation.

Immunosuppressive treatment of OTR with melanoma ($n = 49$)

At time of melanoma diagnosis, 39 patients (80%) were receiving long-term corticosteroids, 42 (86%) were under calcineurin inhibitors (26 cyclosporin/16 tacrolimus) and 31 (63%) were under MMF, in various combinations. Two patients developed melanoma while being on dialysis, 17 and 22 years after their first transplantation, and 21 and 17 months after graft loss, respectively. Data on induction immunosuppression were available for 43 patients. Thirty of them (70%) had received T-cell depleting agents (polyclonal antithymocyte antibodies or anti-CD3 monoclonal antibody), seven had received a monoclonal anti-CD25 antibody, one had received thymoglobulin and anti-CD25 antibody, one had received an anti-CD5 antibody, and five had only received prednisolone boluses. History of acute graft rejection was noted in 23/46 patients (50%), six of whom had been treated with T-cell-depleting antibodies. Graft rejection episodes were more frequent in patients transplanted before, than in those transplanted after 2000 (70% vs. 30%, $P = 0.0080$). Of note, three patients had received immunosuppressive treatment before their first graft. Two patients had received cyclophosphamide

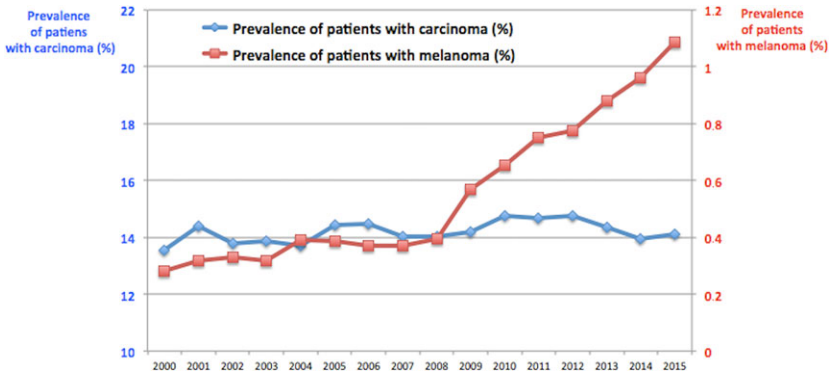

Figure 1 Prevalence of melanoma and skin carcinoma in OTR from 2000 to 2015.

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Table 1. Clinical features of patients with post-transplant melanoma grafted before and after 2000.

	Total number of patients (%) *n* = 49	Patients grafted before 2000 *n* = 26	Patients grafted after 2000 *n* = 23	*P*-value
Transplanted organ				
Kidney	31 (63)	19	12	0.0113
Heart	6 (12)	5	1	
Liver	6 (12)	0	6	
Kidney and pancreas	4 (8)	2	2	
Pancreas	1 (2)	0	1	
Lung	1 (2)	0	1	
Age at first transplantation				
<40 years	10 (21)	8	2	0.0127
40–49 years	7 (14)	3	4	
50–59 years	20 (41)	13	7	
>60 years	12 (24.5)	2	10	
Acute graft rejections				
None	23 (50)	7	16	0.0174
At least one	23 (50)	16	7	
Data not available	3 (7.5)	3	0	
Skin types*				
II	11 (23)	7	4	0.8906
III	34 (71)	18	16	
IV	3 (6)	1	2	
Data not available	1 (2)	0	1	
Atypical nevus syndrome				
Yes	3 (7.5)	2	1	1.000
No	37 (76)	19	18	
Data nonavailable	9 (18)	5	4	
Presence of atypical nevi				
Yes	16 (42)	7	9	0.5118
No	22 (45)	13	9	
Data not available	11 (22)	6	5	
Sun exposure history†				
Low	6 (14)	2	4	0.5314
Intermediate	13 (30)	6	7	
High	24 (56)	14	10	
Data nonavailable	6 (12)	4	2	
Immunosuppressive medication at diagnosis				
CI, MMF ± Co	28 (57)	10	20	0.0072
CI ± Co	8 (16)	5	3	
CI, Azathioprine, Co	4 (8)	4	0	
CI, MMF, everolimus, Co	2 (4)	1	1	
Other combinations‡	5 (10)	5	0	
None (patient on dialysis)	2 (4)	2	0	
Immunosuppressive induction treatment and rejection treatment§				
Thymoglobulin and/or OKT3	30	17	13	0.0068
Anti-CD25 antibody	7	0	7	
Thymoglobulin and anti-CD25 antibody	1	1	0	
Anti-CD5 antibody	1	1	0	
Prednisolone only	4	1	3	
Not available	6	6	0	

CI, calcineurin inhibitor; MMF, mycophenolate mofetil; Co, corticosteroids.

*Fitzpatrick skin types: II = usually burns/sometimes tans; III = usually tans/sometimes burns; IV = always tans/rarely burns.

†High UV-exposure equates to an outdoor occupation; or having lived in a sunny climate for >6 months; or a "sun worshipper" who has actively seeked suntan for >2 weeks per year for >10 years. Low UV-exposure equates to an indoor occupation; has not lived in a sunny climate; avoids the sun/does not sunbathe. Intermediate UV-exposure falls between the "high" and "low" categories.

‡Co and azathioprine; Co and everolimus; calcineurin inhibitor and everolimus; MMF and everolimus; Co, azathioprine and everolimus.

§OKT3 = anti-CD3 monoclonal antibody.

for glomerulonephritis and were treated by azathioprine after kidney transplantation. The third patient had been treated with thalidomide for nodular regenerative hyperplasia.

Melanoma characteristics

Twenty-five of the 53 melanomas (47%) occurred on the trunk, 17 (32%) on the limbs and 12 (23%) on the head and neck. Their histological features are shown in Table 2. Forty-two melanomas were invasive; 35 (66%) were thin (Breslow thickness ≤1 mm), including nine cases with regression. No statistically significant differences in the histological features of melanomas were found according to the period of transplantation (before versus after 2000).

Outcome

All melanomas were treated by wide surgical excision. The mean follow-up was 62 months (median 53). Neither local recurrences nor distant metastases developed in the 11 *in situ* melanomas and the 35 thin ones (developed in 32 patients). The course of the seven patients with melanoma >1 mm is shown in Table 3. Among them, two patients presented with synchronous metastases and died soon after diagnosis.

The overall mortality reached 23% (11/48—one patient was lost to follow-up due to relocation). Melanoma-specific mortality reached 4%. Data on modification of immunosuppression after melanoma diagnosis were available for 47 patients. In 82% of them, the immunosuppression was modified. Of the 32 patients who developed thin invasive melanomas, 12 were switched from calcineurin inhibitors to mammalian target of rapamycin (mTOR) inhibitors, 10 had a reduction in dosages (of at least 25%) or discontinuation of one of their immunosuppressive drugs, and two received mTOR inhibitors in addition. Six patients had no modification of their treatment (data were missing for two patients).

Table 2. Clinicopathologic characteristics of melanomas.

	Number (%) of melanomas
Histological subtype (n = 53)	
SSM	32 (60)
LMM	11 (21)
ALM	3 (6)
Unclassified	7 (13)
Breslow thickness (n = 53)	
In situ	11 (21)
<1 mm	35 (66)
1.01–2 mm	2 (4)
2.01–4 mm	2 (4)
>4 mm	3 (6)
Ulceration (n = 50)	
Yes	3 (6)
No	47 (94)
Regression (n = 45)	
Yes	9 (20)
No	36 (80)
Associated nevus (n = 53)	
Yes	14 (26)
No	39 (74)
AJCC stage (n = 53)	
0	11 (21)
I	36 (68)
II	1 (2)
III	3 (6)
IV	2 (4)

SSM, superficially spreading melanoma; LMM, lentigo maligna melanoma; ALM, acral lentiginous melanoma.

Discussion

The incidence of melanoma in OTR has increased in recent years as suggested by the SIR of 4.52 observed in our cohort of kidney and pancreas transplant recipients since 2005, which is higher than the previously reported SIR (2.5) in a French study on 7896 renal transplant patients grafted before 1997 [11]. Remarkably, the prevalence of melanoma in our center almost quadrupled between 2000 and 2015 (0.28% vs. 1.09%). The prevalence of squamous- and basal-cell carcinomas over the same period in the same patient group remained unchanged. Of note, in our center, all transplanted patients are referred to our department for dermatological follow-up since 1991, at least annually if they have no history of cutaneous malignancy, more often otherwise.

The largest relevant study estimated a 2.38-fold increase in melanoma incidence in OTR in 175 732 patients transplanted in the USA until 2008 [12]. Some European studies of over 5000 OTR found either no increased risk of melanoma, or a statistically nonsignificant increase [13–16]. Of note, SIRs of 7.8 and 8 were reported in two UK studies [17,18], but were not adjusted to the age of the population. Dahlke *et al.* [3] also noted that studies including patients transplanted after 2000 found a higher SIR of melanoma compared with older studies. In addition, studies on renal- or liver transplant patients found a lower SIR for melanoma compared with studies including heart or lung

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Table 3. Outcome of patients with melanoma >1 mm Breslow thickness.

Patient	Grafted organ	Age at 1st transplant (years)	Age at melanoma diagnosis (years)	Duration of immunosuppression (years)	Immunosuppressive drugs at melanoma diagnosis	Histological subtype	Breslow thickness (mm)	Sentinel lymph node biopsy	AJCC stage	Change of immunosuppression	Outcome/ follow-up period after melanoma diagnosis
1	Kidney	27	48	20	None*	Unclassified	7.5	Positive	IV	None	Died after 7 months of melanoma metastasis
2	Kidney–pancreas	44	53	9.1	Co, CyA	LMM	1.62	Not done	I	None	No recurrence/ died 21 months of another cause
3	Kidney	54	63	9.5	Co, Aza, CyA	SSM	13	Positive	IV	Azathioprine withdrawal	Died after 16 months of melanoma metastasis
4	Liver	58	60	2.2	Tacrolimus	Unclassified	1.5	Not done	II	Tacrolimus reduction	No recurrence /154 months
5	Kidney–pancreas	56	68	11.7	Co, CyA, MMF	SSM	2.8	Positive	III	MMF reduction	No recurrence /79 months
6	Pancreas	56	56	0.3	Co, Tacrolimus, MMF	LMM	5.8	Negative	II–III	MMF reduction + switch to sirolimus†	Cutaneous metastasis 48 months after diagnosis treated by surgery/59 months
7	Heart	63	66	2.7	Co, CyA, MMF	SSM	2.2	Positive	IIII	Switch to sirolimus	Cutaneous metastasis 36 months after diagnosis treated by dabrafenib and tramatinib/ 46 months

Co, corticosteroids; CyA, cyclosporine; Aza, azathioprine; MMF, mycophenolate mofetil; LMM, lentigo maligna melanoma; SMM, superficially spreading melanoma.

*This patient had been under corticosteroids and azathioprine during 20 years and developed melanoma after returning to dialysis.

†Graft explantation and withdrawal of immunosuppression 19 months after melanoma.

transplant recipients, probably because of the higher level of immunosuppression in the latter patient groups.

In agreement with previous reports [19–22], the pathologic features of melanoma in our cohort were similar to those of the general population [23]. Most melanomas were thin (≤1 mm), and the most common subtype was superficially spreading melanoma. It seems likely that the regular dermatological follow-up of our OTR allowed the diagnosis of a larger number of thin melanomas.

Several explanations of our findings can be proposed, such as the rising incidence of melanoma in France and worldwide [5,6], and aging of the transplant population. Indeed, we noted an older age at transplantation in patients with melanoma transplanted since 2000 (54.7 vs. 45.6 years). The mean age at transplantation of our cohort of renal transplant recipients was 49.2 years; by comparison, in most studies the mean age at transplantation was around 45 years [19,24–26]. Classical risk factors for melanoma such as heavy sun exposure, a high number of nevi, and fair complexion were also found in our cohort, which was characterized by a frequent history of nonmelanoma skin cancers.

Other risk factors in this specific population could be related to changes in the immunosuppressive regimens, either in the induction or the maintenance phase. The incidence of acute graft rejection has considerably decreased over the past 15 years [27,28]; accordingly, in our cohort, we found a lower rate of acute rejection in patients with melanoma transplanted more recently. The results of various studies on the risk of cancer in patients with acute rejection history vary [29,30], but none of them has reported a significantly increased risk. In a retrospective study on 540 liver transplant recipients, Aberg *et al.* [31] reported a lower SIR of cancer among patients with acute rejection who were not treated with T-cell depleting antibodies. It seems likely that a strong immunosuppression able to completely prevent rejection episodes may increase the incidence of *de novo* cancers. A large Australian study [25] highlighted that the risk of melanoma was associated with the use of T-cell depleting antibodies given for treating rejection, but not with any of the other individual immunosuppressive agents. Another recent study also showed that the risk of late-stage melanoma increased with polyclonal antibody induction therapy [32]. However, most heart and kidney transplant recipients in our center received thymoglobulin as induction immunosuppression since the 1980s. It seems unlikely that the induction immunosuppressive treatment could explain the increasing incidence of melanoma in our cohort, as protocols of induction immunosuppression have remained unchanged for a long time. The significant difference of induction treatment between our patients grafted before versus after 2000 could be accounted for by the six liver transplant recipients who were all grafted after 2000 and received either prednisolone only, or anti-CD25 antibody.

In the maintenance regimens, the main change is the progressive replacement of azathioprine by MMF from 1996 onwards, leading to a decreased rate of rejection and an increased rate of viral infections [33]. Robbins showed that the risk of localized melanoma was higher with azathioprine maintenance therapy [32]. MMF does not seem to exert an effect on tumor cell proliferation [34,35]. Most patients in our cohort were receiving a combination of calcineurin inhibitors and MMF at the diagnosis of melanoma.

Previous data on outcomes of post-transplant melanoma reported a poorer specific survival in OTR with melanoma [20,22,36] compared with the AJCC control population. The prognosis of our patients was better than that reported in previous studies, with a mean follow-up of about 5 years, probably because 90% of melanomas in our cohort belonged to AJCC stages 0 or I. Regular skin examination in our patient group likely allowed detection of early-stage/thin melanomas, a fact that could account for the relatively favorable outcomes. Immunosuppression revision after diagnosis in most patients may also have been beneficial to the outcome. This revision is recommended in the management of post-transplant melanoma [37], including switch from calcineurin- to mTOR inhibitors [38].

The antitumoral effect of mTOR inhibitors on the incidence of nonmelanoma skin cancers is now well established, but remains controversial regarding other cancers [39,40]. A recent trial showed no better efficacy of everolimus in combination with paclitaxel/carboplatin compared with paclitaxel/carboplatin alone in the first-line treatment of advanced melanoma [41]. However the mTOR pathway is activated in most melanomas [42]; furthermore, sirolimus is able to reduce melanoma growth in mice, while maintaining graft survival [43]. Further studies are needed to evaluate the efficacy of mTOR inhibitors in the prevention of melanoma in OTR.

Our study is the first to report an increased number of melanoma occurring in OTR, compared with skin carcinoma. The SIR of 4.52 estimated in our cohort of renal transplant recipients is age and sex-adjusted, and the first observed on patients grafted after 2000. The main limitation of our study is the lack of an estimated incidence of

melanoma in our skin consultation cohort. Using a dermatological registry matched against a cohort of kidney transplant recipients exposes to the risk of missing cases of melanoma, as some OTR transplanted in our center may have been followed outside our Dermatology Department. However this bias can only expose to underestimation of melanoma incidence. In our OTR cohort, four melanomas were diagnosed between the 3rd and 6th post-transplant months, and it cannot be excluded that these melanomas had in fact developed before transplantation; however, these patients were not included in the SIR study. Analysis of a control group of OTR without melanoma is required to investigate risk factors.

In conclusion, the incidence of melanoma in OTR appears to have increased over the past decade. This could be due to an increasing incidence of melanoma in the general population and to an older age of patients at transplantation. Changes in the immunosuppressive regimens, which are currently more powerful than in the early periods of transplantation, could also play a role. Regular follow-up of OTR should allow the detection of early lesions with better prognosis. Revision of immunosuppression should be considered in the management of post-transplant melanoma.

Authorship

KF and SE: conceived the project, elaborated the study design, participated in the acquisition, analysis and interpretation of data and wrote the manuscript. EmD, EM, PB and LS: participated in acquisition of the data. KF and EvD: performed the statistical analysis. EmD, EvD, JK and DJ: critically revised the manuscript.

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Conflict of interests

The authors declare no conflict of interests.

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