

How to account for early overly small risk sets in the analysis of pregnancy outcome data?—Comparison of different methods for stabilizing the Aalen-Johansen estimator

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Abstract

Purpose: In analyzing pregnancy data concerning drug exposure in the first trimester, the risk of spontaneous abortions is of primary interest. For estimating the cumulative incidence function, the Aalen–Johansen estimator is typically used, and competing risks such as induced abortion and livebirth are considered. However, the delayed study entry can lead to overly small risk sets for the first events. This results in large jumps in the estimated cumulative incidence function of spontaneous abortions or induced abortions using the Aalen–Johansen estimator, and consequently in an overestimation of the probability.

Methods: Several approaches account for early overly small risk sets. The first approach is conditioning on the event time being greater than the event time causing the large jump. Second, the events can be ignored by censoring them. Third, the events can be postponed until a large enough number is at risk. These three approaches are compared.

Results: All approaches are applied using data of 54 lacosamide-exposed pregnancies. The Aalen–Johansen estimate of the probability of spontaneous abortion is 22.64%, which is relatively large for only three spontaneous abortions in the dataset. The conditional approach and the ignore approach have an estimated probability of 7.17%. In contrast, the estimate of the postpone approach is 16.45%. In this small sample, bootstrapped confidence intervals seem more accurate.

Conclusions: In the analyses of pregnancy data with rare events, the postpone approach is favorable as no events are excluded. However, the approach that ignores early events has the narrowest confidence interval.

KEYWORDS

Aalen–Johansen estimator, competing risks, left truncation, overly small risk sets, pregnancy outcome

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Key Points

- The choice of stabilization method strongly impacts the estimated cumulative incidence.
- Bootstrapped confidence intervals seem more accurate than those based on the asymptotic theory.
- In a lacosamide-exposed pregnancy cohort, the postpone approach seems favorable as no event is excluded.
- The approach ignoring only early events has the narrowest bootstrapped confidence interval.

Plain Language Summary

Suppose in a pregnancy outcome study, a spontaneous abortion is observed early when only a few other pregnant women have entered the study. In that case, it may result in an unrealistic large probability of spontaneous abortions. There are several possibilities to deal with this. One approach is to start the observation later. Another approach is to ignore the events; a third approach is to postpone the events artificially. Applying these approaches to a dataset regarding lacosamide exposure during pregnancy, the probability of a spontaneous abortion is 16.45% when using the postpone approach. Using one of the other approaches results in a much lower probability estimate of 7.17%. Therefore, the probability estimate of the postpone approach seems to be more realistic and neither too large nor too low. However, the approach ignoring the early events has the smallest variability.

1 | INTRODUCTION

Lacosamide is one of the most often used newer antiseizure medications, but information about its use in pregnancy is limited. A recent study by the Embryotox Center of Clinical Teratology and Drug Safety in Pregnancy (TIS Berlin) focused on the safety of lacosamide exposure during pregnancy.¹ Until larger prospective studies are available, analysis of small cohorts could provide at least some preliminary data for counseling inadvertently exposed women and might identify signals of possible teratogenicity. However, with small sample sizes, choosing the correct statistical analysis method is especially important to avoid wrong conclusions about drug safety.

In the analysis of pregnancy outcomes, for example, after drug exposure during pregnancy, competing events have to be considered.^{2,3} A pregnancy can result in a livebirth (LB), but also a spontaneous abortion (SAB), an induced abortion (IA), or a stillbirth are possible outcomes. Furthermore, pregnancy data are usually not collected upon conception but several weeks later when the pregnancy is confirmed, for example, by a medical consultation or when women or their treating physicians contact a Teratology Information Service (TIS) for drug risk assessment. Therefore, pregnant women enter the cohort delayed, leading to left truncation.³ A consequence is that the risk set does not only decrease over time but increases and decreases alternately. When ignoring these challenges, bias is induced. For example, when ignoring competing events, the probability of SAB is overestimated, or when ignoring left truncation, the probability of SAB is underestimated. In the lacosamide cohort, a third challenge occurred. There was an early SAB while the risk set was still small.

The Aalen–Johansen estimator is the typical choice to estimate cumulative incidences in a left-truncated competing risk setting.⁴ Therefore, it is often used to estimate the event probabilities in pregnancy data. But events in overly small risk sets result in implausibly large jumps in the Aalen–Johansen estimates.^{5,6} Due to these large jumps, the probability of an event might be overestimated. A first way to account for these jumps is to use a conditional approach by conditioning on the event time being greater than the time at which the large jump can be observed. This approach can also be called a landmarking approach using a single landmark.² The conditional approach is easy to implement but limits the interpretability.

As an alternative, Friedrich et al.⁵ suggested *ignoring* these events by censoring them. The approach is the extension of Lai and Ying⁷ to competing risks and is well-motivated based on advanced statistical methods. They suggest only counting events if at least n_{\min} individuals are at risk and censor them otherwise. The choice of n_{\min} was based on tuning parameters. A cross-validation combined with a 632-bootstrap can be used to obtain these tuning parameters while the predictive ability is assessed via the Brier score.⁵ As ignoring events is not the most natural approach, especially for rare events, Rousson et al.⁶ suggest *postponing* the events until the number of events is sufficiently large. Via simulations, they derive a cutoff value of $n_{\min} = 10$ as a rule of thumb.

Friedrich et al.⁵ and Rousson et al.⁶ apply their approaches to the same dataset containing data about pregnancies exposed to statins.⁸ While Rousson et al.⁶ compare their approach to the one of Friedrich et al.,⁵ they apply it slightly differently by only ignoring events at the beginning and not in overly small risk sets at the end of the study observation period. Furthermore, they use the gestational age

measured in weeks on a discrete time scale. In contrast, Friedrich et al.⁵ treat the same measurement as continuous.

In the following, we use the lacosamide data of the TIS Berlin to compare the approaches of Friedrich et al.⁵ and Rousson et al.⁶

2 | METHODS

2.1 | Data

The TIS Berlin offers risk assessment on drug exposure during pregnancy. Each year, there are approximately 15 000 requests from healthcare providers and patients, resulting in more than 4000 follow-ups with complete information on pregnancy outcomes. At the first consultation, drug exposure and maternal characteristics are documented. Information about the pregnancy outcome is collected after informed consent is given by mailed questionnaires about 8 weeks after the expected delivery date. The lacosamide cohort consists of lacosamide-exposed pregnancies prospectively ascertained between 2009 and 2020. One primary outcome was the risk of SAB.

2.2 | Statistical analysis

We consider a competing risk setting subject to left truncation and right-censoring. The competing events are SAB, IA, and LB. The focus is on the cumulative incidence function (CIF), that is, the probability of a specific event, either SAB, IA, or LB, until the end of follow-up.

The following five approaches for estimating the CIF are considered:

1. The standard Aalen–Johansen estimator;
2. The conditional approach using the Aalen–Johansen estimator but conditioning on the event time being large enough that at least n_{\min} individuals are at risk;
3. The ignore approach of Friedrich et al.⁵ censoring events when less than n_{\min} individuals are at risk;
4. The ignore only early approach only censoring events at the beginning of the follow-up until n_{\min} individuals are at risk;
5. The postpone approach of Rousson et al.⁶ postponing events until at least n_{\min} individuals are at risk.

A mathematical formulation of the five approaches is displayed in Section 1 of the Supporting Information.

The focus of comparing the five approaches is on the point estimates at the maximum follow-up time and the corresponding confidence intervals (CIs).

The CIs of the five approaches are calculated in two different ways. First, they are calculated based on the asymptotic theory of weak convergence of the Aalen–Johansen estimators⁹ and using a complementary log-minus-log transformation.^{5,10} However, in small sample sizes, as in the lacosamide cohort, the asymptotic theory might not hold. Therefore, we also use a nonparametric bootstrap in which

we sample $N_{\text{REP}} = 1000$ times with replacement from the data, estimate the variance and apply the complementary log-minus-log transformation afterwards.

3 | RESULTS

The lacosamide study cohort comprised 54 prospectively ascertained pregnancies, resulting in three SABs (5.56%), eight IAs (14.81%), and 43 livebirths (79.63%). These crude event proportions are no valid probability estimates, as they neglect the left truncation.² Compared with Hoeltzenbein et al.,¹ we excluded one stillbirth for technical purposes. Furthermore, we considered a twin pregnancy resulting in two livebirths as one event. More descriptive information of the lacosamide cohort can be found in the Section 2 of the Supporting Information.

The reported pregnancies entered the study cohort between gestational week 4.57 and 40.15, with a median entry time of gestational week 10. Compared with other observational studies based on the Embryotox cohort of the TIS of Berlin, this is late as the median entry time in the other studies is about gestational week 8.^{11,12} The gestational age of enrollment of 13 pregnancies was after gestational week 24, when per definition, SABs can no longer be observed. However, this does not limit the interpretability of the results, as the time-to-event framework can account for this by implicitly letting the hazard of the SAB drop to 0 at week 25.

Figure 1 displays the number of pregnancies under study and the event times of the lacosamide cohort. The first event is a SAB in gestational week 6.00 when only six women are at risk. Twelve pregnancies are already at risk at the time of the second event. Furthermore, at gestational week 40.57, only nine pregnancies are still at risk. The overly small risk set for the first event results in a jump in the Aalen–Johansen estimate of a SAB of $1/6 = 0.167$. There are only three SABs but eight IAs in the data. Nevertheless, the estimated cumulative incidences using the Aalen–Johansen estimator are 22.6% for SAB and 30.49% for IA. Therefore, there is a concern that the cumulative incidence of SAB may be overestimated. In Figure 2, all

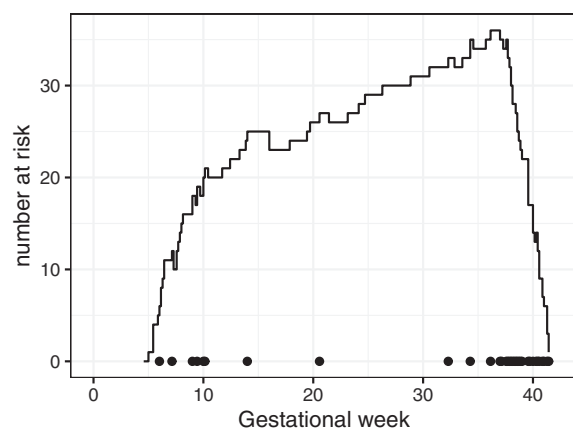


FIGURE 1 Number of pregnancies at risk in the lacosamide cohort. The dots below the curve mark the event times.

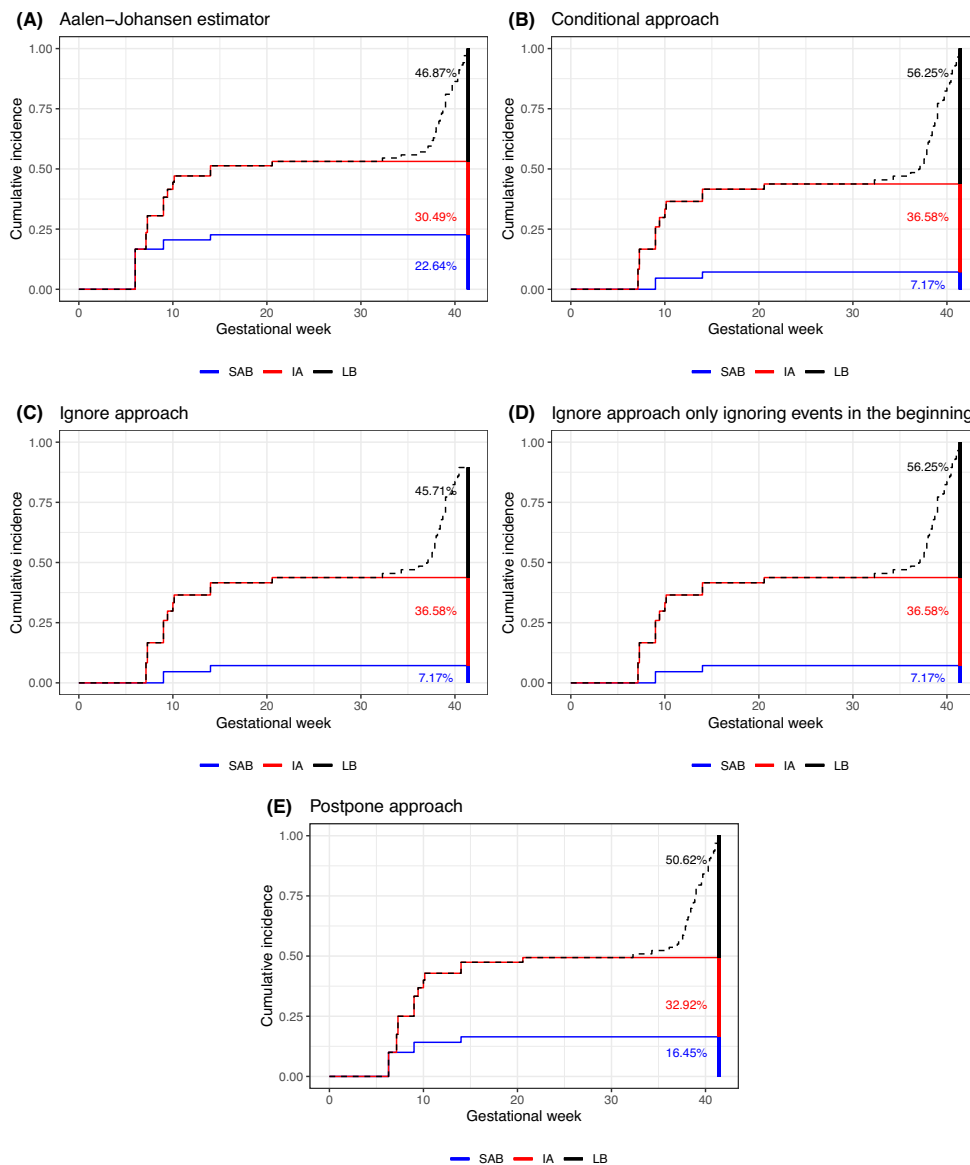


FIGURE 2 Stacked estimated cumulative incidence functions estimated by the five different approaches. SAB, spontaneous abortion; IA, induced abortion; LB, livebirth. [Correction added on 27 October 2023, after first online publication: Figure 2 has been replaced.]

estimated cumulative incidences are displayed, and Table 1 reports the estimated cumulative incidences with corresponding 95% CIs.

In the conditional approach, we condition on the event time to be greater than the event time of the first event (i.e., gestational week 6.00). In the conditional approach, the first SAB is excluded. Consequently, only two SABs are observed, and as a result, the estimated cumulative incidence of a SAB is smaller than the standard Aalen-Johansen estimator. The estimated cumulative incidences of IA and LB are greater than in the standard approach (Figure 2B). The CIs are comparable with the bootstrapped ones being slightly larger (Table 1).

In the ignore approach, deriving the tuning parameter by the cross-validation and the 632-bootstrap resulted in a minimum prediction error for $n_{\min} = 1$, corresponding to the standard Aalen-Johansen estimate. From a practical perspective, the choice of $n_{\min} = 10$ as suggested by Rousson et al.⁶ may be more appropriate. The consequence of using $n_{\min} = 10$ instead of $n_{\min} = 1$ is that the first event is censored instead of counted, and therefore, the rather large jump of 1/6 is avoided. Further choices of n_{\min} are displayed and discussed in the

Section 4 of the Supporting Information. In contrast to the conditional approach, the first SAB is censored and not excluded. When also censoring the events in the end, the estimated cumulative incidences of Figure 2C are obtained. For SAB and IA, they correspond to the ones of the conditional approach. As the last nine events are censored, the estimated cumulative incidence of LB is smaller than the conditional approach. The 95% CIs of the model-based and the bootstrap approach of LB and IA are similar (Table 1). In contrast, the model-based CI of SAB is much wider than the bootstrapped one and hardly informative.

Censoring the last nine LBs has, in this application, the undesirable property of preventing the estimated outcome probabilities from summing up to 100%. Therefore, we restrict the censoring to the first trimester by choosing $s_2 = 13$ in the ignore only early approach (Figure 2D). The estimated cumulative incidences and model-based 95% CIs coincide with the ones of the conditional approach. The ignore only early approach results in the smallest CIs for SAB. Although the point estimate is rather low, the CI is narrow compared with the other approaches.

TABLE 1 Estimated event probability (i.e., the estimated cumulative incidence) at the maximum gestational week 41.43 and 95% confidence intervals (CIs). The CIs are calculated in two different ways: based on the asymptotic theory of the Aalen–Johansen estimator (95% CI) or based on a bootstrap (95% BS CI). LB, livebirth; SAB, spontaneous abortion; IA, induced abortion.

	Probability (in %)	95% CI	95% BS CI
Standard Aalen–Johansen estimator			
LB	46.87	[26.45; 72.81]	[26.26; 73.11]
SAB	22.64	[5.81; 66.74]	[5.51; 68.76]
IA	30.49	[14.72; 56.41]	[13.48; 59.87]
Conditional Aalen–Johansen estimator			
LB	56.25	[36.99; 77.22]	[35.77; 78.64]
SAB	7.17	[1.73; 27.16]	[1.72; 27.32]
IA	36.58	[19.54; 61.48]	[18.41; 63.91]
Ignore approach $n_{\min} = 10$			
LB	45.71	[25.52; 71.83]	[27.80; 68.20]
SAB	7.17	[0.10; 99.49]	[0.92; 45.18]
IA	36.58	[18.01; 64.82]	[19.45; 61.67]
Ignore only early approach $n_{\min} = 10$			
LB	56.25	[36.99; 77.22]	[35.77; 78.64]
SAB	7.17	[1.73; 27.16]	[1.72; 27.32]
IA	36.58	[19.54; 61.48]	[18.41; 63.91]
Postpone approach $n_{\min} = 10$			
LB	50.62	[31.56; 73.10]	[30.81; 74.14]
SAB	16.45	[4.80; 48.17]	[4.85; 47.82]
IA	32.92	[17.02; 57.47]	[16.10; 59.70]

The postpone approach does not censor or delete the events in small risk sets. The SAB at gestational week 6.00 is postponed 2 days to gestational week 6.29. Figure 1 shows that at 6.29, there are nine pregnancies at risk and, due to still counting the postponed event, $n_{\min} = 10$ is reached. Furthermore, we restricted the postpone approach to the first trimester by choosing $s_2 = 13$. The estimated cumulative incidence of SAB using this approach is greater than the one excluding or ignoring the first event but smaller than the one obtained with the standard Aalen–Johansen estimator (Figure 2E). Compared with the ignore early approach, the other two estimated cumulative incidences are reduced in the postpone approach. However, in comparison with the standard Aalen–Johansen estimates, they are increased. Both approaches to calculating 95% CIs obtain similar results, with the bootstrapped ones being slightly larger.

The CIs of all approaches are substantially overlapping. However, the bootstrapped CIs of the conditional and the approach ignoring only early events are smaller than the other approaches.

4 | DISCUSSION

The standard Aalen–Johansen estimator can overestimate a cumulative incidence if an event occurs in an overly small risk set. The conditional

approach restricts the interpretability of the resulting cumulative incidences. The ignore approach also accounts for late small risk sets, which are a minor problem compared with early ones. In the ignore only early approach, events are ignored, which strongly affects the estimated cumulative incidence if the number of events of this type is small. However, in the postpone approach, the event times are artificially alternated.

If the dataset is small, bootstrapped CIs are more appropriate. For the lacosamide data, the results of the approach ignoring only early events and of the conditional approach are equal. Furthermore, both have smaller bootstrapped CIs than the other approaches. A small simulation study (see Section 3 of the Supporting Information) showed that if the focus is on the probability of a rare event that may occur early, the postpone approach seemed the most favorable. However, at the same time, there might be a bias in estimating the probability of the competing event. In the lacosamide data, one SAB is either ignored or postponed by using the different approaches. But as there are only three SABs in total, not counting the one event strongly impacts the estimate. From an applied point of view, excluding or ignoring may not be favorable if the events are rare. In the postpone approach, the event is counted but delayed by 2 days. From a clinical perspective, it is of minor importance if one SAB occurred at week 6.00 or week 6.29. Moreover, the exact time of SABs is often unknown. Therefore, the point estimate of the postpone approach seems the most realistic as a SAB probability of 7.17% is highly protective and seems a result of excluding one SAB. In contrast, a probability of 22.64% obtained with the standard Aalen–Johansen estimator resulted from one event while the risk set was still small. Consequently, in the published analysis of the lacosamide data,¹ we decided to report the postpone approach. In general, the choice between the ignore early approach and the postpone approach depends on the application and the focus of estimation. In datasets with rare events where the exact event times are of less importance and the main interest is in the point estimate of the CIF, as in pregnancy data, postponing may be favorable to avoid losing events. However, if the interest is in obtaining the smallest CI, the approach of ignoring early events can be preferred. Furthermore, artificially postponing events may be unreasonable, for example, in transplant data, where the exact day of transplantation is important.

Due to the small number of SABs, one might argue that calculating an estimator of the CIF is not meaningful with only three events. Nevertheless, reporting the crude rate of 5.56% is more misleading as the left truncation is neglected, leading to an arguably underestimated risk of a SAB after lacosamide exposure.

The sample size in the lacosamide cohort is rather small. If possible, larger numbers of exposed pregnancies are required to evaluate pregnancy outcomes. However, the number of exposed pregnancies, especially for newer drugs, is limited, as these are usually avoided during pregnancy. Nevertheless, information about possible risks associated with exposure might be required for counseling women inadvertently exposed.

A more formal way to decide what stabilization method to use might be with a cross-validated Brier score similar to the cross-validation and 632-bootstrap of the tuning parameter in Friedrich et al.⁵

Here, the choice of $n_{\min} = 10$ is based on simulations conducted by Rousson et al.⁶ A modification based on the postpone approach was already applied to pregnancy data by Suarez et al.¹³ They used $n_{\min} = 50$ and estimated the cumulative incidences using the Fine and Gray model.¹⁴ However, their cohort is quite large compared with the one of Rousson et al.⁶ and the lacosamide cohort. The cross-validation in the approach of Friedrich et al.⁵ was rather unsatisfying in the lacosamide cohort in that it led to $n_{\min} = 1$. In the lacosamide cohort, the standard Aalen–Johansen estimator is used if n_{\min} is smaller than 6. If n_{\min} is between 6 and 11, the displayed results are obtained. The results for $n_{\min} = 12$ are displayed in the [Supporting Information](#). However, $n_{\min} = 12$ limits the interpretability of the results as no conclusions about abortions before gestational week 9 can be made as all events prior are censored or omitted. Furthermore, in the postpone approach, another large jump occurs at the gestational week of the first events.

The lacosamide cohort differs from the statin cohort of Friedrich et al.⁵ and Rousson et al.⁶ as, for example, the gestational age is reported more precise in week plus days and not only in weeks. Often only single individuals entered at a particular entry time. Therefore, when we postponed the first event, we postponed it until exactly 10 individuals were at risk. In contrast, in the statin cohort, the event is postponed to the next week when 28 other individuals are at risk. In the lacosamide data, summarizing the time in weeks does not alter the estimated probabilities much. Moreover, using discrete-time survival methods¹⁵ does not solve the problem in the lacosamide data.

The information on whether the study entry time alters the risk of experiencing an event can be investigated.^{16–18} In the lacosamide data, for IA and SAB, there may be a dependence between the risk and the study entry time. There are several ways to account for dependent left truncation (e.g., Beaudoin and Lakhali-Chaieb,¹⁹ Stegherr et al.,¹⁸ and Vakulenko-Lagun et al.²⁰). Using these approaches while simultaneously accounting for overly small risk sets is a point of future research.

AUTHOR CONTRIBUTIONS

Maria Hoeltzenbein, Anne-Katrin Fietz and Katarina Dathe were responsible for generating the lacosamide dataset, check the data for plausibility and developed the observational study approach. Regina Stegherr, Anne-Katrin Fietz and Jan Beyersmann outlined the analysis, which was performed by Regina Stegherr and Anne-Katrin Fietz. All authors interpreted the results. Regina Stegherr, Anne-Katrin Fietz and Jan Beyersmann developed the first draft of the manuscript, which all other authors revised. Each author has reviewed the final version of the manuscript and has approved it for publication.

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CONFLICT OF INTEREST STATEMENT

JB has received personal fees for statistical consultancy from Pfizer and Roche, all outside the submitted work.

ETHICS STATEMENT

The study protocol was approved by the ethics committee of the Charité-Universitätsmedizin Berlin (EA4/O15/20), and the study was registered with the German Clinical Trial register (DRKS00021001) and listed at the WHO International Clinical Trials Registry Platform.


PRIOR POSTINGS AND PRESENTATIONS

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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