Prognostic impact of paraneoplastic syndromes on patients with non-metastatic renal cell carcinoma undergoing surgery: Results from Canadian Kidney Cancer information system

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Abstract

Introduction: The impact of paraneoplastic syndromes (PNS) on survival in patients with renal cell carcinoma (RCC) is uncertain. This study was conducted to analyze the association of PNS with recurrence and survival of patients with non-metastatic RCC undergoing nephrectomy.
Methods: The Canadian Kidney Cancer information system is a multi-institutional cohort of patients started in January 2011. Patients with nephrectomy for non-metastatic RCC were identified. PNS included anemia, polycythemia, hypercalcemia, and weight loss. Associations between PNS and recurrence or death were assessed using Kaplan-Meier curves and multivariable analysis.
Results: Of 4337 patients, 1314 (30.3%) had evidence of one or more PNS. Patients with PNS were older, had higher comorbidity, and had more advanced clinical and pathological tumor characteristics as compared to patients without PNS (all p<0.05). Kaplan-Meier five-year estimated recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) were significantly worse in patients with PNS (63.7%, 84.3%, and 79.6%, respectively, for patients with PNS vs. 73.9%, 90.8%, and 90.1%, respectively, for patients without PNS, all p<0.005). On univariable analysis, presence of PNS increased risk of recurrence (hazard ratio [HR] 1.67, 95% confidence interval [CI] 1.48–1.90, p<0.0001) and cancer-related death (HR 1.85, 95% CI 1.34–2.54, p=0.0002). Adjusting for known prognostic factors, PNS was not associated with recurrence or survival.
Conclusions: In non-metastatic RCC patients undergoing surgery, presence of PNS is associated with older age, higher Charlson comorbidity index score, advanced tumor stage, and aggressive tumor histology. Following surgery, baseline PNS is not strongly independently associated with recurrence or death.

Introduction

Paraneoplastic syndrome (PNS) is a collection of clinical signs and symptoms in cancer patients as a result of systemic effects from the tumor, unrelated to metastasis, infection, or treatment.[1] This phenomenon has been postulated to arise from aberrant hormonal regulations related to mediator proteins produced by the underlying neoplasm, but the exact molecular mechanism remains unknown.[1] Renal cell carcinoma (RCC) is well-known to be associated with PNS, with an estimated 10–40% of RCC patients developing paraneoplastic manifestations.[1,2] The associated PNS are wide-ranging, including hematological (anemia,[3] polycythemia[4]), metabolic (hypercalcemia,[5] hyperglycemia[6]), hepatic (Stauffer's syndrome[7]), and constitutional (fever, weight loss[8]).

On average, symptomatic patients have more advanced disease and worse survival compared to those with RCC who are asymptomatic.[8,9] Recent studies have found that abnormal laboratory values in otherwise asymptomatic patients, such as hypercalcemia and anemia, were associated with worse survival outcomes after nephrectomy.[10] However, the prognostic impact of PNS in patients with RCC is uncertain; the incidence or severity of PNS has not consistently correlated with tumor size, pathology, and metastasis.[11] Therefore, PNS are not always linked to poor prognosis and it remains unknown whether their presence in patients with localized disease have significant

prognostic implications. In this study, we aimed to determine if pre-surgical PNS was associated with risk of cancer recurrence and survival for patients with non-metastatic RCC.

Methods

Patient selection

The Canadian Kidney Cancer information system (CKCis) is a prospective cohort of RCC patients from 16 academic sites in six provinces. Patients who underwent radical or partial nephrectomy for non-metastatic RCC from January 2011 to December 2019 were identified and included. All participating institutions received appropriate institution-specific research ethics board approval.

Data collection

Baseline and clinical parameters included age, sex, race, family history, smoking history, Charlson comorbidity index (CCI), and preoperative clinical stage. For calculation of CCI, current diagnosis of kidney cancer was not included. The postoperative pathological parameters studied included histological subtype, pathological grade, presence of necrosis, sarcomatoid differentiation, stage, surgical margin, and lymph node metastases. To assess for PNS, preoperative symptoms and laboratory measurements were assessed. In this study, PNS included anemia (Hb <125 g/L for male, Hb <115 g/L for female), polycythemia (Hb >170 g/L for male, Hb >155 g/L for female), hypercalcemia (serum calcium >2.7 mmol/L), and weight loss (any of abnormal weight loss, excessive weight loss, unexplained weight loss, or recent weight loss recorded as described by the patient). Patients with benign histology or metastases were excluded. Following surgical recovery, patients without metastases were updated annually. Those that developed metastases were updated every three months until death.

Statistical analysis

Clinical and pathological features between patients with and without PNS were summarized using means and proportions. Statistical comparisons in baseline factors were performed using t-tests or Chi-squared tests. Patient outcomes included recurrence, cancer-specific death, and death from any cause. Time to these outcomes were estimated using the Kaplan-Meier method.[12] Survival intervals were defined as the time from nephrectomy to time of recurrence (recurrence-free survival [RFS]), time of death related to RCC (cancer-specific survival [CSS]), and time of death related to any cause (overall survival [OS]). The log-rank tests were used for univariable analyses and the Cox proportional hazards models were used to adjust for potential confounders. A priori, models for cancer outcomes were adjusted for by known prognostic factors (tumor size, tumor grade, margin status). OS was also adjusted for baseline comorbidity. The comparisons were summarized with hazard ratios (HRs) and 95% confidence intervals (CIs). All tests were two-sided and p-values of 5% or less were considered statistically significant. No adjustment was made for multiple testing.

Results

Of 4337 patients, 1314 (30.3%) had evidence of one or more PNS. The most common PNS in this cohort was anemia (90.0%), followed by weight loss (11.8%), polycythemia (3.6%), and hypercalcemia (1.1%). Clinical and pathological features are summarized in Table 1. There was no significant difference in sex, race, family history of kidney cancer, or smoking history between those with and without PNS. Median followup was similar in both groups. Patients with PNS were older, had higher CCI score, more advanced clinical and pathological tumor stage, higher tumor grade, advanced clinical and pathological lymph nodal involvement, positive tumor margin, and presence of tumor necrosis and sarcomatoid differentiation as compared to those without PNS. PNS was present more frequently in patients with clear-cell RCC as compared to papillary and chromophobe RCC (p=0.009).

Anemia alone was present more frequently in patients with older age, higher CCI score (both p<0.0001), advanced clinical and pathological T stage (p<0.0001), advanced clinical (p<0.0001) and pathological lymph nodal stage (p=0.009), higher tumor grade (p<0.0001), positive tumor margin (p=0.0002), and clear-cell RCC (p=0.016). Weight loss was associated with older age (p=0.02), advanced clinical and pathological T stage (p<0.0001), higher tumor grade (p<0.0001), and advanced clinical (p<0.0001), and pathological lymph nodal stage (p=0.03).

Kaplan-Meier estimated survival curves are shown in Fig. 1. Five-year estimated RFS, CSS, and OS were significantly worse in patients with PNS (63.7% [95% CI 59.7, 67.5], 84.3% [95% CI 80.7, 87.2], and 79.6% [95% CI 75.8, 82.9], respectively, for patients with PNS vs. 73.9% [95% CI 71.2, 76.4], 90.8% [95% CI 88.8, 92.5], and 90.1% [95% CI 88.1, 91.8], respectively, for patients without PNS, all p<0.005).

Associations of clinical and pathological parameters with RFS, CSS, and OS are summarized in Table 2. During study period, 720 patients had evidence of tumor recurrence. Of 286 patients that died during study period, 48 patients did not have known cause of death and were excluded from CSS analysis. Older age at nephrectomy, higher CCI score, tumor size, grade, and stage were all significant predictors of worse RFS, CSS, and OS (all p<0.05) on univariable and multivariable analysis. Positive tumor margin was asso-

Table 1. Comparison of baseline clinical and pathological characteristics (n=4337)

	No paraneoplastic syndrome (n=3023)	Paraneoplastic syndrome (n=1314)	p
Age in years (median [IQR])	60.9 (52.8, 68.7)	63.6 (55.3, 70.7)	<0.0001
Gender			
Male	2033 (67.3%)	849 (64.6%)	0.091
Female	990 (32.7%)	465 (35.4%)	
Race (n=2955)			
White	1758 (85.2%)	734 (82.4%)	0.055
Non-white	306 (14.8%)	157 (17.6%)	
Positive family history	142 (4.7%)	59 (4.5%)	0.765
Smoking history (n=3871)	1570 (57.8%)	697 (60.2%)	0.166
CCI score (median [IQR]), (n=4124)	2 (1,3)	2 (1,3)	<0.0001
Clinical stage (n=4294)			
T1	2244 (75.1%)	839 (64.3%)	<0.0001
T2	419 (14.0%)	235 (18.0%)	
T3/4	326 (10.9%)	231 (17.7%)	
Clinical node positivity (n=3547)	43 (1.4%)	44 (3.3%)	<0.0001
Pathological grade			
G1	232 (7.7%)	75 (5.7%)	<0.0001
G2	1477 (48.9%)	522 (39.7%)	
G3	1099 (36.3%)	512 (39.0%)	
G4	215 (7.1%)	205 (15.6%)	
Pathological stage			
T1	2058 (68.1%)	758 (57.7%)	<0.0001
T2	197 (6.5%)	87 (6.6%)	
T3/4	768 (25.4%)	469 (35.7%)	
Margin positivity	197 (6.5%)	125 (9.5%)	<0.0005
Pathological node positivity (n=4334)	38 (1.3%)	30 (2.3%)	0.013
Tumor necrosis (n=3339)	638 (27.2%)	383 (38.5%)	<0.0001
Sarcomatoid differentiation (n=3322)	70 (3.0%)	70 (6.9%)	<0.0001
Histological subtype			
Clear-cell RCC	2441 (80.7%)	1110 (84.5%)	0.009
Papillary RCC	498 (16.5%)	169 (12.9%)	
Chromophobe RCC	84 (2.8%)	35 (2.7%)	

CCI: Charlson comorbidity index; IQR: interquartile range; PNS: paraneoplastic syndrome; RCC: renal cell carcinoma.

ciated with poor RFS (p<0.0001), CSS (p=0.0002), and OS (p<0.0001) on univariable analysis but only predicted poor RFS on multivariable analysis (p=0.003). On univariable analysis, presence of PNS adversely affected RFS (HR 1.67, 95% CI 1.48–1.90, p<0.0001) and CSS (HR 1.85, 95% CI 1.34–2.54, p=0.0002) (Table 1). When adjusted for age, CCI score, tumor size, grade, pathological stage, tumor margin, and histological subtype on the multivariable analysis, PNS only trended towards worse RFS and CSS. Presence of PNS did not affect OS on univariable or multivariable analysis.

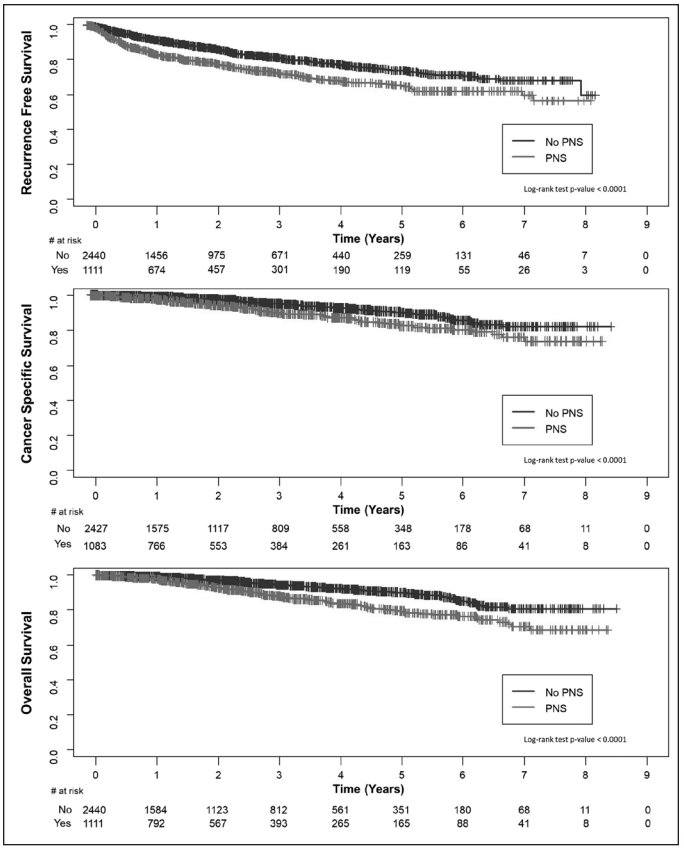

Fig. 1. Kaplan-Meier curve estimates of recurrence-free survival, cancer-specific survival, and overall survival. PNS: paraneoplastic syndrome.

Discussion

In this cohort study, one or more PNS were present in about 30% of patients. This is consistent with other studies that suggest PNS is prevalent in up to 40% of RCC patients.[1,2] On average, patients with PNS had more advanced and aggressive cancer. While patients with PNS have worse prognosis compared to those without PNS, this difference seems to be explained by other known prognostic factors.

Implications of PNS for those presenting with localized RCC remains unclear. Few studies have evaluated the effect of PNS on oncological outcomes after nephrectomy. Some studies found that preoperative cachexia and weight loss were associated with more advanced tumors,[3,13] and more recently, a study by Moreira et al found that those with PNS undergoing nephrectomy had significantly worse cancer-specific and disease-free survival owing to adverse pathological features.[14] Similar to other studies, we found that

Table 2. Univariable and multivariable analysis on survival outcomes

		Univariable analysis				Multivariable analysis			
Parameter		**HR**	**95% CI**		**p**	**HR**	**95% CI**		**p**
Paraneoplastic syndrome									
Yes vs. no	RFS	1.67	1.48	1.90	<0.0001	1.13	0.98	1.31	0.079
	CSS	1.85	1.34	2.54	0.0002	1.29	0.96	1.74	0.096
	OS	1.04	0.78	1.39	0.789	1.22	0.96	1.55	0.10
Age at nephrectomy									
Increase by 1 year	OS	1.05	1.04	1.06	<0.0001	1.04	1.03	1.06	<0.0001
CCI score									
Increase by 1 unit	OS	1.42	1.32	1.4	<0.0001	1.40	1.28	1.53	<0.0001
Fuhrman grade									
G1 vs. G4	RFS	0.05	0.03	0.09	<0.0001	0.20	0.13	0.31	<0.0001
	CSS	0.01	0.003	0.08	<0.0001	0.05	0.01	0.21	<0.0001
	OS	0.05	0.02	0.11	<0.0001	0.16	0.06	0.42	0.0002
G2 vs. G4	RFS	0.11	0.08	0.15	<0.0001	0.33	0.26	0.41	<0.0001
	CSS	0.11	0.07	0.18	<0.0001	0.26	0.18	0.38	<0.0001
	OS	0.12	0.08	0.18	<0.0001	0.25	0.17	0.36	<0.0001
G3 vs. G4	RFS	0.29	0.21	0.38	<0.0001	0.52	0.39	0.68	<0.0001
	CSS	0.28	0.18	0.40	<0.0001	0.41	0.29	0.58	<0.0001
	OS	0.28	0.19	0.42	<0.0001	0.39	0.28	0.54	<0.0001
Tumor margin									
Positive vs. negative	RFS	2.14	1.68	2.72	<0.0001	1.45	1.13	1.85	0.003
	CSS	2.44	1.53	3.87	0.0002	1.49	0.95	2.34	0.08
	OS	2.46	1.63	3.71	<0.0001	1.54	0.98	2.43	0.062
Tumor size									
Increase by 1 cm	RFS	1.22	1.18	1.25	<0.0001	1.12	1.09	1.14	<0.0001
	CSS	1.18	1.13	1.24	<0.0001	1.08	1.03	1.13	0.001
	OS	1.17	1.13	1.22	<0.0001	1.10	1.06	1.15	<0.0001
Pathological stage									
T1 vs. T3/T4	RFS	0.12	0.10	0.14	<0.0001	0.30	0.24	0.37	<0.0001
	CSS	0.15	0.10	0.23	<0.0001	0.37	0.26	0.52	<0.0001
	OS	0.18	0.14	0.24	<0.0001	0.56	0.41	0.76	0.0002
T2 vs. T3/T4	RFS	0.50	0.40	0.61	<0.0001	0.56	0.43	0.73	<0.0001
	CSS	0.44	0.29	0.66	<0.0001	0.54	0.36	0.82	0.004
	OS	0.51	0.34	0.76	0.001	0.72	0.46	1.14	0.16
Histological subtype									
Chromophobe vs. clear-cell	RFS	0.47	0.29	0.75	0.002	0.45	0.29	0.68	0.0002
	CSS	0.31	0.16	0.60	0.0004	0.40	0.21	0.75	0.004
	OS	2.09	1.60	2.74	<0.0001	0.45	0.23	0.86	0.015
Papillary vs. clear-cell	RFS	0.62	0.48	0.81	0.0004	0.96	0.75	1.25	0.78
	CSS	1.07	0.78	1.69	0.69	1.87	1.35	2.61	0.0002
	OS	0.34	0.20	0.59	0.0001	1.52	1.15	2.03	0.004

CCI: Charlson comorbidity index; CI: confidence interval; CSS: cancer specific survival; HR: hazard ratio; OS: overall survival; RFS: recurrence-free survival.

patients with preoperative PNS were more likely to have advanced tumor stage and grade (p<0.0001) compared to those without. In addition, we further report significant associations of PNS with older age, higher CCI score, clinical and pathological nodal involvement, positive margins, presence of tumor necrosis, and sarcomatoid differentiation on histology, all of which may further explain the markedly worse survival for those with PNS. Indeed, our univariate analysis showed that PNS was predictive of significantly worse RFS and CSS (p<0.0001) over a median followup of around two years. However, when adjusted for age, CCI, tumor size, grade, stage, margin status, and histological subtype, PNS did not predict worse survival outcomes. Therefore, the presence of PNS may be predictive of more advanced and aggressive tumors, along with unfavorable baseline patient characteristics, which in turn leads to worse postoperative survival outcomes. In other words, these results suggest that PNS may be a reflection of the underlying ability of the tumor to behave aberrantly against the patient's innate defense, rather than a direct cause of morbidity and mortality.

RCC is commonly diagnosed incidentally through abdominal imaging performed for investigation of non-specific abdominal complaints or surveillance of other conditions. Those symptomatic at presentation, including hematuria, mass effect, and flank pain, are known to have worse tumor characteristics and survival outcomes. For example, they were found to have

Table 3. Summary of previous studies on the prognostic significance of paraneoplastic syndromes in RCC

Author	Year	Subjects	PNS studied and prevalence (%)	Findings
Kim et al[3]	2003	n=1046 patients undergoing nephrectomy for RCC	Anemia (52%); cachexia (35%); hepatic dysfunction (32%); weight loss (23%); malaise (19%); hypercalcemia (13%); anorexia (11%); fever (7.8%), hypertension (2.5%)	Cachexia, weight loss, anorexia, and malaise, predicts worse disease-specific survival
Magera et al[10]	2008	n=1707 patients undergoing radical nephrectomy for localized clear-cell RCC	Elevated ALP (81%); elevated ESR (44%); anemia (35%); hypercalcemia (9%)	Anemia, hypercalcemia, elevated ESR are independently associated with worse cancer-specific survival
Ding et al[13]	2012	n=1512 patients undergoing nephrectomy for RCC	Any PNS (68%); elevated ESR (36%); hypertension (25%); cachexia (23%); anemia (21%); pyrexia (16%); liver dysfunction (9.7%); hypercalcemia (4.6%); polycythemia: (4.1%); varicocele (1.9%); neuromyopathy (0.7%)	Pyrexia, elevated ESR, cachexia and varicocele were associated with advanced clinical and pathological stage
Moreira et al[14]	2016	n=2865 patients undergoing nephrectomy for localized RCC	Any PNS (22%); anemia (23%); liver dysfunction (10%); hypercalcemia (9%); hypertension (2%); polycythemia (1%)	Presence of any PNS was associated with worse tumor characteristics (larger size, higher stage, higher grade) and cancer-specific survival. On multivariate analysis, PNS did not remain associated with worse survival
Sun et al (current study)	2020	n=4337 patients from CKCis database undergoing radical or partial nephrectomy for localized RCC	Any PNS (30.3%); anemia (90% of all PNS); weight loss (11.8% of all PNS); polycythemia (3.6% of all PNS); hypercalcemia (1.1% of all PNS)	PNS associated with older age, higher comorbidity score, advanced tumor stage and aggressive tumor histology. On multivariable analysis, baseline PNS not independently associated with recurrence or death

ALP: alkaline phosphatase; CKCis: Canadian Kidney Cancer information system; ESR: erythrocyte sedimentation rate; PNS: paraneoplastic syndromes; RCC: renal cell carcinoma.

higher likelihood of high tumor grade, stage,[8] and metastatic spread,[3] which account for an observable survival difference between those with incidental and symptomatic disease.

Based on the literature, the most commonly reported PNS is anemia, with a prevalence range of 20–40%.[1,14] In our study, anemia was similarly found to be the most prevalent PNS, accounting for 27% of all patients and present in 90% of the patients identified with PNS. This high prevalence has been explained by two primary reasons unrelated to bleeding: poor nutritional status and tumor production of iron-binding proteins such as ferritin and lactoferrin.[15,16] Recent meta-analysis found that anemic patients who required perioperative blood transfusion undergoing radical and partial nephrectomy for localized RCC had significantly worse survival outcomes.[17] Another meta-analysis looking at prognostic significance of preoperative anemia in patients undergoing surgery for localized RCC concluded that anemia was associated with earlier recurrence and worse survival after nephrectomy.[18] Similarly, our study showed that anemia was associated with worse survival with significantly higher stage, grade, tumor margin positivity, nodal positivity, age, and higher CCI score. Thus, it is important to recognize RCC as one of the differential diagnosis among patients with intractable anemia in the absence of other clearly causative medical conditions.

The prevalence of other PNS in RCC is estimated at 10–20% for hypercalcemia, 10–30% for constitutional symptoms, and 1–8% for polycythemia (Table 3).[1,11] In our cohort, the prevalence of polycythemia was 3.6% and weight loss was 11.8% of all the PNS observed, which are in line with findings in the literature. Hypercalcemia was present in only 1.1% of our cohort with PNS, which is likely due to different thresholds at which hypercalcemia is defined. For example, one study in the U.S. defined hypercalcemia at serum calcium >10.1 mg/dL (2.5 mmol/L),[14] whereas our study in Canadian centers defined hypercalcemia at serum calcium >2.7 mmol/L to capture more clinically significant hypercalcemia. The lower prevalence of hypercalcemia may also be due to a high proportion of patients (84%) from the current study who did not have a preoperative calcium level recorded, which is often due to one not being drawn, as shown in other studies.[19] The implications of PNS from this study should be further evidence for urologists to ensure a full preoperative chemistry panel is obtained. Previous studies have shown that any PNS, regardless of subtype, is associated with poorer outcomes. Similarly, our analysis of PNS stratified by specific manifestations showed persistent association with unfavorable tumor characteristics and survival outcomes.

To our knowledge, this is one of the largest multicentered studies evaluating the prognostic impact of PNS on patients with localized RCC undergoing surgery. Several implications can be derived from the findings. First, PNS is strongly predictive of worse patient and tumor characteristics, which in turn impacts survival after nephrectomy and can, therefore, be useful as a prognostic tool for risk stratification. Second, preoperative evaluation of clinical and laboratory PNS should be obtained in all localized RCC patients. And third, the presence of PNS may be a marker of higher-risk disease that warrants changes in postoperative followup protocols

and consideration of additional therapeutic measures. More research is needed to elucidate the mechanisms of PNS and optimize the management of patients with this seemingly high-risk manifestation of RCC.

Limitations

Potential limitations of the study may include missing data, lack of centralized pathology review, lack of data on extended PNS manifestations (such as Stauffer's syndrome), lack of differentiation of PNS from signs and symptoms related to other comorbidities, and shorter followup. In addition, this paper only looked at the patients who underwent surgery and it is possible that surgically unfit patients with PNS were excluded.

Conclusions

In the multi-institutional, Canadian cohort of patients undergoing partial or radical nephrectomy for non-metastatic RCC, the presence of PNS is associated with advanced age, higher comorbidity score, and adverse clinical and histological tumor characteristics, which in turn leads to worse oncological outcomes. When accounting for age, comorbidities, and tumor characteristics, PNS is not independently associated with worse survival outcomes, suggesting that it may be a reflection of underlying tumor aggressiveness relative to the patient's resilience. Although not an independent prognosticator, presence of PNS should be taken into consideration for timely surgical planning and proper followup.

Competing interests: Dr. Breau is an advisory board member for Ferring (bladder cancer). Dr. Tanguay has been an advisory board member for Pfizer; and has received travel grants from Sanofi. Dr. Pouliot has been an advisory board member for Amgen, Astellas, AstraZeneca, Bayer, Janssen, Sanofi, and TerSera; a speakers' bureau member for Astellas and Janssen; and has received payment, honoraria, and/or grants from Amgen, Astellas, AstraZeneca, Bayer, Janssen, Sanofi, and TerSera. Dr. Kapoor is an advisory board member for Amgen, BMS, Eisai, Ipsen, Merck, Novartis, Pfizer, Roche, and Verity; has received grants and/or honoraria from Amgen, Novartis, and Pfizer; and has participated in clinical trials supported by Amgen, BMS, CCTG, Merck, Novartis, and Pfizer. Dr. Lavallée has been an advisory board member for AbbVie, Bayer, Ferring, Sanofi, and TerSera; and has received an unrestricted research grant from Sanofi. Dr. Finelli has been an advisory board member for AbbVie, Amgen, Astellas, Bayer, Janssen, Roche, and Sanofi. Dr. So has been an advisory board member for AbbVie, Amgen, Astellas, Bayer, Janssen, Ferring, and TerSera; and has participated in clinical trials supported by Astellas, Ferring, and Janssen. Dr. Rendon has been an advisory board and speakers' bureau member for, and has received honoraria from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Jansen, and Sanofi. Dr. Fairey has received speaker honoraria from J&J and Roche. Dr. Lattouf has been an advisory board member for and received payment from Astellas, BMS, Merck, Novartis, and Pfizer; and has participated in clinical trials supported by BMS. Dr. Kawakami has been a procter for Minogue Medical and is a stockholder in and advisor for Vibe Bioscience. Dr. Basappa has been an advisory board member for Astellas, AstraZeneca, BI, BMS, Janssen, Novartis, and Pfizer; and has received honoraria from Astellas, BMS, Janssen, Novartis, and Pfizer. Dr. Wood has received research funding from Aragon Pharmaceuticals, AstraZeneca, BMS, Exelixis, Merck, Novartis, Pfizer, and Roche. Dr. Bjarnason has been an advisory board member for, has received speaker honoraria from, and has participated in clinical trials supported by Ipsen, MBS, Merck, and Pfizer; and owns stock in Abbott and Pfizer. Dr. Heng has been and advisor for Astellas, BMS, Eisai, Ipsen, Janssen, Merck, Novartis, and Pfizer; and has received research funding from BMS, Exelixis, Ipsen, Novartis, and Pfizer. The remaining authors report no competing personal or financial interests related to this work.

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