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The risk of febrile seizures following influenza and 13-valent pneumococcal conjugate vaccines

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ABSTRACT

Background: Evidence on the risk of febrile seizures after inactivated influenza vaccine (IIV) and 13-valent pneumococcal conjugate vaccine (PCV13) is mixed. In the FDA-sponsored Sentinel Initiative, we examined risk of febrile seizures after IIV and PCV13 in children 6–23 months of age during the 2013–14 and 2014–15 influenza seasons.

Methods: Using claims data and a self-controlled risk interval design, we compared the febrile seizure rate in a risk interval (0–1 days) versus control interval (14–20 days). In exploratory analyses, we assessed whether the effect of IIV was modified by concomitant PCV13 administration.

Results: Adjusted for age, calendar time and concomitant administration of the other vaccine, the incidence rate ratio (IRR) for risk of febrile seizures following IIV was 1.12 (95% CI 0.80, 1.56) and following PCV13 was 1.80 (95% CI 1.29, 2.52). The attributable risk for febrile seizures following PCV13 ranged from 0.33 to 5.16 per 100,000 doses by week of age.

The age and calendar-time adjusted IRR comparing exposed to unexposed time was numerically larger for concomitant IIV and PCV13 (IRR 2.80, 95% CI 1.63, 4.83), as compared to PCV13 without concomitant IIV (IRR 1.54, 95% CI 1.04, 2.28), and the IRR for IIV without concomitant PCV13 suggested no independent effects of IIV (IRR 0.94, 95% CI 0.63, 1.42). Taken together, this suggests a possible interaction between IIV and PCV13, though our study was not sufficiently powered to provide a precise estimate of the interaction.

Conclusions: We found an elevated risk of febrile seizures after PCV13 vaccine but not after IIV. The risk of febrile seizures after PCV13 is low compared to the overall risk in this population of children, and the risk should be interpreted in the context of the importance of preventing pneumococcal infections.

1. Introduction

Several studies conducted in the United States in influenza seasons prior to 2010–2011 did not observe an elevated risk of seizures following influenza vaccination [1–4]. However, during the 2010–2011 influenza season, an increased risk of febrile seizures following inactivated influenza vaccine (IIV) was reported by the Vaccine Safety Datalink (VSD). VSD investigators conducted a study among U.S. children ages 6–59 months to assess the risk of febrile seizures 0–1 days following the trivalent influenza vaccine (TIV) in the 2010–2011 season and found an incidence rate ratio

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(IRR) of 2.4 (95% CI 1.2, 4.7) for TIV adjusted for concomitant 13-valent pneumococcal conjugate vaccine (PCV13) and an IRR of 2.5 (95% CI 1.3, 4.7) for PCV13 adjusted for concomitant TIV [5]. The IRR for febrile seizures after concomitant TIV and PCV13 was 5.9 (95% CI 3.1, 11.3). The findings prompted further investigation of post-vaccination febrile seizures during the 2010–2011 season among children ages 6–59 months in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program, a component of the FDA-sponsored Sentinel Initiative [6,7]. Using a self-controlled risk interval (SCRI) design, the PRISM study reported IRRs of febrile seizure to be 1.36 (95% CI 0.78, 2.39) for TIV, 1.02 (95% CI 0.53, 1.96) for diphtheria tetanus and pertussis (DTaP), and 1.61 (95% CI 0.91, 2.82) for PCV13, after adjusting for concomitant vaccination, age, and calendar time. Same day vaccination with TIV and PCV13 did not show a statistically significant association with febrile seizures when compared to separate day vaccination.

During the 2013–2014 influenza season, the risk of seizures in children after influenza vaccination was examined prospectively in sequential analysis within PRISM using the SCRI design (primary) and a cohort design with historical comparator (secondary) [8]. A statistical signal was identified at the 7th "look" in children 6–23 months who received inactivated influenza vaccine (IIV) with concomitant PCV13, where the comparison group was IIV vaccinees from historical seasons prior to the widespread use of PCV13. In contrast, the primary SCRI analysis conducted within the study did not reveal any statistical signals. Furthermore, no statistical signal was identified for seizures in children 6–23 months without concomitant PCV13 in either the current vs. historical or the SCRI design.

Lacking data on the risk of seizures in PCV13 vaccinees not receiving IIV, the PRISM prospective surveillance study was unable to determine whether the signal, if real, was due to the PCV13 vaccine entirely, or due to some interaction between the 2013–2014 IIV and PCV13. Using PRISM health care claims data from two influenza seasons with the same IIV strain composition, 2013–2014 and 2014–2015, the purpose of this study was to examine the relative risk of febrile seizures following IIV and following PCV13 in children 6 through 23 months of age utilizing a self-controlled risk interval design.

2. Methods

2.1. Study population

The study population consisted of children 6 through 23 months of age who were members of one of four participating Sentinel Data Partners, Aetna, HealthCore, Humana, or OptumInsight Life Sciences, for all or a portion of the period of interest, July 1, 2013 to June 30, 2015. Children were included in the study if they received a dose of IIV or PCV13 during the study period and were enrolled in a health plan with medical coverage for, at minimum, the 180 days preceding vaccination through 20 days after vaccination.

2.2. Study design

We used a self-controlled risk interval design, comparing the risk of an adverse event in a post-vaccination risk interval to that in a control interval within the same individual [5,7]. The risk and control intervals for IIV and PCV13 were defined as days 0 to 1 and 14 to 20, respectively, after each of these vaccinations. The 0–1 day risk window aligns with windows used in earlier studies and was based on biological plausibility [8]. The control interval was selected to avoid overlap with the known increased risk of febrile seizures in the 7–10 days following measles-containing vaccines that may have been given on the same day. A post-vaccination control window was preferred over a pre-vaccination window in order to avoid bias due to providers or caregivers delaying vaccination after the outcome under study, thereby decreasing the rate of seizures in the control intervals.

2.3. Outcome

Potential cases of febrile seizure were identified in the claims data using two case definitions, based on International Classification of Diseases, 9th Edition (ICD-9-CM) diagnosis codes. The primary (and more specific) definition required the presence of a claim associated with diagnosis code 780.31 (febrile seizure [simple], unspecified) or 780.32 (complex febrile seizures) in the inpatient or emergency department (ED) setting [7]. We excluded potential cases if they had another seizure code in any medical care setting (inpatient, ED, or outpatient) in the 42 days before the index seizure code. In a prior PRISM study, this case definition had a positive predictive value of 91% and accounted for >90% of the chart-confirmed febrile seizures ascertained with a broad definition [7]. The secondary case definition required the presence of a claim with any of the following ICD-9-CM diagnosis codes occurring in the inpatient or ED setting: 780.3 (seizure), 780.31 (febrile seizure [simple], unspecified), 780.32 (complex febrile seizure), or 780.39 (other seizure). This broad case definition was utilized in a sensitivity analysis to mirror the sequential surveillance analysis where the signal was found and to increase power [9].

2.4. Exposures

Exposures to IIV and PCV13 were identified in claims data using Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), National Drug Codes (NDC), and ICD-9-CM procedure codes. Codes for a dose of Fluzone® or Fluzone Quadrivalent® (the only FDA-approved IIVs for the age range of interest during the two study seasons) or a 'generic' code for influenza vaccination were included as exposures; we excluded exposures to influenza vaccines that were not approved for use within our study age range. We included all exposures to IIV and PCV13 and did not limit to the first dose.

2.5. Statistical analysis

2.5.1. IRR estimates

We used conditional Poisson regression to estimate IRRs for febrile seizures in the risk vs. control intervals following vaccination. We first implemented 2 unadjusted models, each containing a term for IIV or PCV13, to estimate unadjusted IRRs for each of these exposures. Because a child's baseline risk for febrile seizures differs between the risk and control intervals due to both age and seasonal effects, we added adjustments for age and calendar time in weeks to each of the 2 models. The self-controlled risk interval design intrinsically adjusts for time-stable confounders. The final primary analytic model adjusted for age in weeks, calendar time, and concomitant administration of PCV13 or IIV vaccine [7,10,11]. We used splines to adjust for changes in age and seasonality using the underlying cohort in our models.

2.5.2. Sensitivity and exploratory analyses

Two separate sensitivity analyses were conducted to (1) adjust for concomitant DTaP and (2) utilize an alternative broad definition for febrile seizures described in the above section on outcome definitions [8]. Finally, an exploratory analysis assessed whether the relative risk of febrile seizures after IIV was modified by concomitant vaccination with PCV13, by adding an interaction term between IIV and PCV13 to the primary analytic model.

2.5.3. Attributable risk estimates

For descriptive purposes, we estimated attributable risks by age in weeks, comparing the difference in risk between exposed and unexposed intervals for PCV13, which was associated with febrile seizures in the primary analytic model. A pointwise 95% confidence band was estimated using the bootstrap. We did not estimate attributable risks for IIV since it was not associated with febrile seizures in unadjusted or adjusted models.

The Sentinel Initiative is a public health surveillance activity [12]. Thus, this study was not under the purview of institutional review boards.

3. Results

During the study period from July 1, 2013 through June 30, 2015, 735,425 children ages 6 through 23 months of age had at least 180 days of continuous enrollment in the health plan. Of these, 355,486 (48%) received at least one dose of IIV and 581,868 (79%) received at least one dose of PCV13 during the study period. We identified 321 episodes of febrile seizures following IIV and/or PCV13 (202 following IIV exposure and 173 following PCV13 exposure), occurring primarily in children ages 12 through 15 months. More than 90% were diagnosed in the ED setting (Table 1).

3.1. IRR estimates

In the adjusted and unadjusted analyses, IIV was not found to be associated with risk of febrile seizures, defined as at least one code for febrile seizure (Table 2). The IRR adjusted for age, calendar time and PCV13 was 1.12 (95% CI 0.80, 1.56). PCV13 was found to be associated with the risk of febrile seizures in the unadjusted and adjusted analyses. The IRR adjusted for age, calendar time and IIV was 1.80 (95% CI 1.29, 2.52).

Table 1
Characteristics of febrile seizure cases by administration of IIV and PCV13.

Characteristic	Cases in risk or control interval following IIV (%) N = 202	Cases in risk or control interval following PCV13 (%) N = 173
Age at vaccination		
6–11 months	53 (26.2%)	32 (18.5%)
12–15 months	80 (39.6%)	113 (65.3%)
16–23 months	69 (34.2%)	28 (16.2%)
Setting of diagnosis		
ED	185 (91.6%)	164 (94.8%)
Inpatient	17 (8.4%)	9 (5.2%)
Season		
2013–2014	100 (49.5%)	81 (46.8%)
2014–2015	102 (50.5%)	92 (53.2%)
Vaccines received		
IIV or PCV13	148 (73.3%)	119 (68.8%)
IIV and PCV13	54 (26.7%)	54 (31.2%)

3.2. Sensitivity and exploratory analysis

When we further adjusted the primary analytic model for concomitant DTaP-containing vaccines, the IRR for IIV remained similar 1.06 (95% CI 0.75, 1.49), while the IRR for PCV13 was slightly attenuated, 1.56 (95% CI 1.09, 2.25). In a separate sensitivity analysis using the broad definition for febrile seizures, results were consistent with the narrow definition; IIV was not found to be associated with the risk of febrile seizures, and PCV13 remained associated with the risk of febrile seizures, though the effect estimate was attenuated (Table 3).

3.3. Exploratory analysis of effect modification of IIV-febrile seizures association by concomitant PCV13

In the model that included IIV, PCV13, age, and calendar time, the p-value for the 2-way interaction of IIV*PCV13 was 0.10, and the exponentiated estimate, the multiplier of the IRR, for the interaction term was 1.93 (95% CI 0.88, 4.24). The study was not powered to assess interaction between IIV and PCV13, so to further explore the possibility of an interaction between the two vaccines, we ran analyses restricted to children receiving IIV without concomitant PCV13, PCV13 without concomitant IIV, and IIV and PCV13 administered on the same day while adjusting for age and calendar time (Table 4). IIV alone does not seem to confer an increased risk of febrile seizures, IRR adjusted for age and calendar time, 0.94 (95% CI 0.63, 1.42), while PCV13 alone does appear to have an increased risk of febrile seizures, IRR adjusted for age and calendar time, 1.54 (95% CI 1.04, 2.28). Furthermore, the stratified IRRs suggest that there may be a synergistic effect between IIV and PCV13. Specifically, the IRR of PCV13 and IIV together (IRR adjusted for age and calendar time 2.80 [95% CI 1.63, 4.83]) is numerically larger than that of PCV13 alone.

3.4. Attributable risk estimates

Attributable risk estimates of PCV13 vaccine varied by age (Fig. 1) due to the varying baseline risk of febrile seizures, with the highest estimates at 65 weeks of age (5.16 per 100,000 doses) and the lowest estimates at 25 weeks of age (0.33 per 100,000 doses).

4. Discussion

We found no evidence for an increased risk of febrile seizures following IIV in unadjusted models or adjusted models (IRR adjusted for age, calendar time, and concomitant PCV13 1.12 [95% CI 0.80, 1.56]). Additionally, sensitivity analyses consistently found no evidence of an association between IIV and febrile seizures. The lack of association is consistent with prior evaluations [7,13]. By contrast, we observed an increased risk of febrile seizures following PCV13 in both the unadjusted and adjusted models (IRR adjusted for age, calendar time and concomitant IIV 1.80 [95% CI 1.29, 2.52]). Although we did not find clear evidence for an elevated risk after concomitant vaccination with IIV and PCV13 by adding an interaction term between IIV and PCV13 to the primary

Table 2
Risk of febrile seizure following IIV and PCV13 vaccines.

Exposure	Cases in risk interval (0–1 day)	Cases in control interval (14–20 days)	Unadjusted IRR (95% CI)	IRR, adjusted for age and calendar time (95% CI)	Primary analysis: IRR, adjusted for age, calendar time, and concomitant IIV or PCV13 vaccine (95% CI)
IIV	51	151	1.18 (0.86, 1.62)	1.33 (0.96, 1.82)	**1.12 (0.80, 1.56)**
PCV13	57	116	1.72 (1.25, 2.36)	1.87 (1.36, 2.57)	**1.80 (1.29, 2.52)**

Table 3
Sensitivity Analysis: Risk of febrile seizures using a broad definition following IIV and/or PCV13 vaccines.

Exposure	Cases in risk interval (0–1 day)	Cases in control interval (14–20 days)	Unadjusted IRR (95% CI)	IRR, adjusted for age and calendar time (95% CI)	IRR, adjusted for age, calendar time, and concomitant IIV or PCV13 vaccine (95% CI)
IIV	64	207	1.08 (0.82, 1.43)	1.18 (0.89, 1.56)	1.04 (0.77, 1.39)
PCV13	71	169	1.47 (1.11, 1.94)	1.57 (1.19, 2.07)	1.55 (1.16, 2.07)

Table 4
Exploratory analysis: Risk of febrile seizures following IIV without PCV13, PCV13 without IIV and concomitant IIV and PCV13.

Exposure	Cases in risk interval ble(0–1 day)	Cases in control interval (14–20 days)	Unadjusted IRR (95% CI)	IRR, adjusted for age and calendar time (95% CI)
IIV without PCV13	29	119	0.85 (0.57, 1.28)	0.94 (0.63, 1.42)
PCV13 without IIV	35	84	1.46 (0.98, 2.16)	1.54 (1.04, 2.28)
IIV and PCV13	22	32	2.41 (1.40, 4.15)	2.80 (1.63, 4.83)

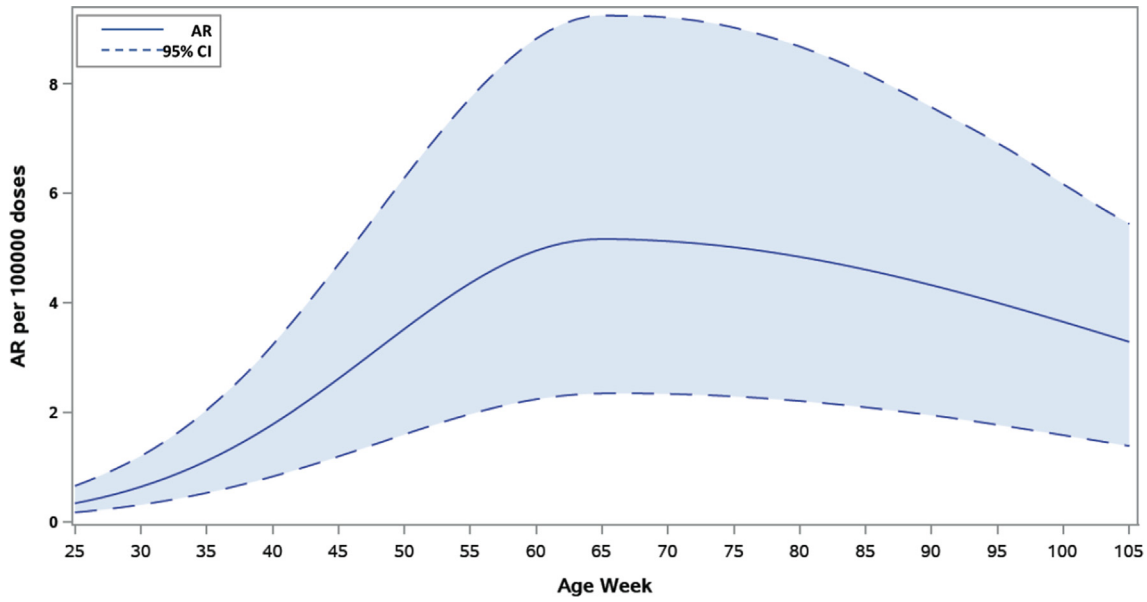

Fig. 1. Attributable risk (AR) estimates for febrile seizures following PCV13 by age in weeks.

analytic model, the study was not powered to assess the possibility of such an interaction, and the stratified analyses of IIV and PCV13 suggest that administration of IIV with PCV13 may increase the risk of febrile seizures to a greater degree than expected based on the independent effects of PCV13 alone.

Notably, the age at which the attributable risk of febrile seizures was highest (at 65 weeks of age) occurs within the age range when PCV13 is recommended, 12–15 months (52–65 weeks) of age. However, the risk following PCV13 is low and transient, compared to the 2 to 5% overall risk of febrile seizures among children between the ages of 6 and 60 months [14]. Vaccine providers can consider counseling the families of patients about the risk of fevers and febrile seizures, but these findings should be considered in the context of the importance of preventing pneumococcal infections and associated complications.

The association between the pneumococcal conjugate vaccine and febrile seizures is consistent with prior studies, including a recent publication by Duffy et al. that noted an independent risk of febrile seizures with PCV7 [7,13,15]. The authors also evaluated the association between PCV13 and febrile seizures and found an IRR of 1.4 (95% CI 0.27, 7.22); however, the power was limited due to the fact that few doses of PCV13 were administered during the study period. The prior PRISM study of the 2010–2011 season found an increased risk of febrile seizures after PCV13 that was statistically significant when adjusting for age and seasonality [7] but not when also adjusting for concomitant IIV and DTaP. The IRR point estimates for PCV13 from that study (1.74 [adjusted for age and seasonality] and 1.61 [adjusted for age, seasonality and concomitant TIV and DTaP]) were similar to the point estimates found in the current evaluation (1.87 and 1.80, respectively). The current study increases the power and ability to more precisely quantify the associations. The current evaluation is also consistent with the statistical signal detected in the prospective sequential analysis in PRISM during the 2013–2014 season, in which a signal for an elevated risk of febrile seizures was identified among children 6–23 months of age who received IIV with concomitant PCV13 but not in those receiving IIV without PCV13 [14].

This study has a number of strengths. We included a large nationally representative commercially insured study population and data from two influenza seasons. Combining data from two seasons was possible because of the same influenza virus strain composition of IIV, and this increased the power to evaluate the possible association between febrile seizures and IIV and/or PCV13. The use of the self-controlled risk interval design adjusted inherently for fixed confounders and avoided bias from misclassification of exposure because it only included vaccinated cases.

We carefully selected the control interval for our study (14–20 days post-vaccination) to avoid overlap with the risk window for febrile seizures following measles, mumps, rubella, and varicella vaccination (7–10 days post-vaccination) [16]. Despite the short time period comprised by the risk and control windows, we adjusted for time-varying age and calendar time using spline modeling of background rates in the PRISM population. Finally, we were able to adjust for some concomitant vaccinations, including DTaP-containing vaccines, PCV13, and IIV. The study results were robust to adjustments for age, calendar time, and concomitant vaccines with IIV or PCV13.

Limitations of the study include the fact that cases of febrile seizure were identified in claims data and not validated using medical record review. However, based on prior validation activities in PRISM, we expect that the febrile seizure definition had a positive predictive value (PPV) of approximately 91% [7]. We included a broader definition of febrile seizure as a sensitivity analysis, but this definition only had a PPV of 70% in a prior evaluation in the PRISM population. Vaccination confirmation rates in claims data ranged from 94 to 100% in the prior study identifying TIV, PCV13, and DTaP vaccinations [7], and we expect that these rates would have been similar. Finally, although the PCV13 vaccine has not changed, the IIV formulation does vary by year which may limit the applicability of the findings to other influenza seasons. The reason for using the years included was to explore the signal noted in the PRISM prospective surveillance study among children receiving both IIV and PCV13 vaccines (9) and to include two years of data with the same IIV strain composition to increase the power of the study.

Although PRISM is one of the largest cohorts used to evaluate vaccine safety, this study was not powered to determine if same day IIV and PCV13 vaccine synergistically increased the risk of febrile seizures. We did not collect data on vaccines other than PCV13, DTaP, and IIV, so the role of additional concomitant vaccinations in causing febrile seizures and the possibility of synergy among them could not be evaluated.

5. Conclusions

We found an elevated risk of febrile seizures after PCV13 vaccine but not after IIV. The risk of febrile seizures associated with PCV13, however, is low and transient compared to the overall risk of febrile seizures in this population of children, and these results should be interpreted in light of the importance of preventing pneumococcal infections in young children.

CRediT authorship contribution statement

Meghan A. Baker: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Christopher Jankosky**: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing - review & editing. **W. Katherine Yih**: Conceptualization, Formal analysis, Investigation, Methodology, Writing - review & editing. **Susan Gruber**: Formal analysis, Visualization, Writing - review & editing. **Lingling Li**: Formal analysis, Visualization, Writing - review & editing. **Noelle M. Cocoros**: Conceptualization, Formal analysis, Investigation, Methodology, Writing - review & editing. **Hana Lipowicz**: Data curation, Investigation, Project administration, Writing - review & editing. **Claudia Coronel-Moreno**: Data curation, Methodology, Project administration, Writing - review & editing. **Sandra DeLuccia**: Data curation, Funding acquisition, Project administration, Resources, Writing - review & editing. **Nancy D Lin**: Data curation, Investigation, Resources, Writing - review & editing. **Cheryl N. McMahill-Walraven**: Data curation, Investigation, Resources, Writing - review & editing. **David Menschik**: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing - review & editing. **Mano S. Selvan**: Data curation, Investigation, Resources, Writing - review & editing. **Nandini Selvam**: Data curation, Investigation, Resources, Writing - review & editing. **Rong Chen Tilney**: MS Data curation, Formal analysis, Methodology, Writing - review & editing. **Lauren Zichittella**: Data curation, Formal analysis, Methodology, Writing - review & editing. **Grace M. Lee**: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - review & editing. **Alison Tse Kawai**: Conceptualization, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [CJ and DM are employed by the Food and Drug Administration and participated in the design and conduct of the study, interpretation of the data, review and approval of the manuscript, and decision to submit the manuscript for publication. WKY receives research support from GlaxoSmithKline. ATK is currently an employee of RTI Health Solutions, a business unit of Research Triangle Institute, which conducts work for government, public and private organizations, including pharmaceutical companies. The work described in this manuscript was completed while AK was an employee of the Harvard Pilgrim Health Care Institute before she became an employee of RTI Health Solutions. LZ and RCT are currently employees of RTI International, and LL is currently and employee of Karyopharm Therapeutics Inc. All other authors have no potential conflicts of interest.].

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