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ARTICLE

Outreach to new mothers through direct mail and email: recruitment in the Early Check research study

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Abstract

Meeting recruitment targets for clinical trials and health research studies is a notable challenge. Unsuccessful efforts to recruit participants from traditionally underserved populations can limit who benefits from scientific discovery, thus perpetuating inequities in health outcomes and access to care. In this study, we evaluated direct mail and email outreach campaigns designed to recruit women who gave birth in North Carolina for a statewide research study offering expanded newborn screening for a panel of rare health conditions. Of the 54,887 women who gave birth in North Carolina from September 28, 2018, through March 19, 2019, and were eligible to be included on the study's contact lists, we had access to a mailing address for 97.9% and an email address for 6.3%. Rural women were less likely to have sufficient contact information available, but this amounted to less than a one percentage point difference by urbanicity. Native American women were less likely to have an email address on record; however, we did not find a similar disparity when recruitment using direct-mail letters and postcards was concerned. Although we sent letters and emails in roughly equal proportion by urbanicity and race/ethnicity, we found significant differences in enrollment across demographic subgroups. Controlling for race/ethnicity and urbanicity, we found that direct-mail letters and emails were effective recruitment methods. The enrollment rate among women who were sent a recruitment letter was 4.1%, and this rate increased to 5.0% among women who were also sent an email invitation.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Under-representation by traditionally underserved populations in clinical trials and health research is a challenge that may in part reflect inequitable opportunities to participate.

WHAT QUESTION DID THIS STUDY ADDRESS?

Are direct-mail and email outreach strategies effective for reaching and recruiting women from traditionally underserved and rural populations to participate in large-scale, population-based research?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Despite sending recruitment letters and email invitations in roughly equal proportion by urbanicity and race/ethnicity, women living in rural areas were less likely to enroll (2.8%) than women from urban areas (4.2%). Additionally, enrollment rates decreased as the probability that women were members of a racial or ethnic minority group increased.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Results from this study might encourage researchers to take a holistic and participant-centered view of barriers to study enrollment that may disproportionately affect underserved communities, including differences in willingness to participate, trust, and access to resources needed for uptake.

INTRODUCTION

Investigators leading clinical trials and health research studies often have difficulty recruiting sufficient numbers of research participants to meet study targets, and engaging individuals from traditionally underserved populations is an additional challenge.[1–4] In the United States, traditionally underserved populations, including members of racial-ethnic minority groups and people living in rural areas, experience disproportionate barriers to health services. Recruitment challenges are amplified when attempting to study rare health conditions and outcomes. Failure to recruit traditionally underserved populations in health research may exacerbate uncertainty about the prevalence of a condition or outcome within subpopulations and have the unintended effect of minimizing the benefits of scientific discovery for under-represented groups.[5,6]

Here, we evaluate direct mail and email outreach approaches implemented during phase I of a multiphase recruitment strategy for Early Check, an ongoing statewide newborn screening (NBS) research study.[7] Early Check is a large-scale, population-based study designed to expand the evidence base available to inform NBS policy by offering screening for a panel of conditions not included in standard NBS. In additional to the indirect societal benefit, Early Check returns screening results to parents. Newborns who screen positive may benefit from shortening the diagnostic process or the potential for earlier access to recommended care and management, investigational interventions, genetic counseling, and other resources made available through Early Check. The large majority (estimated at > 95%) of newborns will not screen positive through Early Check, and thus will not benefit in these ways. Recruitment for Early Check aims to inform all eligible parents about the opportunity to enroll their infants, with broad representation across racial-ethnic groups and other sociodemographic characteristics (for example, urbanicity[8]).

Recruitment context: The Early Check research study

Early Check screens newborns for a panel of pediatric-onset conditions, beginning with spinal muscular atrophy (SMA) and fragile X syndrome as initial prototypes. SMA is a rare life-threatening genetic condition that affects about 1 in 10,000 newborns in the United States.[9] Fragile X syndrome is the most common single-gene cause of inherited intellectual disability, affecting ~ 1 in 7,000 men and 1 in 11,000 women.[10] All newborns were eligible for Early Check during phase I if they were < 4 weeks old at the time of enrollment, had NBS in North Carolina, and were residents of either North Carolina (NC) or South Carolina (hereafter referred to collectively as the Carolinas). The legally authorized representative of an eligible newborn—typically the biological mother—is able to give permission for her infant to participate in Early Check through an online permission portal that was launched on October 15, 2018 (https://portal.EarlyCheck.org).

Through a data sharing agreement with the NC State Laboratory of Public Health (NCSLPH), Early Check conducts postnatal outreach by direct mail and email using contact information for mothers who gave birth and whose newborns had NBS in the state. Once a mother enrolls her newborn, investigators match demographic data collected on NBS cards with enrollment data from the Early Check online permission portal. Once matched, the Early Check laboratory pulls samples from the dried bloodspots of enrolled newborns and tests them for the Early Check conditions.

At the start of phase I, a 28-day postnatal enrollment window was set retroactively so that mothers who had given birth as early as September 17, 2018, were eligible to enroll their newborns. The enrollment window was changed to 31 days on January 3, 2019, and carried through the remainder of phase I. As a result, babies born on the last day of this outreach phase (March 19, 2019) remained eligible to enroll through April 19, 2019. Early Check also allows prenatal enrollment for residents of the Carolinas who are at least 13 weeks pregnant and plan to have their baby in North Carolina.

Statewide outreach and recruitment approach

The principal phase I outreach activities included (1) a personalized, direct-mail letter printed on letterhead from the NCSLPH signed by an NCSLPH designated representative (initially the NCSLPH director and subsequently the NC Chief Medical Officer), along with an Early Check-branded flyer insert, and (2) an email invitation with content matching the direct-mail letter. The letters and emails were sent postnatally to all women listed along with a valid mailing or email address in the NC NBS records. The initial outreach mailing lists were compiled on the day the permission portal was made public and included all women who had sufficient contact information and had given birth as early as September 28, 2018 (18 days before launch). Subsequent mailing lists were compiled daily with new data received from the NCSLPH.

Secondary outreach activities implemented before and during phase I included creation of an informational Early Check website (www.EarlyCheck.org); presentations and meetings with health care providers, hospital staff, and relevant professional organizations in NC; press releases and local media coverage[11]; and minimal social media activities designed to establish a barebones presence on Facebook and Twitter (i.e., Early Check pages that we made public on October 1, 2018, along with 8 Facebook posts and 6 Tweets that month announcing the Early Check launch). The social media component was expanded in phase II—which began March 20, 2019—to include more frequent posts and paid advertising on Facebook and Instagram (see Guillory *et al.*[12]). During phase I, we also conducted a statewide experiment to test whether enrollment rates would be improved by sending a reminder postcard to women who had been sent a letter 7 days earlier. The first batch of postcards was sent on February 20, 2019, and the experiment continued into phase II, with the last postcards sent April 1, 2019. For additional information about the rationale and formative work behind the Early Check outreach strategy, please see Bailey *et al.*[7]

In this paper, we examine the following research questions:

- *Research Question 1*: Are traditionally underserved or rural populations less likely to have sufficient contact information in NBS records and thus less likely to be sent a direct-mail or email invitation to enroll in Early Check?
- *Research Question 2a*: How do direct-mail recruitment letters, email invitations to enroll, and reminder postcards affect enrollment, controlling for race/ethnicity, urbanicity, and birth hospital affiliation with Early Check research partners?
- *Research Question 2b*: Are enrollment rates lower among traditionally underserved populations?
- *Research Question 3*: Did sending a reminder postcard a week after the recruitment letter improve enrollment rates?

METHODS

We used several data sources to conduct these analyses: (1) NBS records gathered from the NCSLPH and augmented with data collected as part of the Early Check laboratory workflow; (2) information collected from mothers through the Early Check electronic permission portal at the time of enrollment; (3) census-tract level population data from the 2013–2017 American Community Survey 5-year estimates (ACS);[13–16] (4) 2010 Rural-Urban Commuting Area codes[17]; (5) web analytics data gathered through Google Analytics to track permission portal traffic and usage; and (6) undeliverable-mail summary reports from Professional Mail Services, Inc. (PMSI), our direct mail service provider. When possible, we merged data from the first four sources—NCSLPH, the Early Check permission portal, tract-level population data, and Rural-Urban Commuting Area codes—to create an analytic dataset for which birth mothers were the unit of analysis. Google Analytics data were not linked to any personal information, and in accordance with our privacy policy, we made no effort to connect website user data with individual-level data from other sources. PMSI submitted undeliverable mail reports to us that we aggregated into monthly counts, precluding us from combining these with data from the other sources. As a result, analyses involving the Google Analytics or undeliverable-mail data were treated separately from the primary analytic dataset.

The combined dataset includes all records for babies born from September 17, 2018, through March 19, 2019, using the date of birth listed in the NCSLPH data as the filtering variable. Because women could enroll newborns up to 4 weeks after they were born, we waited to gather and consolidate records until April 19, 2019, the last possible postnatal enrollment date for those born during phase I. Women were allowed to enroll prenatally, so we included records for babies with an enrollment date on or before March 19, 2019, even if they were born after that date. We excluded these records from some analyses examining the effects of our direct mail and email campaigns.

Starting on February 20, 2019, and continuing through April 1, 2019, we mailed reminder postcards to a random half of NC residents who had given birth and whose newborn underwent NBS in the state. Postcards were scheduled to be sent 7 days after the initial recruitment letters, so women who were sent letters from February 13, 2019, through March 25, 2019, were included in the experiment.

Please see Supplementary Material for methodological details concerning data preparation, measures, and statistical analysis. In addition to describing our approach to geocoding, deduplication, and random assignment in the postcard experiment, these materials also include operationalization details for enrollment, contact via direct mail and email, urbanicity,

race/ethnicity, birth hospital affiliation with Early Check research partners, and enrollment-window adjustments. The Office of Human Research Ethics at the University of North Carolina at Chapel Hill (UNC-CH) serves as the central Institutional Review Board for the Early Check research study.

RESULTS

Descriptive statistics

After removing duplicate NBS records associated with repeat samples and multiple births per mother, we estimated that 56,457 women living in the Carolinas gave birth to babies who underwent NBS in NC (see Table 1). As expected, most were NC residents (97.9%), and many lived in an urban area (81.2%). A notable proportion of women (17.7%) gave birth at one of six hospitals affiliated with Early Check's institutional research partners (i.e., UNC-CH School of Medicine; Wake Forest School of Medicine; or Duke University. See Supplementary Material for a list of affiliated hospitals).

Most women (97.9%) who gave birth on or after September 28, 2018, and thus met the minimum qualification to be added to the recruitment letter mailing lists, had sufficient contact information to do so. Including women who gave birth before that date, we sent letters to 95.1% of all families who were eligible to enroll in Early Check during phase I. A total of 2,531 letters were returned as undeliverable through March 2019 (~ 4.7% of the letters that were sent). By way of contrast, only 6.3% of women who gave birth on or after September 28, 2018, had an email address listed in their NBS records (6.2% of all eligible). In practice, everyone who was sent an email was also sent a letter. Reminder postcards were sent to a randomly selected group comprising half of NC residents listed in the NCSLPH dataset during a 6-week pilot study. In all, 11.4% of new mothers were sent a postcard, not accounting for 358 postcards that were returned as undeliverable. We estimate that 3,110 people from the Carolinas visited the permission portal at least once from October 15, 2018, through March 19, 2019. Overall, 4.0% ($n = 2,257$) of the women who were eligible during the phase I period enrolled their newborns in Early Check. Only 38 women enrolled prenatally, which is not surprising given the emphasis on postnatal outreach and recruitment in phase I.

Race and ethnicity estimates from the permission portal, NBS records, and the imputation approach using 2013–2017 ACS 5-year data are shown in Table 2. The NBS records were missing race and ethnicity data from 15.0% ($n = 8,285$) of NC residents and appear to overestimate the white, black, and other racial categories while underestimating the American Indian or Alaska Native and Hispanic categories compared with the race and ethnicity distributions reported in NC Department of Health and Human Services (NCDHHS) fertility statistics for the year 2018. The ACS estimates for all births appear to under-represent the proportion of non-Hispanic white alone, non-Hispanic black alone, and Hispanic women who gave birth during the phase I period. The ACS estimates also appear to exaggerate the proportion of non-Hispanic women of other races or who are multiracial. Among women who enrolled their newborns in Early Check during phase I, just over half (50.4%; $n = 1,111$) provided self-reported race and ethnicity information when they signed up. Given the large amount of missing race and ethnicity data from the permission portal and NBS records, we used the ACS estimates when constructing our predictive models. Results concerning racial and ethnic differences should be interpreted cautiously, recognizing that they are based on rough estimates.

TABLE 1 Characteristics of North or South Carolina residents who gave birth in North Carolina or enrolled in Early Check from September 17, 2018, through March 19, 2019 ($N = 56,457$)

Characteristic	*n*	%
Enrolled in Early Check		
Postnatal	2,219	3.9
Prenatal	38	0.1
Did not enroll	54,200	96.0
Outreach methods		
Recruitment letter		
Sent a recruitment letter	53,716	95.1
No recruitment letter sent	2,741	4.9
Personalized email invitation		
Sent a personalized email invitation	3,476	6.2
Not sent an email invitation	52,981	93.8
Reminder postcard		
Sent a reminder postcard	6,425	11.4
Not sent a reminder postcard	50,032	88.6
State of residence		
North Carolina	55,268	97.9
South Carolina	1,189	2.1
Urbanicity		
Urban	45,861	81.2
Rural	10,575	18.7
Unknown	21	0.1
Birth hospital affiliation		
Yes, affiliated with an Early Check research partner	10,018	17.7
No, not affiliated with an Early Check research partner	46,439	82.3

Note: In the case of multiple births and repeat samples, we used location data from the earliest record for each mother to establish residency.

TABLE 2 Estimated race and ethnicity of North Carolina residents who gave birth from September 17, 2018, through March 19, 2019

	Early Check enrollees (N = 2,204)			All births (N = 55,268)			2018 NCDHHS
	Self-report		ACS estimate	NBS record		ACS estimate	
Race/ethnicity	*n*	%	%	*n*	%	%	%
White	753	67.8***	63.4***	26,179	55.7***	55.3***	54.3
Black	76	6.8***	15.7***	12,040	25.6***	22.4***	24.1
American Indian	10	0.9	0.9*	558	1.2**	1.4	1.4
Hispanic	119	10.7***	11.3***	5,643	12.0***	13.9***	15.4
Other	153	13.8***	8.7***	2,563	5.5***	7.0***	4.7
Total	1,111	100.0[a]	100.0[b]	46,983	100.0[c]	100.0[d]	100.0

Note: Self-report = Self-reported race and ethnicity collected through the permission portal from motherss who enrolled a child in Early Check. ACS estimate = Race and ethnicity based on census tract–level proportions among women of reproductive age who reported giving birth in the past 12 months on the ACS, using 5-year estimates for the years 2013–2017. NBS record = Race and ethnicity recorded on the NBS bloodspot form and reported in NCSLPH data. 2018 NCDHHS = NC resident birth for female mothers ages 15–44 by race and ethnicity of the mother, drawn from 2018 NCDHHS fertility statistics. Significance levels reported in the Self-report, ACS estimate, and NBS record columns are from two-sample tests of proportions comparing proportions by race and ethnicity in the 2018 NCDHHS percentage column.

ACS, American Community Survey; EC, Early Check; NBS, newborn screening; NC, North Carolina; NCDHHS, North Carolina Department of Health and Human Services; NCSLPH, NC State Laboratory of Public Health.

[a]There were 1,093 (49.6%) NC residents who enrolled in Early Check in this time period and did not provide race or ethnicity information when they signed up. These missing cases were excluded from the data reported in the self-report columns.

[b]There were 91 (4.0%) NC residents who enrolled in Early Check in this time period and could not be matched to the relevant ACS race and ethnicity data. These missing cases were excluded from the data reported in the estimate columns.

[c]There were 8,285 (15.0%) NC residents who gave birth during this time period and did not have race or ethnicity information recorded when the bloodspot was collected. These missing cases were excluded from the data reported in the NBS record column.

[d]There were 2,216 (4.0%) NC residents who gave birth during this time period and could not be matched to the relevant ACS race and ethnicity data. These missing cases were excluded from the data reported in the estimate column.

***p < 0.001; **p < 0.01; *p < 0.05.

Disproportionate representation in contact lists

To address research question 1, we conducted three logistic regression models examining whether traditionally underserved or rural populations were less likely to be added to the Early Check direct-mail or email contact lists because their data were not listed in NBS records (see Table 3). As a standard operating procedure, Early Check sent outreach materials to all women who had not already enrolled and who had sufficient contact information listed in the NBS records that we received from the NCSLPH. With that in mind, differences by urbanicity or race and ethnicity reflect variations in record-keeping standards at hospitals across the state or individual differences among new mothers in the availability of postal or email addresses.

Urbanicity significantly affected whether women were sent recruitment letters and email invitations, but not reminder postcards. Residents of urban census tracts were more likely to have been sent recruitment letters (97.94%; SE = 0.08) compared with residents of rural areas (97.16%; SE = 0.19), odds ratio (OR) = 1.39; 95% confidence interval (CI) 1.19–1.63; p < 0.001. Urban mothers were also more likely (6.67%; SE = 0.20) than rural mothers (4.63%; SE = 0.33) to have been added to the email contact list, OR = 1.48; 95% CI 1.26–1.74; p < 0.001.

Giving birth in a hospital affiliated with one of Early Check's institutional research partners—UNC-CH, Wake Forest School of Medicine, or Duke University—was also significantly associated with the likelihood of being added to the recruitment letter mailing list and the email contact list. Controlling for other variables in the model, we found that a greater percentage of women who gave birth at a partner-affiliated hospital (98.78%; SE = 0.11) were sent recruitment letters compared with women who gave birth elsewhere in the state (97.59%; SE = 0.09), OR = 2.00; 95% CI 1.64–2.43; p < 0.001. Women who gave birth at partner-affiliated hospitals were also more likely to have an email address available and thus to have been sent an email invitation (12.10%; SE = 0.50) than were new mothers who gave birth at other facilities (5.04%; SE = 0.18), OR = 2.60; 95% CI 2.32–2.91; p < 0.001.

The only differences by race and ethnicity were observed in the model for the email contact list. For each percentage point increase in the likelihood that a new mother was non-Hispanic American Indian or Alaska Native alone relative to the likelihood she was non-Hispanic white alone given her census tract of residence, the odds that she had an email address listed and thus was sent an email invitation significantly decreased, OR = 0.98; 95% CI 0.97–0.99; p < 0.001.

TABLE 3 Logistic regression analysis predicting whether North or South Carolina residents who gave birth in North Carolina from September 28, 2018, through March 19, 2019, were added to the Early Check mailing lists by urbanicity, estimated race and ethnicity, and Early Check birth hospital affiliation

	Letter		Email		Postcard	
Predictor	**OR**	**SE**	**OR**	**SE**	**OR**	**SE**
Urbanicity (reference = rural)						
Urban	1.39***	0.11	1.48***	0.12	1.02	0.42
Race/ethnicity (reference = white)						
Black	1.00	0.00	1.00	0.00	1.00	0.00
American Indian	1.00	0.00	0.98***	0.01	0.99	0.02
Hispanic	1.00	0.00	1.00	0.00	1.01	0.01
Other	1.00	0.00	1.00	0.00	1.00	0.01
Birth hospital affiliation (reference = not affiliated)						
Affiliated with an Early Check research partner	2.00***	0.20	2.60***	0.15	0.82	0.32
Constant	31.01	2.36	0.04	0.00	161.66	67.91
Model fit statistics						
N	54,887	54,887	6,433			
LL	−5,777.54	−12,573.83	−221.18			
$\chi^2(6)$	75.03***	352.36***	1.78			
$R^2_{\text{McFadden's}}$	0.01	0.03	0.01			

Note: The analysis excludes 18 women for whom geolocation data were insufficient to compute urbanicity. In the case of multiple births and repeat samples, we used location data from the earliest record for each mother.

OR, odds ratio; SE, robust standard errors that allow for clustering by census tracts.

***p < 0.001.

Postnatal enrollment rates

With regard to research question 2a, results from our logistic regression model predicting Early Check enrollments (see Table 4) show that recruitment letters had the strongest overall impact on enrollment rates (OR = 39.07; 95% CI 12.32–123.95; p < 0.001). Converting this effect into estimated marginal proportions controlling for all other variables in the model, we found that 4.13% (SE = 0.11) of women who were sent a recruitment letter ultimately enrolled in Early Check versus only 0.11% (SE = 0.07) of women who were not sent a letter. Email invitations had an additional positive impact on enrollments, such that the odds of enrolling among women who were sent an email was 1.33 times the odds among women who were not sent an email (95% CI 1.14–1.55; p < 0.001). In other terms, holding all else constant, 5.03% (SE = 0.36) of women who were sent an email invitation enrolled in Early Check versus 3.85% (SE = 0.10) of women who were not sent an email. In answer to research question 3, the reminder postcards did not have a significant impact on enrollments (OR = 0.98; SE = 0.08; p = 0.802). This last finding is consistent with results from a cluster-adjusted, stratified Mantel-Haenszel test of independence restricted to data from the postcard experiment and testing whether assignment to the letter-plus-postcard condition influenced enrollment, $\chi^2_{\text{Mantel-Haenszel}}$ (1, *N* = 12,365) = 0.35; p = 0.557.

In response to research question 2b, we found that several demographic characteristics affected whether women enrolled in Early Check postnatally. Women who lived in urban census tracts were more likely to enroll (4.16%; SE = 0.11) compared with women in rural areas (2.85%; SE = 0.19), OR = 1.48; 95% CI 1.29–1.71; p < 0.001. Giving birth in a hospital affiliated with one of Early Check's institutional research partners significantly affected how likely women were to enroll, OR = 1.68; 95% CI 1.50–1.89; p < 0.001. All else being equal, a greater percentage of women who gave birth at a partner-affiliated hospital enrolled in Early Check (5.75%; SE = 0.29) compared with women who gave birth elsewhere in the state (3.51%; SE = 0.10). We also found evidence of differences in whether women enrolled a newborn in the study given the estimated racial and ethnic distribution among women who had given birth in the past 12 months within the census tract where she lived. The odds of enrolling decreased for each percentage point increase in the likelihood that a birth mother was non-Hispanic black alone (OR = 0.99; 95% CI 0.99–0.99; p < 0.001), non-Hispanic American Indian or Alaska Native alone (OR = 0.99; 95% CI 0.99–1.00; p = 0.023), or Hispanic (OR = 0.99; 95% CI 0.99–1.00; p < 0.001). Last, the odds of enrolling increased with the number of days that a woman's postnatal enrollment window crossed into the phase II outreach period (OR = 1.01; 95% CI 1.01–1.02; p < 0.001), hinting at the effectiveness of

TABLE 4 Logistic regression analysis predicting postnatal Early Check enrollments among North or South Carolina residents who gave birth in North Carolina from September 17, 2018, through March 19, 2019, by phase I outreach method, urbanicity, estimated race and ethnicity, and Early Check birth hospital affiliation

Predictor	OR	SE	p	95% CI LL	95% CI UL
Letter (reference = Not sent a recruitment letter)					
Sent a recruitment letter	39.07	23.01	<0.001	12.32	123.95
Email (reference = Not sent an email invitation)					
Sent a personalized email invitation	1.33	0.10	<0.001	1.14	1.55
Postcard (reference = Not sent a reminder postcard)					
Sent a reminder postcard	0.98	0.08	0.802	0.83	1.15
Urbanicity (reference = Rural)					
Urban	1.48	0.11	<0.001	1.29	1.71
Race/ethnicity (reference = White)					
Black	0.99	0.00	<0.001	0.99	0.99
American Indian	0.99	0.00	0.023	0.99	1.00
Hispanic	0.99	0.00	<0.001	.99	1.00
Other	1.00	0.00	0.141	1.00	1.01
Birth hospital affiliation (reference = Not affiliated)					
Affiliated with an Early Check research partner	1.68	0.10	<0.001	1.50	1.89
State of residence (reference = South Carolina)					
North Carolina	0.84	0.11	0.191	0.65	1.09
Baby's date of birth	1.00	0.00	0.237	1.00	1.00
Number of days enrollment window crossed into phase II	1.01	0.00	<0.001	1.01	1.02
Number of days permission portal unavailable	1.01	0.01	0.241	0.99	1.02
Additional days postnatal enrollment window	0.94	.03	0.083	0.89	1.01
Constant	0.00	.00	0.152		

Note: Log-likelihood = −9060.03, $\chi^2(14) = 339.93$, $p < 0.001$, $R^2_{\text{McFadden's}} = 0.03$. $N = 56{,}398$. The analysis excluded 21 women for whom geolocation data were insufficient to compute urbanicity and 38 women who enrolled their children prenatally. In the case of multiple births and repeat samples, we used location data from the earliest record for each mother.

CI, confidence interval; LL, lower limit of the 95% CI; OR, odds ratio; SE, robust standard errors that allow for clustering by census tracts; UL, upper limit of the 95% CI.

social media campaigns implemented after March 19, 2019 (see Guillory *et al.*[12]).

Discussion

Early Check was envisioned as a research study that would enroll diverse participants from across NC while supporting meaningful, voluntary informed permission. As an expression of the core values of the project, we set out to develop a system in which the opportunity to participate would be presented to nearly all eligible birthing mothers (~ 120,000 per year), to routinely evaluate and improve our outreach and recruitment methods, and to establish an electronic permission (i.e., consent) procedure that extends beyond minimal legal requirements to more fully promote autonomous choice.[18–20]

To achieve education about the project and parental permission on a statewide scale, we could not rely primarily on an in-person recruitment model. Although permission rates in other NBS studies using in-person recruitment have been as high as 73%,[21,22] eligibility in these studies was restricted to a small number of birth hospitals in a single city. Reaching as many eligible families about Early Check as we did through direct mail or email in phase I would not have been possible—financially or logistically—using an in-person process

over the same time period. However, the benefit of reaching more people across the state was likely tempered by the requirement that mothers enroll within 4 weeks of giving birth. This narrow postnatal enrollment window was set to ensure that newborns with SMA would be identified before the onset of signs and symptoms.

Under-representation in clinical trials and health research may reflect unwillingness to participate but may also be a matter of unequal access.[6,23] Our findings indicate that rural women and those who did not give birth in a partner-affiliated hospital were somewhat less likely to have sufficient contact information collected through NBS records, leading to disproportionate omission from the Early Check direct-mail and email contact lists. However, the differences in the proportion who were sent recruitment letters were less than one percentage point between urban and rural women and only a little more than a percentage point between those who gave birth at affiliated versus unaffiliated hospitals. These results provide little evidence of systemic bias in terms of who was sent at least one type of outreach material. That said, we are unable to determine whether letters were disproportionately returned as undeliverable for some demographic subgroups compared with others. Notwithstanding this limitation, the results demonstrate that equitable distribution of information about Early Check was possible through a combination of direct mail and email.

Direct-mail letters had the largest impact on enrollment, followed by email invitations. Roughly 4% of the women who were sent a recruitment letter enrolled in the study. The overall enrollment rate among women who were also sent a personalized recruitment email was about 5%—a 25% increase in enrollments compared with direct mail alone. Our use of these outreach strategies tracked well with response rates in consumer marketing applications, where response rates across sectors range from 1% to 3% for letter-size mailings and < 1% for email.[24] Outreach in Early Check was several times more effective than recruitment outcomes observed in other large-scale studies using direct-mail and email outreach, where reported enrollment rates from these methods range from less than 1% to 2%.[25–27] Although Baca-Motes *et al.*[28] achieved a 9% enrollment rate from an optimized recruitment campaign comprising 3 emails plus 2 mailings sent over a 3-week period, their enrollment rates from direct mail alone, email alone, or an email with a single reminder did not exceed 1%. Our findings indicate that the reminder postcards were ineffectual, and we discontinued sending them after the pilot experiment ended. Despite the added efficacy of email invitations over letters alone, this strategy had substantially lower reach because of the limited number of NCSLPH records with an email address listed. Naturally, some records lacked an email address because the birth mother had none to record; however, we presume that the majority were left blank because of the novelty of the fields used to collect emails and phone numbers on the NC NBS filter forms, which were added shortly before Early Check launched.

Although we sent letters in roughly equal proportion by urbanicity and race/ethnicity, we found significant differences in enrollment across demographic subgroups. Women living in rural areas were less likely than women from urban areas to enroll a child in Early Check. Additionally, the higher the probability that the birth mother was a member of a minority racial or ethnic group, the lower the likelihood that she enrolled her child in Early Check. We also found greater enrollment rates among women who gave birth at a hospital affiliated with an Early Check research partner. All of these demographic associations with study enrollment were additive and not dependent on the outreach methods used.

The reasons for these demographic differences are likely complex and might reflect concerns about participating in research that stem from a history of exclusion or salient past examples of unethical treatment of racial and ethnic minority populations in medical research.[29] Relatedly, lower enrollment rates may partly be an expression of completely legitimate preferences not to be involved in the project. We also recognize that the opportunity to enroll may have been blunted in practice by limited availability of internet access. For example, in 2018, 86% of NC households had internet access at home, ranging from 68% in predominantly rural Robeson County to as high as 95% in Wake County where the city of Raleigh is located. Visiting the online permission portal is likely a barrier for some women.

Overall, direct-mail recruitment letters and email invitations were effective outreach methods showing a positive impact on Early Check enrollment rates, controlling for race/ethnicity, urbanicity, and birth hospital affiliation with Early Check research partners. Following up recruitment letters with a reminder postcard a week later showed no improvement in enrollment rates. Traditionally underserved or rural populations were not substantially less likely to have sufficient contact information listed in NBS records, nor were they disproportionately excluded from the Early Check contact lists. However, echoing findings from other studies, we found decreased enrollment rates among underserved populations and rural populations.

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CONFLICT OF INTEREST

All authors declared no competing interests for this work.

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AUTHOR CONTRIBUTIONS

R.S.P., M.A.L., B.A.H., R.M., L.M.G., H.L.P., N.M.P.K., and D.B.B. wrote the manuscript. R.S.P., M.A.L., B.A.H., R.M., A.G., L.M.G., H.L.P., M.D., M.R., A.C.W., C.M.P., N.M.P.K., S.M.S., and D.B.B. designed the research. R.S.P., M.A.L., B.A.H., R.M., A.G., L.M.G., H.L.P., M.D., M.R., A.C.W., C.M.P., N.M.P.K., S.M.S., and D.B.B. performed the research. R.S.P. and A.G. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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