


## SHORT COMMUNICATION

# Early childhood outcomes of NICU graduates with cytomegalovirus infection in California

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## Abstract

**Background:** To assess demographics and outcomes up to 3 years of age among children with cytomegalovirus (CMV) infection in California neonatal intensive care units (NICUs) during 2010–2021.

**Methods:** The California Perinatal Quality Care Collaborative (CPQCC) collects data on all very low birth weight (VLBW, birth weight  $\leq 1500$  g) and acutely ill infants with birth weight  $> 1500$  g across 92% of NICUs in California. VLBW infants and those with neurological conditions are referred to a statewide high-risk infant follow-up (HRIF) program. CMV infection was defined as a positive culture or PCR identified during the NICU hospitalization.

**Results:** During 2010–2021, CMV reporting rates averaged 3.5/1000 VLBW infants ( $n = 205$ ) and 1.1/1000 infants  $> 1500$  g ( $n = 128$ ). Among all 333 infants with CMV, 314 (94%) were discharged home alive, 271 (86%) were referred for HRIF and 205 (65%) had  $\geq 1$  visit. Whereas infants born to mothers  $< 20$  years of age had highest CMV reporting rates and those born to Hispanic mothers comprised 49% of all infected infants, they had the highest loss of follow-up. At the 12-month visit ( $n = 152$ ), 19 (13%) infants with CMV had bilateral blindness and 18 (12%) had hearing loss. At the 24-month visit, 5 (5%) of 103 had severe cerebral palsy.

**Abbreviations:** CMV, cytomegalovirus; CPQCC, California perinatal quality care collaborative; HRIF, high-risk infant follow-up; NICU, neonatal intensive care unit; VLBW, very low birth weight.

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**Conclusions:** Among infants admitted to the NICU, those with CMV diagnoses may over represent infants with more severe CMV disease and outcomes. The CPQCC and HRIF program findings may help inform implementation of surveillance for congenital CMV infection in other U.S. states and guide strategies to reduce disparities in access to services.

**KEYWORDS**

congenital infection, cytomegalovirus, premature infant, prevalence, very low birth weight infant

## 1 | INTRODUCTION

Congenital cytomegalovirus (CMV) infection is the leading infectious cause of sensorineural hearing loss and developmental disabilities in U.S. children (American Academy of Pediatrics, 2018). With a prevalence of 4.5 per 1000 live births, up to 10% of infants with congenital CMV infection have been identified in the neonatal intensive care unit (NICU) (Fowler et al., 2017). Whereas postnatal CMV infection may cause severe disease (e.g., sepsis-like syndrome) and has been associated with a failed hearing screen in very low birth weight (VLBW) and premature infants, evidence of its association with poorer neurodevelopmental outcomes is not definitive (Gunkel et al., 2018; Turner et al., 2014; Weimer et al., 2020). Infants in the NICU are typically tested for CMV upon clinical suspicion (Tran et al., 2020). A reliable distinction between congenital and postnatal CMV infection requires laboratory testing on clinical specimens collected within 2–3 weeks of birth (Lazzarotto et al., 2008).

During 2005–2016, CMV infection, reported in 2.7/1000 VLBW infants and 1.2/1000 infants >1500 g in California NICUs, was associated with longer hospital stay in both infant groups, and with increased mortality among infants >1500 g (Tran et al., 2020). Early childhood outcomes of NICU graduates with CMV infection have not been assessed. A statewide high-risk infant follow-up (HRIF) program ensures that VLBW and other high-risk infants discharged from NICUs are monitored for growth and neurodevelopment outcomes through age 3 years to receive early intervention if subsequent complications are identified (Pai et al., 2020). In this study, we describe demographics, clinical characteristics, and outcomes up to 3 years of age among NICU graduates reported with CMV infection in California during 2010–2021.

## 2 | METHODS

We used linked data from the California Perinatal Quality Care Collaborative (CPQCC) and California

Children's Service (CCS) HRIF program. CPQCC collects data for infants admitted to a member NICU at birth or within 28 days of life with one of the following eligibility criteria: (a) birth weight between 401 and 1500 g; (b) gestational age between 22 and 31 weeks 6 days at birth; or (c) for infants with birth weight >1500 g, either death, surgery, ventilation for >4 h, severe hyperbilirubinemia, early bacterial sepsis, therapeutic hypothermia, or acute transfer. Trained NICU personnel conduct data abstraction using a standardized questionnaire which is electronically submitted. When appropriate, definitions align with those of the Vermont Oxford Network (2022). Data include demographics, maternal and delivery history, post-delivery diagnoses and interventions (Tran et al., 2020).

The HRIF program provides a series of visits for eligible children through age 3 years (Pai et al., 2020). Infants who were cared for in a CCS-approved NICU with birth weight  $\leq 1500$  g, <32 weeks gestational age, or birth weight >1500 g,  $\geq 32$  weeks gestational age with documented qualifying criteria are eligible for HRIF (Department of Health Care Services, California Children's Services, 2016). Assigned personnel at the discharging NICU complete a web-based referral/registration form referring the infant to one of approximately 70 HRIF clinics across California. The statewide program includes 3 standard visits performed at approximately 4–8 months, 12–16 months, and 18–36 months (adjusted for chronological age) including comprehensive history, physical examination, neurological, developmental, psychosocial, hearing, and ophthalmologic assessments, and additional visits as deemed necessary. The CPQCC and HRIF databases are linked via a probabilistic linkage algorithm with >99% success (Pai et al., 2020).

VLBW infants and eligible infants >1500 g admitted to CPQCC-member NICUs during 2010–2021 were included in this study. The CPQCC NICU Admission/Discharge data collection form includes a specific field for recording congenital infections which include (but are not limited to) syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (2022). A case of CMV

infection is defined as a documented positive viral culture or polymerase chain reaction assay for CMV at any time since birth in an infant in the NICU. CMV laboratory testing is performed during diagnostic workup under the discretion of providers. However, data on specimen types or collection date are not recorded, precluding categorization of CMV cases as congenital or postnatal (Tran et al., 2020).

Among infants reported with CMV infection, we assessed the proportions with the following: small for gestational age (SGA), microcephaly, congenital anomalies, preterm morbidities, and neonatal death. SGA and microcephaly were defined as birth weight < 10th percentile and birth head circumference < 3rd percentile for their gestational age and gender, respectively, using the 2013 Fenton Preterm Growth Chart (Fenton & Kim, 2013). Among those who were discharged home alive, we assessed the proportions referred to the HRIF program and with at least one HRIF visit, by NICU care level, maternal age, maternal race or Hispanic origin, and health insurance type. We also assessed the median age at each standard visit, and the proportions of infants with CMV identified with visual impairment, hearing loss and interventions, neurological abnormalities, and cerebral palsy, among those seen at recommended ages 4–8, 12–16, and 18–36 months (adjusted for chronological age) for each standard follow-up visit.

We calculated reporting rates as the number of infants reported with CMV infection divided by the

number of live births meeting CPQCC eligibility criteria, using binomial proportion and exact confidence intervals (CI). We assessed reporting rates by birth year, NICU care level, maternal age, and maternal race or Hispanic origin, separately for VLBW infants and infants >1500 g. To compare reporting rates by subgroups, we estimated reporting rate ratios and 95% CI using a modified Poisson regression model with a robust error variance. We used SAS version 9.4 (SAS, Cary, NC) for all analyses.

### 3 | RESULTS

In CPQCC-member NICUs, 333 infants were reported with CMV infection during 2010–2021; 205 (62%) were VLBW infants and 128 (38%) were infants >1500 g. During the 12-year period, CMV reporting rates averaged 3.5/1000 VLBW infants and 1.1/1000 infants >1500 g. Among VLBW infants, reporting rates fluctuated between 2.2 and 4.9/1000 with a decreasing trend during 2010–2016, increased from 3.5/1000 in 2017 to 6.7/1000 in 2020, and decreased to 1.8/1000 in 2021 (Figure 1). Among infants >1500 g, reporting rates ranged 0.3–1.7 per 1000.

Most VLBW infants and infants >1500 g with CMV infection were born at community or regional (i.e., tertiary) hospitals (Table 1). Among VLBW infants, there was no significant differences in reporting rates by maternal age, but infants born to Hispanic and Asian or

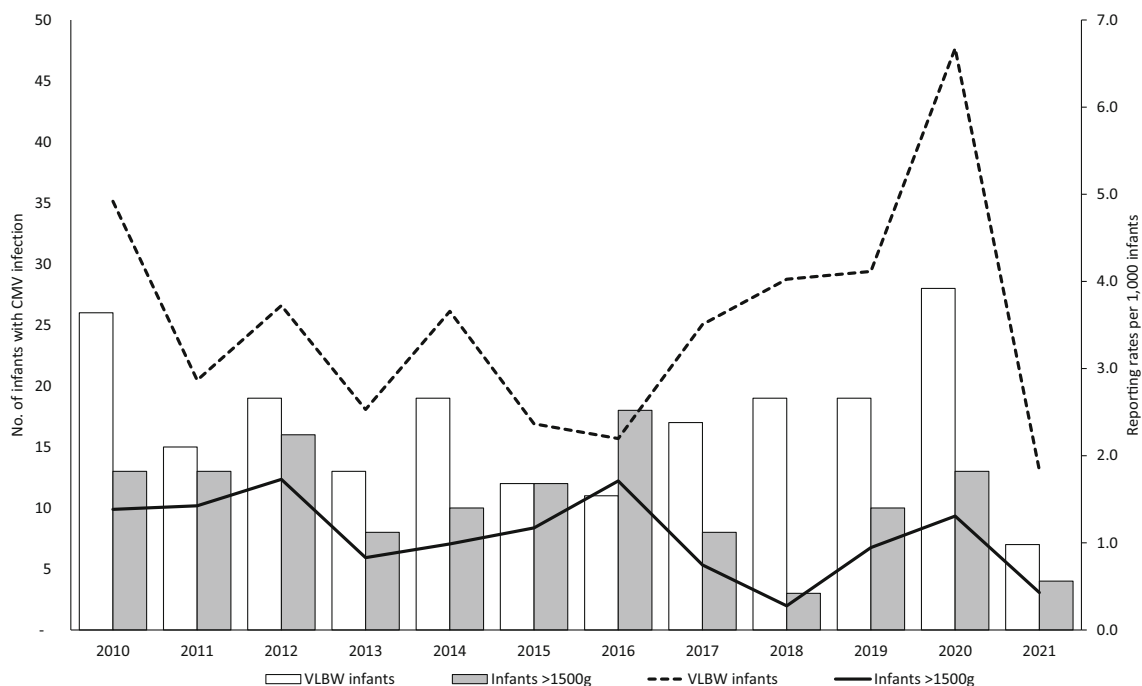


FIGURE 1 Number of VLBW infants and infants >1500 g with CMV infection and CMV reporting rates in NICUs, California, 2010–2021. Dashed and solid lines represent reporting rates for VLBW infants and infants >1500 g, respectively.

**TABLE 1** NICU level and maternal demographics of infants with CMV infection reported among VLBW infants and infants >1500 g in CPQCC-member NICUs, California, 2010–2021.

Characteristic	VLBW infants reported with CMV infection <i>n</i> (%), <i>n</i> = 205	CMV reporting rate per 1000 (95% CI)	Rate ratio (95% CI)	Infants >1500 g reported with CMV infection, <i>n</i> (%), <i>n</i> = 128	CMV reporting per 1000 (95% CI)	Rate ratio (95% CI)
Birth hospital level (NICU level) <sup>a</sup>						
Intermediate (II)	1 (0.5)	0.9 (0.0–4.9)	0.3 (0.0–1.9)	5 (3.9)	2.1 (0.8–1.3)	1.9 (0.8–4.8)
Community (IIIA/B)	115 (56.1)	3.5 (2.9–4.2)	Reference	52 (40.6)	1.1 (0.8–1.4)	Reference
Regional (IIIC/D)	86 (42.0)	4.1 (3.3–5.0)	1.2 (0.0–1.9)	67 (52.3)	1.0 (0.8–1.3)	1.0 (0.7–1.4)
Non-CCS	3 (1.5)	1.2 (0.2–3.4)	0.3 (0.1–1.1)	4 (3.1)	1.0 (0.3–2.4)	0.9 (0.3–2.5)
Maternal age, years						
<20	16 (7.8)	4.8 (2.7–7.7)	1.4 (0.8–2.4)	21 (16.4)	3.0 (1.9–.6)	2.5 (1.5–4.1)
20–29	80 (39.0)	3.5 (2.8–4.3)	Reference	61 (47.7)	1.2 (0.9–1.5)	Reference
30–39	94 (45.9)	3.4 (2.8–4.2)	1.0 (0.7–1.3)	38 (29.7)	0.7 (0.5–1.0)	0.6 (0.4–0.9)
≥40	15 (7.3)	3.6 (2.0–5.9)	1.0 (0.6–1.8)	7 (5.5)	1.0 (0.4–2.0)	0.8 (0.4–1.8)
Maternal race or Hispanic origin						
Hispanic <sup>b</sup>	105 (51.2)	4.1 (3.3–4.9)	1.9 (1.1–3.1)	59 (46.1)	1.1 (0.8–1.4)	0.7 (0.4–1.2)
Non-Hispanic						
Black	17 (8.3)	2.2 (1.3–3.5)	Reference	15 (11.7)	1.6 (0.9–2.7)	Reference
White	36 (17.6)	2.5 (1.7–3.4)	1.1 (0.6–2.0)	40 (31.3)	1.0 (0.7–1.4)	0.6 (0.4–1.1)
Asian or Pacific Islander	38 (18.5)	5.0 (3.5–6.8)	2.3 (1.3–4.0)	9 (7.0)	0.7 (0.3–1.4)	0.4 (0.2–1.1)
American Indian, Alaska Native or Other	8 (3.9)	4.2 (1.8–8.2)	1.9 (0.8–4.4)	4 (0.0)	0.9 (0.3–2.3)	0.6 (0.2–1.7)

Abbreviation: CCS, California Children's Service.

<sup>a</sup>NICUs were categorized into three levels (intermediate, community, and regional) based on CCS guidelines, American Academy of Pediatrics designation, and the services provided at each NICU. NICUs that choose not to participate in the CCS program were defined as non-CCS.

<sup>b</sup>Hispanic includes all Hispanics regardless of race.

Pacific Islanders mothers were approximately two times as likely to be reported with CMV infection as those born to Black mothers. In contrast, among infants >1500 g, infants born to mothers <20 years of age were almost three times as likely to be reported with CMV infection as compared with infants born to mothers 20–29 years of age, but no significant differences by maternal race or Hispanic origin were found.

Clinical characteristics and in-hospital outcomes of infants with CMV infection are described in Table S1. Among 314 (94%) infants with CMV infection who were discharged home alive, 271 (86%) were referred to the HRIF program. The most common eligibility criteria for HRIF referral among infants with CMV infection was birth weight ≤ 1500 g (58%), gestational age < 32 weeks (52%), neurological abnormalities (48%), and intracranial pathology with potential adverse neurological outcome (25%). Overall, 205 (65%) infants had ≥1 follow-up visit, with the lowest proportions among infants born to mothers <20 years, of Hispanic origin, or without health insurance (Table S2). The proportion reported with visual

impairment ranged from 7% to 14% between the first and second visit, respectively, and with hearing loss from 10% to 12% (Table 2). Among the 103 (38%) infants returning for a third visit, 6% were reported with moderate or severe cerebral palsy.

## 4 | DISCUSSION

We have used CPQCC data to describe trends in CMV infection among infants hospitalized in NICUs in California, identify groups at higher risk of disease, and describe outcomes up to 3 years of age among infants eligible for follow-up. During 2010–2021, CMV reporting rates averaged 3.5/1000 VLBW infants and 1.1/1000 infants >1500 g, much lower than the prevalence of congenital CMV infection among infants in the NICU (13.9 per 1000) estimated in a large newborn screening study in the United States (Fowler et al., 2017). Considering data since 2005 (Tran et al., 2020), CMV reporting rates among VLBW infants increased over time, reaching

**TABLE 2** Outcomes of infants reported with CMV infection enrolled in the high-risk infant follow-up program in California, 2010–2021.

Outcomes	No. (%) of infants with CMV infection <sup>a</sup>					
	First visit (4–8 months)		Second visit (12–16 months)		Third visit (18–36 months)	
	<i>n</i> = 205		<i>n</i> = 152		<i>n</i> = 103	
Visual impairment						
Yes	14	(7)	22	(14)	11	(11)
No	174	(85)	122	(80)	87	(84)
Unknown	17	(8)	8	(5)	5	(5)
Blindness						
Bilateral	9	(4)	19	(13)	9	(9)
Unilateral	3	(1)	3	(2)	1	(1)
Unknown	1	(0)	0	(0)	1	(1)
Hearing loss						
Yes	21	(10)	18	(12)	6	(6)
No	165	(80)	116	(76)	84	(82)
Unknown	5	(2)	6	(4)	6	(6)
Assessment in progress	14	(7)	12	(8)	7	(7)
Hearing loss (laterality)						
Bilateral	10	(5)	9	(6)	4	(4)
Unilateral	10	(5)	9	(6)	1	(1)
Assessment in progress	0	(0)	0	(0)	1	(1)
Unknown	1	(0)	0	(0)	0	(0)
Assisted listening device						
Yes, recommended and received	9	(4)	10	(7)	5	(5)
Yes, recommended but not received	6	(3)	2	(1)	0	(0)
No	6	(3)	5	(3)	1	(1)
Unknown	0	(0)	1	(1)	0	(0)
Type of assisted listening device						
Cochlear implant	1	(0)	0	(0)	0	(0)
Hearing aid	11	(5)	9	(6)	5	(5)
Unknown	2	(1)	4	(3)	0	(0)
Neurological status						
Abnormal or suspect	87	(42)	58	(38)	31	(30)
Normal	105	(51)	85	(56)	66	(64)
N/A	13	(6)	9	(6)	6	(6)
Cerebral palsy status (18–36 months)						
Mild—GMFCS level I			0	(0)	0	(0)
Moderate—GMFCS level II to III			2	(1)	1	(1)
Severe—GMFCS level IV to V			3	(2)	5	(5)
Unable to determine			3	(2)	2	(2)
No			35	(23)	93	(90)
N/A			109	(72)	1	(1)
Autism spectrum screen (18 months)						
Not pass					12	(12)
Pass					40	(39)

(Continues)

TABLE 2 (Continued)

Outcomes	No. (%) of infants with CMV infection <sup>a</sup>		
	First visit (4–8 months) <i>n</i> = 205	Second visit (12–16 months) <i>n</i> = 152	Third visit (18–36 months) <i>n</i> = 103
Referred for further autism spectrum assessment			
Yes			6 (6)
No			45 (44)

Note: GMFCS: Gross Motor Function Classification System. Level I: has functional gross motor skills, though may struggle with speed, balance, and coordination; moves independently without the aid of adaptive equipment. Level II: can walk with limitations and may need assistance with inclined or uneven surfaces; moves without the aid of adaptive equipment. Level III: can walk with the use of hand-held adaptive equipment and may need a wheelchair to move on inclined or uneven surfaces, or to travel long distances. Level IV: is self-mobile only with significant limitations; many use powered wheelchairs, require significant help with transfers, and are dependent on adaptive and assistive equipment. Level V: typically has limitations that impair all voluntary movement and is extremely dependent on adaptive equipment, assistive technology, and other people for mobility.

<sup>a</sup>Proportions of infants with CMV identified with an outcome among those seen at recommended ages 4–8 months, 12–16 months, and 18–36 months (adjusted for chronological age) for each standard follow-up visit. The median age (interquartile range) was 6 (5–7) months for the first visit, 13 (12–16) months for the second visit, and 26 (23–29) months for the third visit.

6.7/1000 in 2020, and was stable (range: 0.7–1.5/1000) among infants >1500 g. Data from VLBW infants are nearly population-based, though generalizability of the findings for the infants >1500 g is less clear, as data collection for that subgroup is limited to those with certain eligibility criteria. Of note, CMV reporting rates among VLBW infants decreased to 1.8/1000 in 2021, consistent with findings of a newborn screening study in Minnesota which documented a 70% reduction in congenital CMV prevalence during the COVID-19 pandemic (Schleiss et al., 2022). It is possible that testing practices among VLBW infants have changed due to increased awareness of both congenital CMV infection and risk of postnatal CMV infection through human milk feeding (Lanzieri et al., 2013). We have found that ~50% of CPQCC-member NICUs had quality improvement projects on human milk feeding during 2010–2021 but no project specifically mentioning CMV prevention or testing (California Perinatal Quality Care Collaborative, 2023).

CMV reporting rate among infants >1500 g was highest among infants born to mothers ≤20 years of age. Among VLBW infants, we observed higher reporting rates among those born to Hispanic mothers and Asian or Pacific Islander mothers. Although our study does not distinguish congenital from postnatal infection, unpublished national data indicate ~90% of infants tested for CMV in the NICU had specimens collected within 21 days of life (Raines et al., 2023). A prior study in California noted higher prevalence of congenital CMV infection among infants born to Hispanic and Black mothers (Kharrazi et al., 2010). More recent newborn screening studies in other regions of the United States have shown a lower prevalence among Hispanic infants compared to

White infants, and either higher or similar prevalence among Black infants (Fowler et al., 2018; Schleiss et al., 2022). Maternal CMV seroprevalence among Hispanic and Asian individuals in California is nearly 90% (Kharrazi et al., 2010), which increases the risk of postnatal CMV infection through breastmilk feeding. In addition, among infants referred to follow-up, the proportion with ≥1 visit varied with maternal age, race or Hispanic origin and health insurance support. Prior analysis of CPQCC and HRIF data revealed racial disparities on referral rates among VLBW infants, which lessened following implementation of a state-wide initiative in 2013 to address disparities in referrals (Pai et al., 2020). Identifying groups at higher risk of CMV infection and loss of follow-up may help guide strategies to prevent CMV infection and to reduce disparities in access to services.

This study has several limitations. First, date of specimen collection for CMV testing to distinguish congenital from postnatal infection, and data on most clinical signs of congenital CMV at birth or antiviral treatment were not captured. Second, cases identified in NICUs would over represent infants with more severe disease and outcomes in comparison to those that would be identified by newborn screening, 90% of whom have no clinical signs at birth. For example, 19%–27% of infants with CMV infection had microcephaly, a greater proportion than observed in cohorts of >50 infants with congenital CMV infection identified through newborn screening (0.8%–2.5%) (Ahlfors et al., 1999; Boppana et al., 1999; Koyano et al., 2011; Peckham et al., 1983; Saigal et al., 1982; Yamamoto et al., 2011). Third, not all infants referred to the HRIF program returned for any or all of the three standard visits at the time of this analysis, either due to



loss of follow-up (37%) or for being too young (25%). By the second follow-up visit, at median age 13 months, 14% of infants with CMV infection enrolled in the HRIF program had visual impairment, 12% had hearing loss and 38% suspected or confirmed neurological problems, which may or may not be attributed to CMV infection. Loss to follow up is unlikely to be random, and children with neurodevelopment concerns may have been more likely to return for visits. However, this study was descriptive in nature and did not include comparisons of outcomes among infants without reported CMV infection.

Among infants admitted to the NICU, those with CMV diagnoses may over represent infants with more severe CMV disease and outcomes. We found increased reporting of CMV infection among VLBW infants within NICUs in California during 2010–2021. Surveillance for congenital CMV is not conducted in California; thus, these data have been useful to monitor trends in CMV infection among NICU infants and describe clinical outcomes in a subset of infants who were eligible for the HRIF program. The work from the CPQCC and HRIF program may be informative to the wider implementation of congenital CMV surveillance efforts by health departments. Only 10 U.S. states conduct congenital CMV surveillance and case definitions are not standardized (Raines et al., 2022). Collecting data on clinical signs at birth, laboratory results, including specimen type, age at specimen collection, and testing methods, and outcomes such as hearing loss, would be important to accurately classify cases of congenital CMV and document the disease burden.

#### CONFLICT OF INTEREST STATEMENT

Dr. Megan Pesch serves on the executive board for the National CMV Foundation (unpaid), and is a paid consultant for MedScape/WebMD and DiaSorin Molecular. None of these organizations played any role in the conceptualization, analysis, data interpretation or writing of this manuscript. All other authors have no conflicts of interest to disclose.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from CPQCC and CCS-HRIF Program. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of CPQCC and CCS-HRIF Program.

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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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