Supplementary appendix to:

Development and validation of a new clinical decision support tool to optimize screening for retinopathy of prematurity

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eAppendix 1. Statistical methods

Modelling in model development group (DevGroup)

At birth only individual probabilities from DIGIROP-Birth were used. Multivariable logistic regression was applied over postnatal ages (PNAs) 6 to 14 weeks. In the subsequent models over PNA the log-odds for DIGIROP-Birth (log[probability/(1-probability)]), the status (yes/no) and timing (PNA week) of the first retinopathy of prematurity (ROP) diagnosis, weeks since first ROP diagnosis (piecewise linear with break point at 3 weeks), and interactions between the three variables (DIGIROP-Birth probability, PNA week at first ROP and weeks since first ROP) and sex, gestational age (GA) and birth weight standard deviation score (BWSDS) were studied as potential predictors. The break point at 3 weeks for weeks since first ROP diagnosis was defined based on the review of Epanechnikov's hazard functions for ROP treatment. The final model for PNA 6-14 weeks included following predictors: log-odds for DIGIROP-Birth, status (yes/no) for first ROP diagnosis, (timing for first ROP diagnosis) * (status for first ROP diagnosis), (timing for first ROP diagnosis) * (status for first ROP diagnosis) * (log-odds for DIGIROP-Birth). For simplicity and consistency reasons across the time points, the final models for PNA 6-14 weeks included the same set of variables, even though not all prediction variables were significant at all time points. The logistic regression models were tested for goodness-of-fit using Hosmer-Lemeshow test and were all non-significant, i.e. the observed vs estimated number of events in 10 strata were well calibrated. The selected models for DevGroup are presented in the eTable 3.

GA- and PNA-specific cut-offs based on estimated probabilities for reaching 100% sensitivity in DevGroup (or maximum risk estimation of 0.05) were obtained and saved for use in ValGroups (eTable 4). Parameter estimates, standard errors and p-values from the multivariable logistic models are described along with the area under the receiver operating characteristic curve (AUC). Sensitivity, specificity and cumulative specificity (calculated as union of specificities from the prediction model at birth and up to a certain PNA model) over PNA with 95% confidence interval (CI) based on selected cut-offs were the main measures.

Internal validation

Internal validation was performed applying 10-fold cross-validation. Cumulative specificity was obtained based on estimated probabilities from the cross-validation data set using cut-offs for 100% sensitivity. The certainty of the performance of the internal validation was presented as range of specificities obtained using 10 randomly selected seeds.

External validation

The predicted probabilities were calculated as:

$1/(1+e^{-LC})$, where LC is the linear predictor for a vector X of explanatory variables, i.e.

$LC = \alpha + \beta X$; α is intercept; β is a vector of parameter estimates for each explanatory variable.

External validation was performed together for all four external validation groups (ValGroups). AUC with 95% CI, sensitivity, specificity and cumulative specificity with 95% CI were calculated based on cut-offs obtained from the DevGroup.

Graphical illustration of the clinical implication of DIGIROP-Screen prediction tool was made presenting number of infants released from screening for ROP over postnatal ages based on actual ROP screening performed (based on last date for ROP examination), and predictions from DIGIROP-Screen in DevGroup and ValGroups.

Comparison to other retinopathy of prematurity prediction models

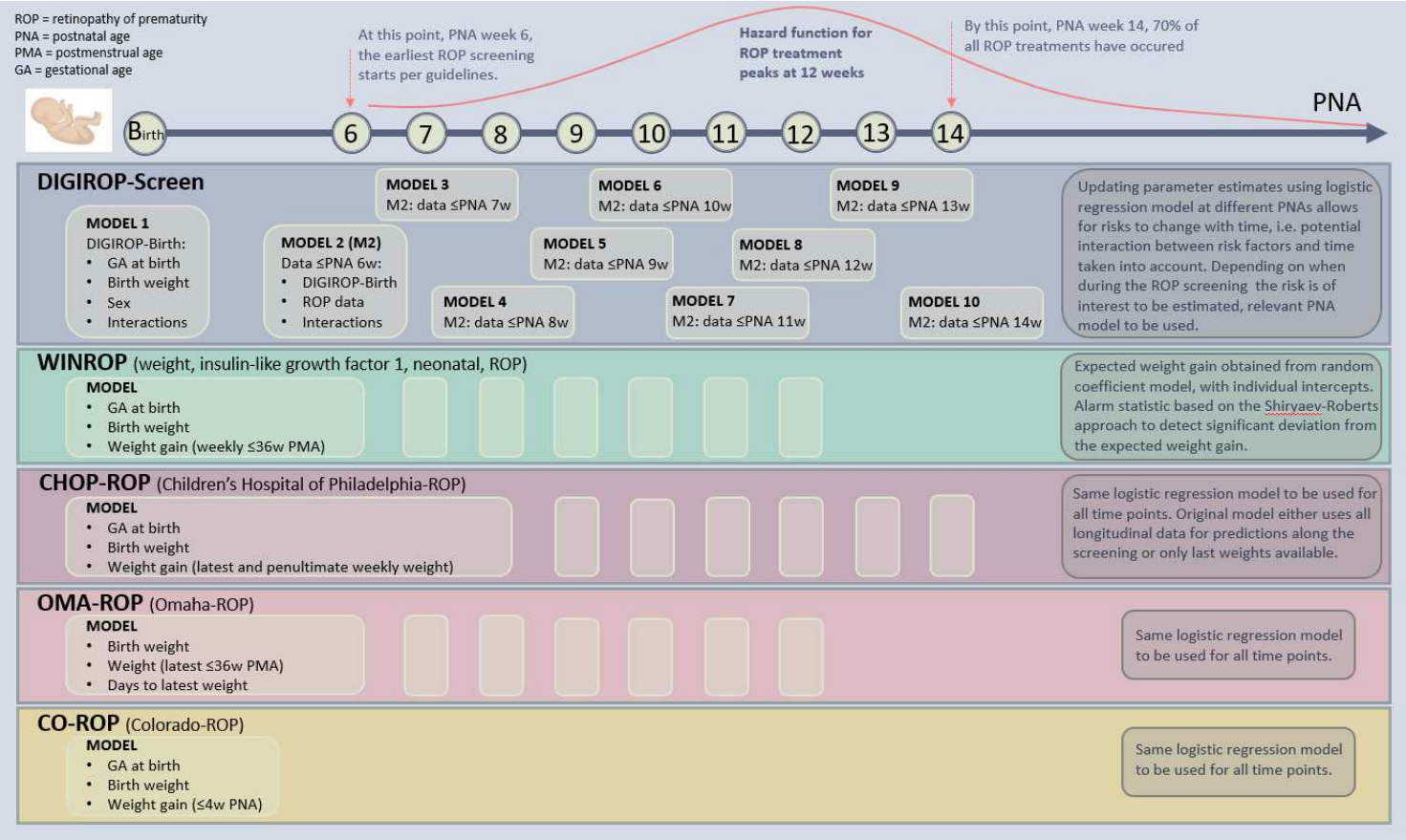
The two US external validation cohort files provided weekly weights that were applied in the algorithms for four existing prediction models, Children's Hospital of Philadelphia–ROP (CHOP-ROP), Omaha-ROP (OMA-ROP), weight, insulin-like growth factor 1, neonatal, ROP (WINROP) and Colorado-ROP (CO-ROP).

Sensitivity and cumulative specificity/specificity with 95% CI were calculated based on each model's recommended cut-offs based on estimated probabilities.

eAppendix 2. Supplementary figures and tables

eFigure 1. Work-flow for DIGIROP-Screen and four comparison models

Illustration: Aldina Pivodic (first author)



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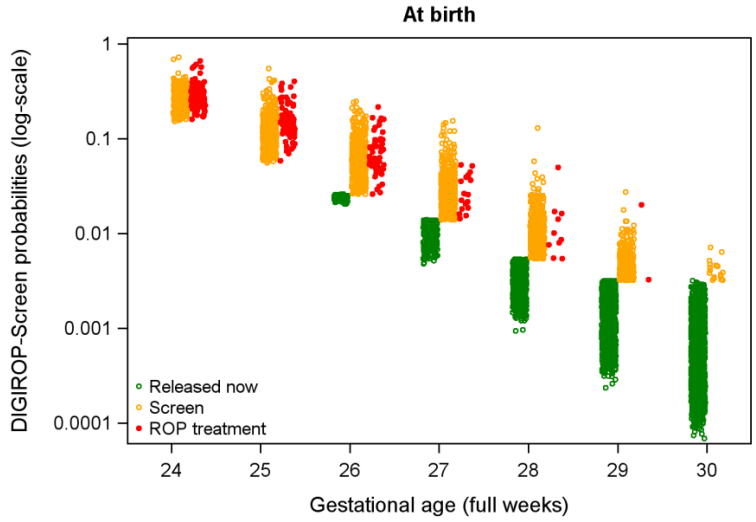
These figures show the estimated probabilities at birth and over postnatal ages obtained from DIGIROP-Screen. Y-axis has the logarithmic scale in order to be distinguish low probabilities.

A



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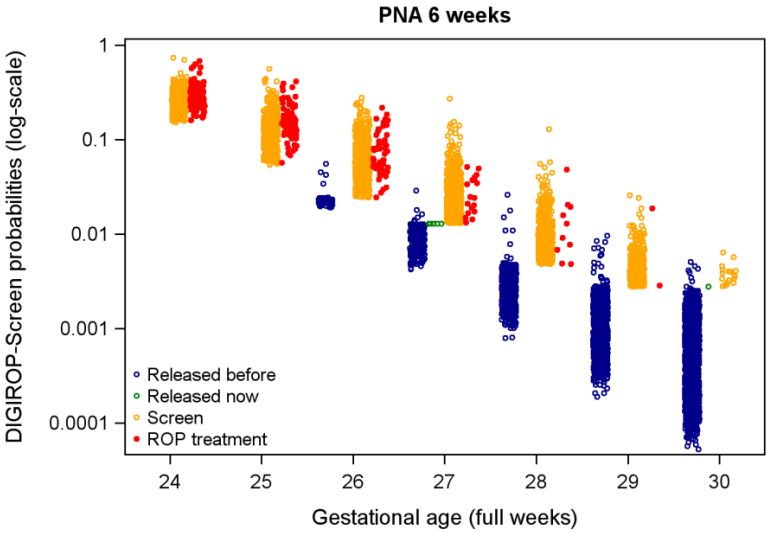

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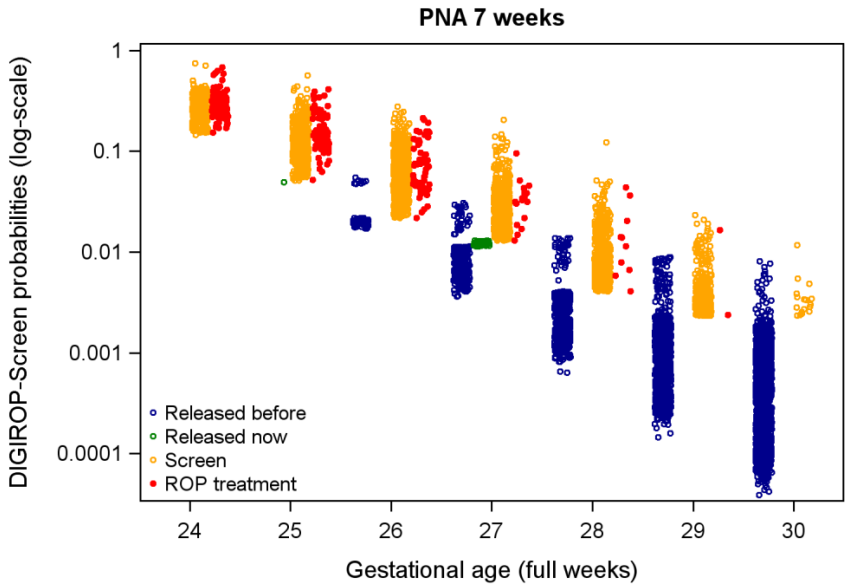
PNA 7 weeks
DIGIROP-Screen probabilities (log-scale)
1
0.1
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Gestational age (full weeks)

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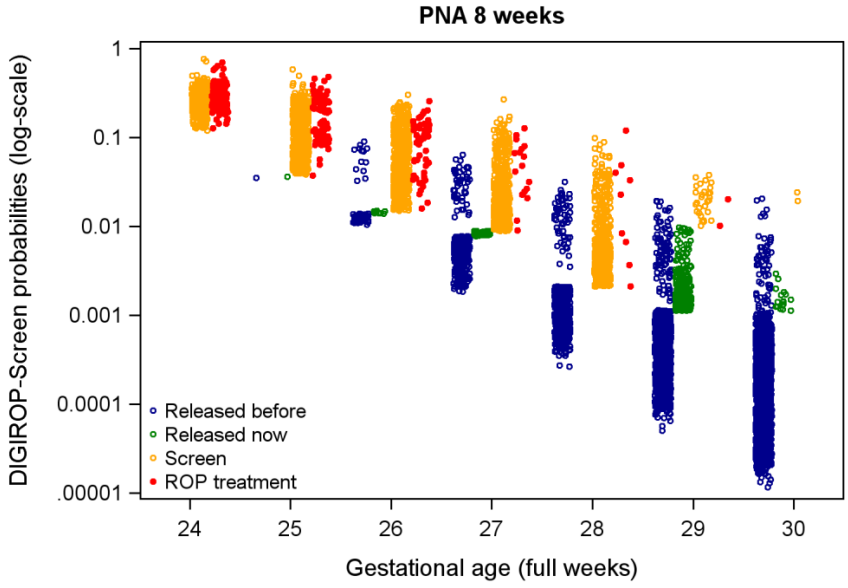
PNA 8 weeks
DIGIROP-Screen probabilities (log-scale)
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Gestational age (full weeks)

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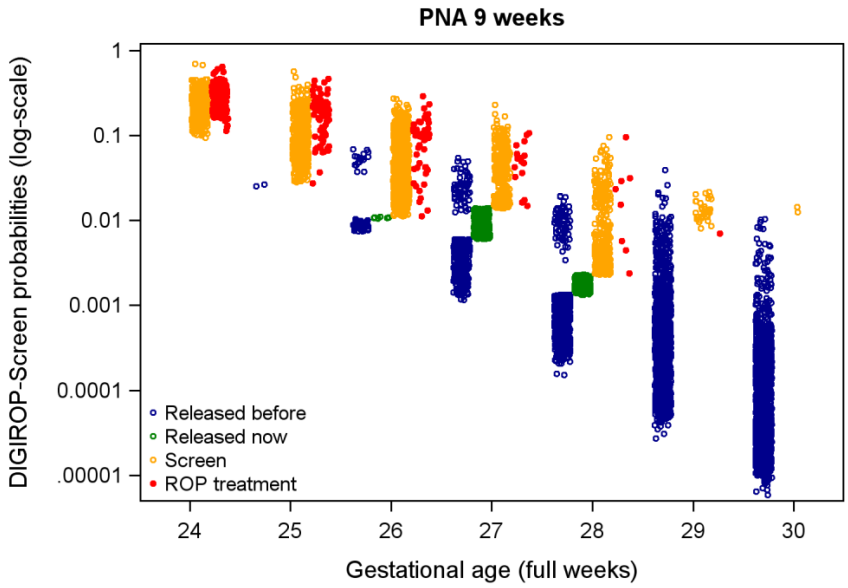
PNA 9 weeks
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Gestational age (full weeks)

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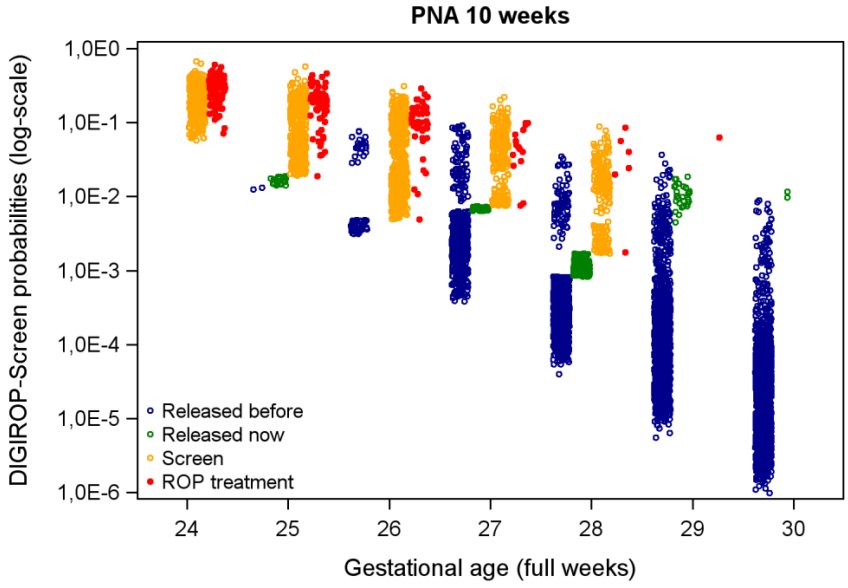
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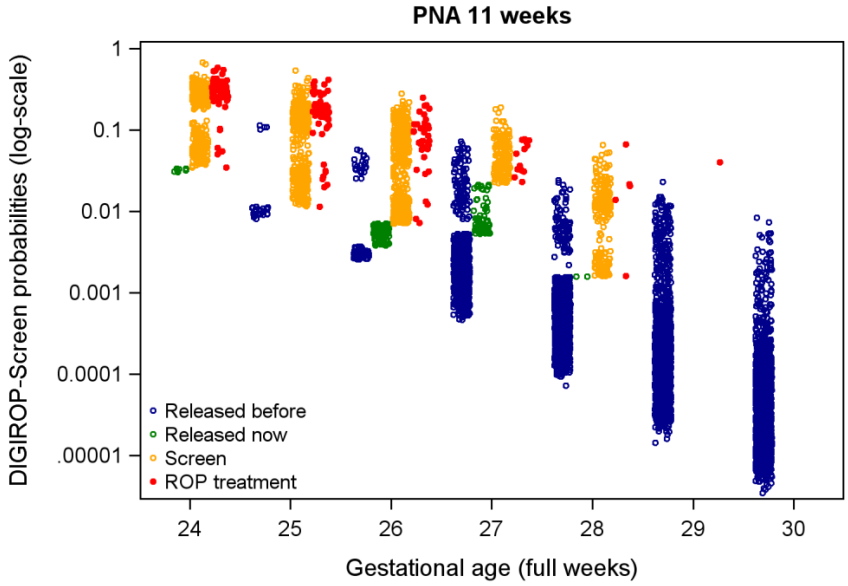
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Gestational age (full weeks)

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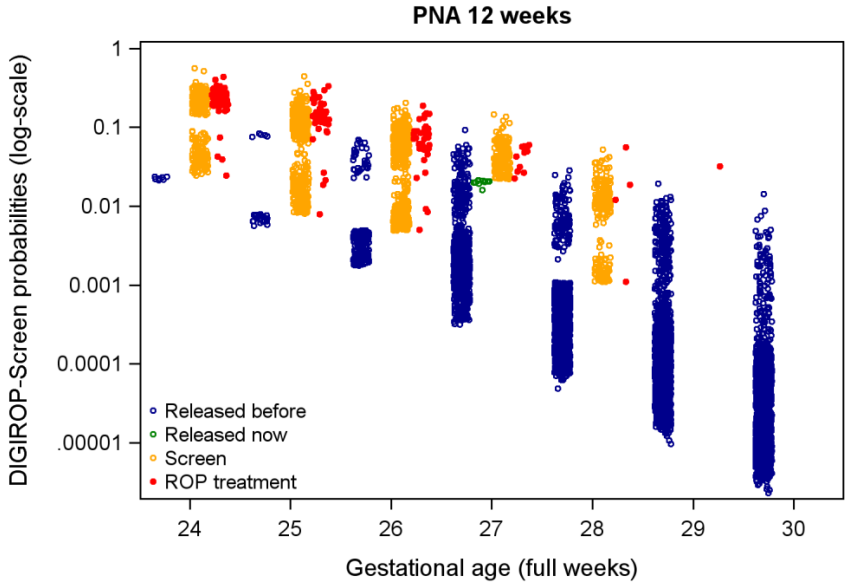
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Gestational age (full weeks)

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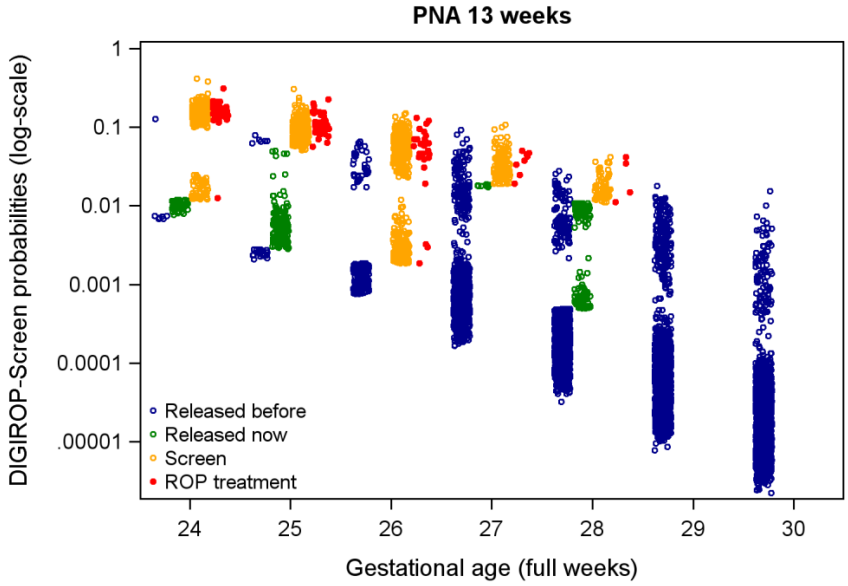
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Gestational age (full weeks)

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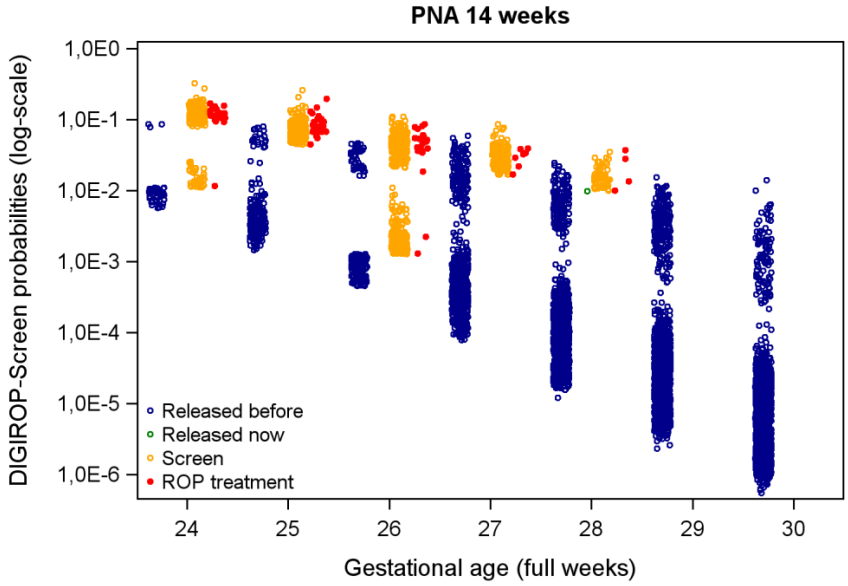
PNA 14 weeks
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Gestational age (full weeks)

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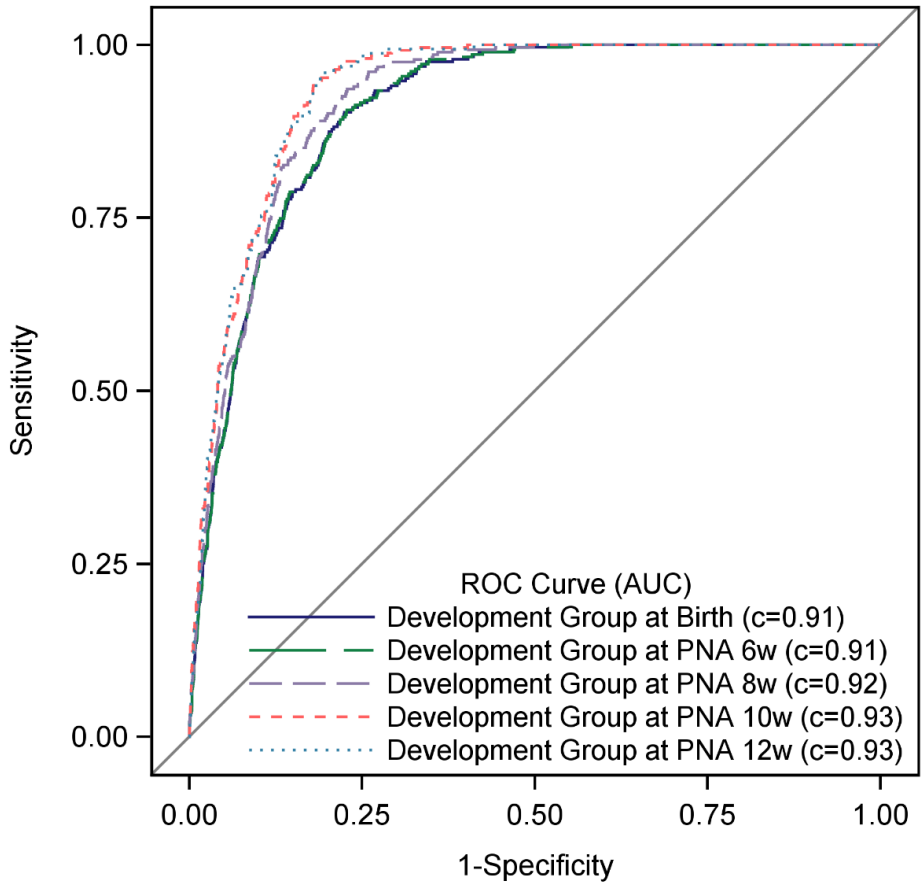

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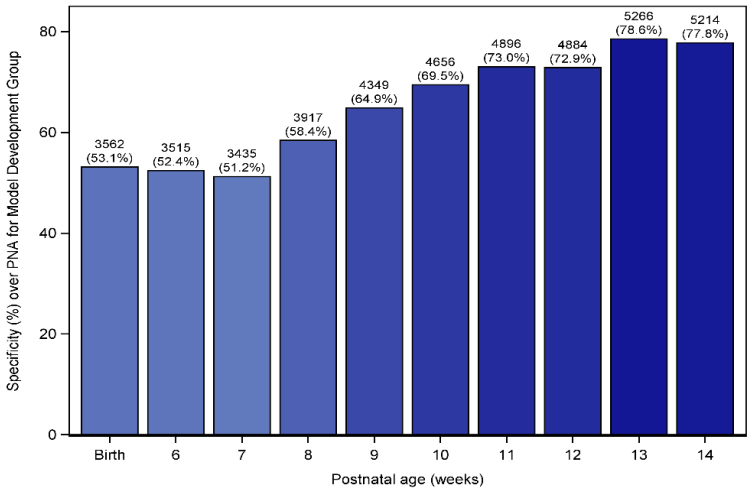
Cumulative specificity at a certain postnatal age is calculated as a union of specificities up to and including that certain postnatal age. Cumulative specificity means here the percentage of infants that are not requiring treatment that might be released based on DIGIROP-Screen if applied continuously over time.

A



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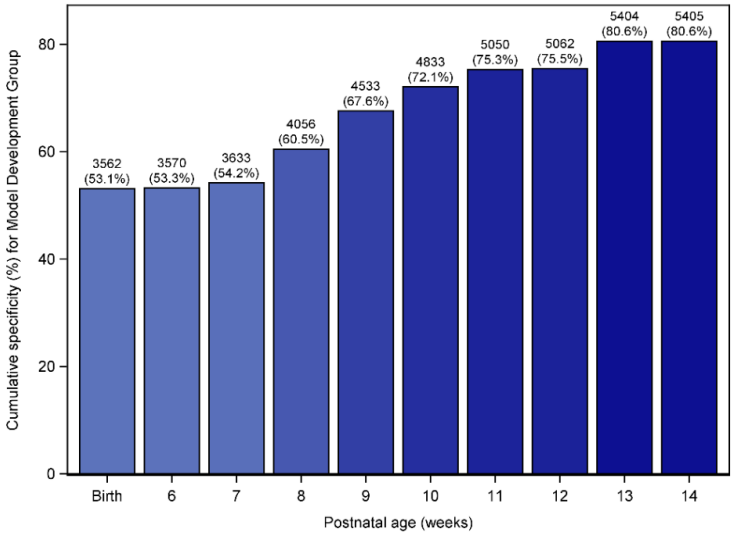

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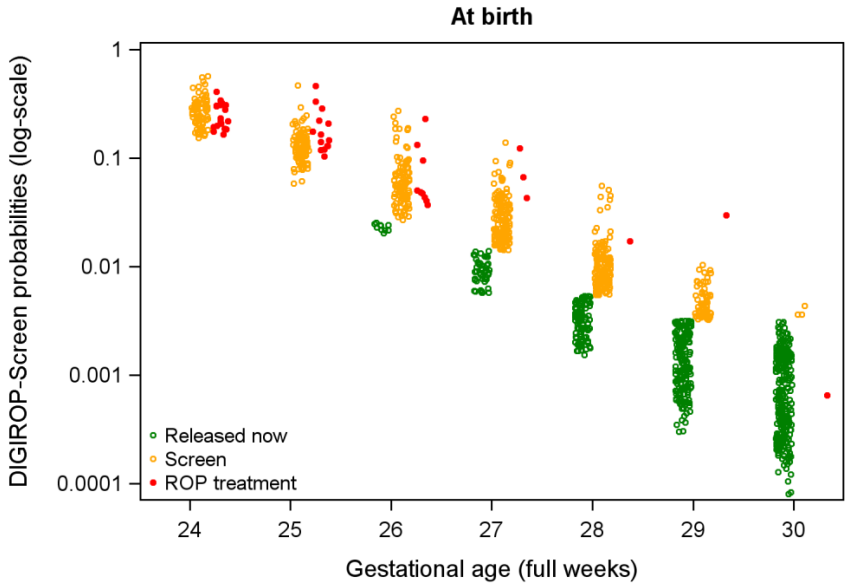

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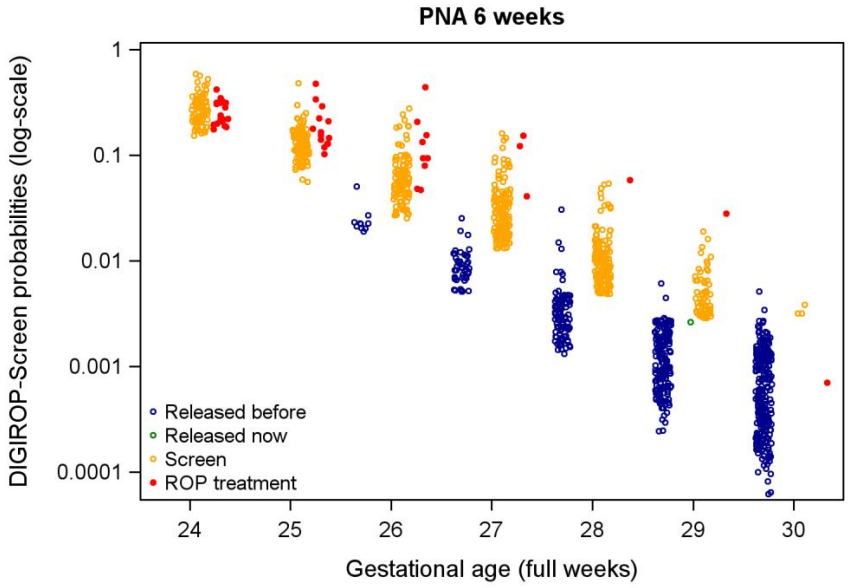

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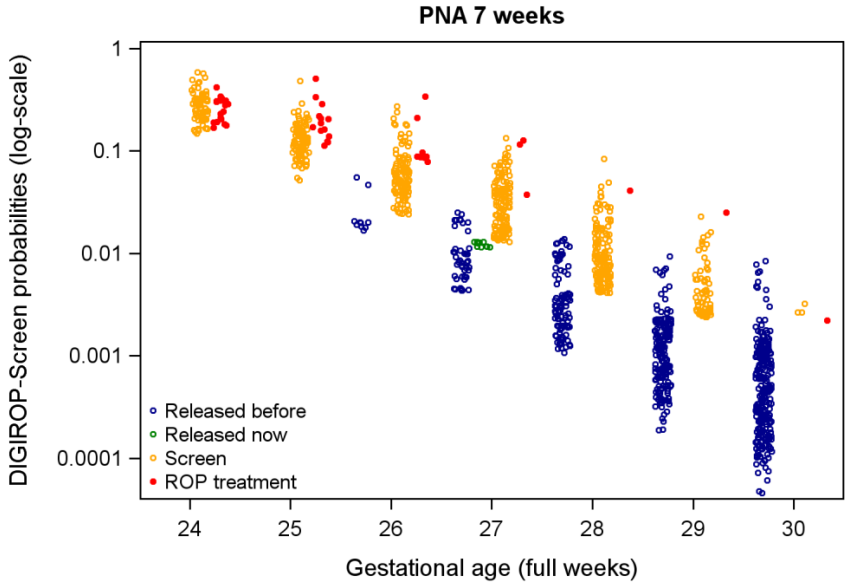
PNA 7 weeks
DIGIROP-Screen probabilities (log-scale)
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Gestational age (full weeks)

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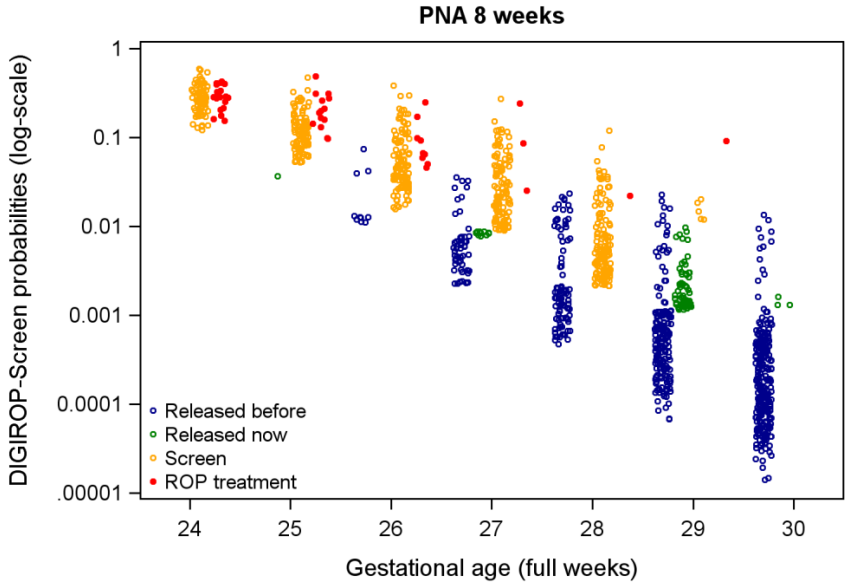
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Gestational age (full weeks)

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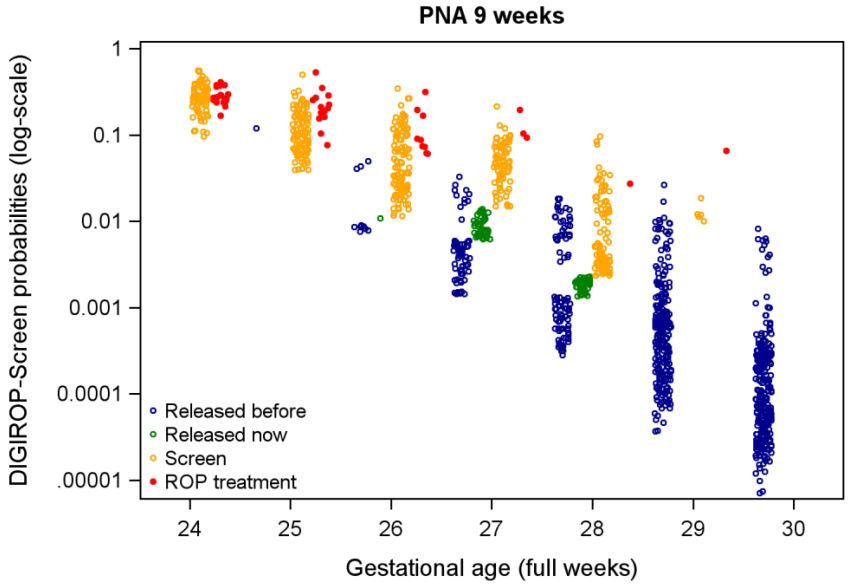
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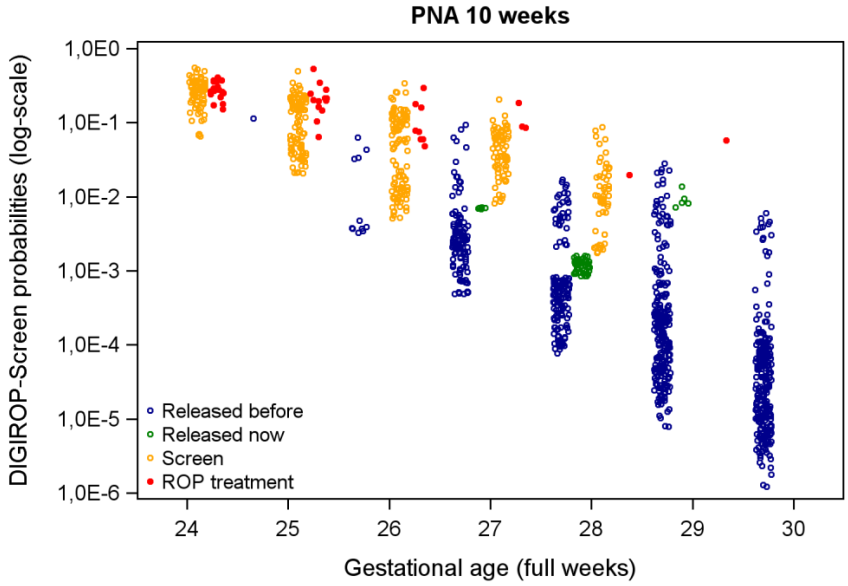
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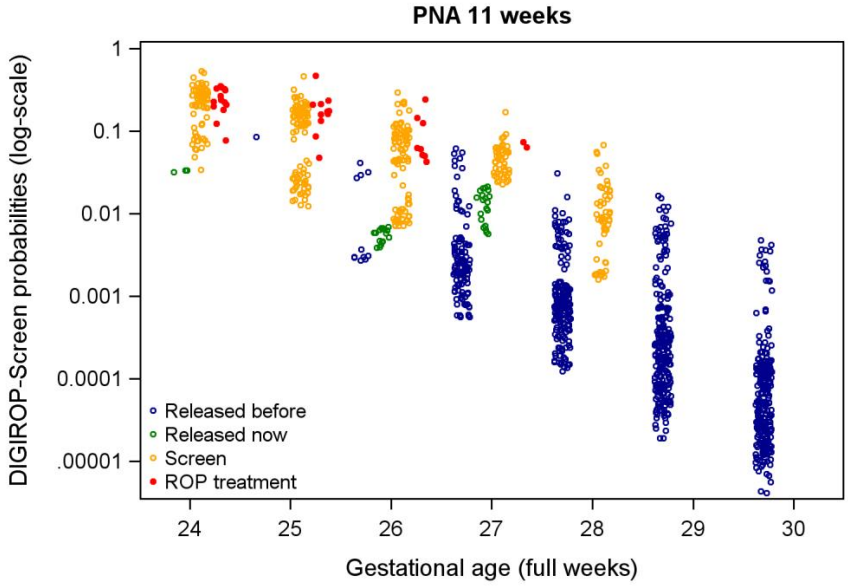
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Gestational age (full weeks)

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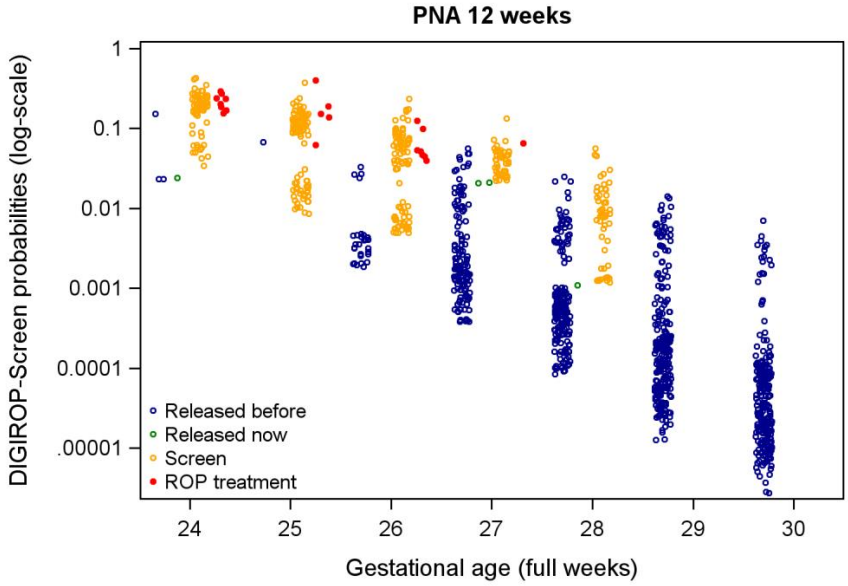
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Gestational age (full weeks)

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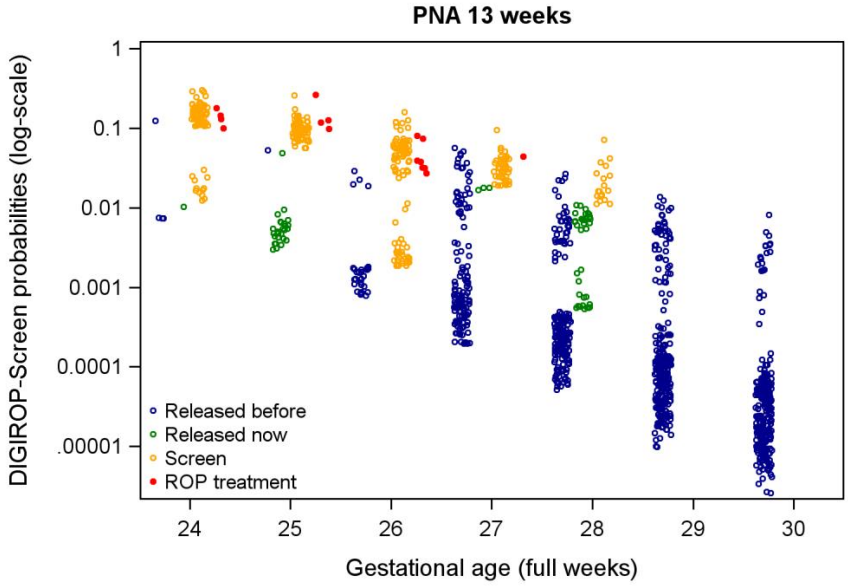
PNA 13 weeks
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Gestational age (full weeks)

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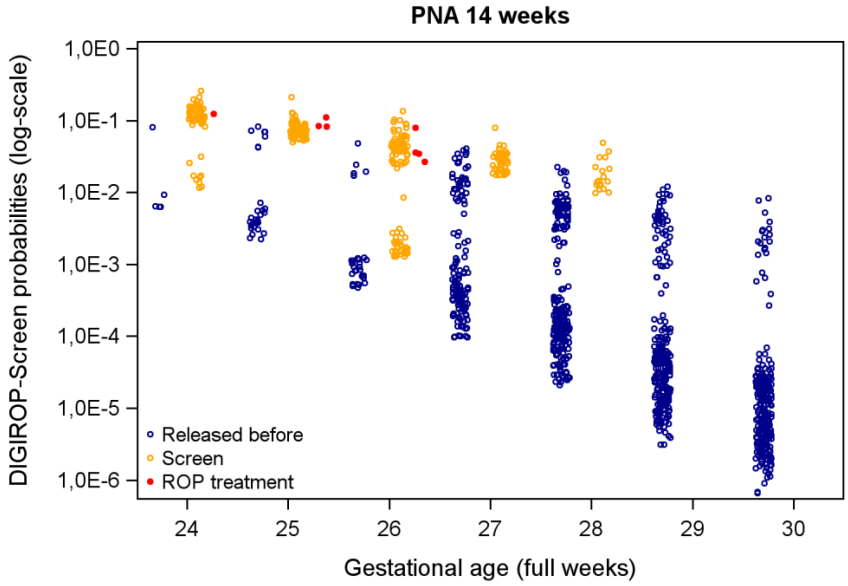
PNA 14 weeks
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Gestational age (full weeks)

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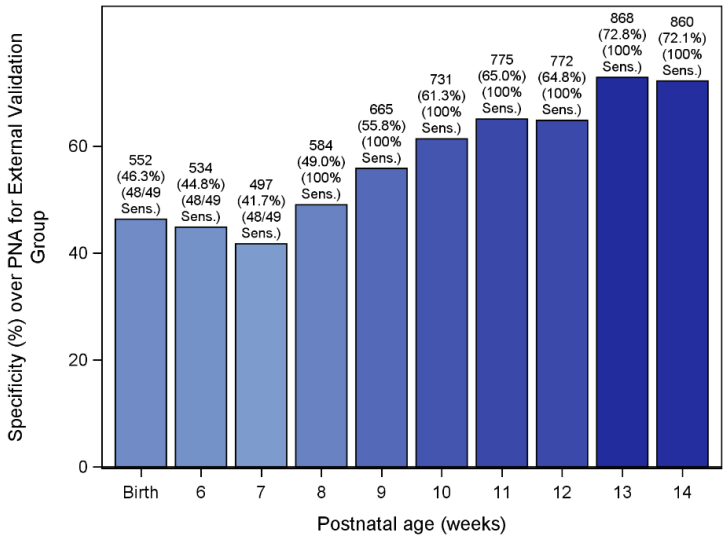
Cumulative specificity at a certain postnatal age is calculated as a union of specificities up to and including that certain postnatal age. Cumulative specificity means here the percentage of infants that are not requiring treatment that might be released based on DIGIROP-Screen if applied continuously over time.

A



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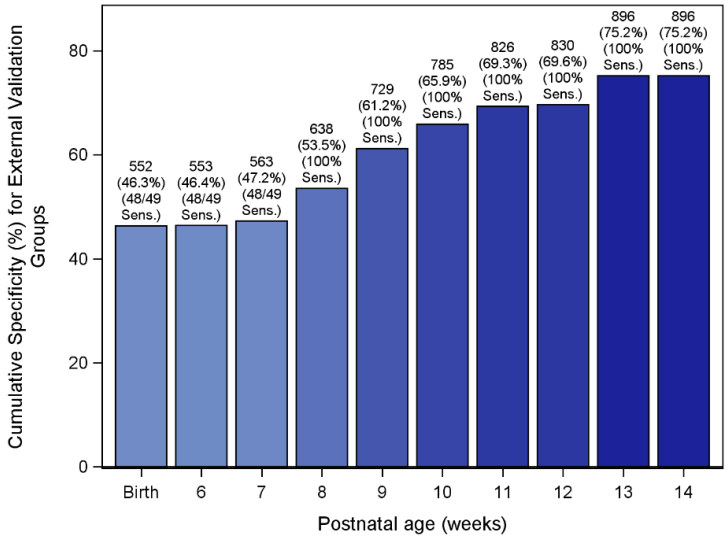
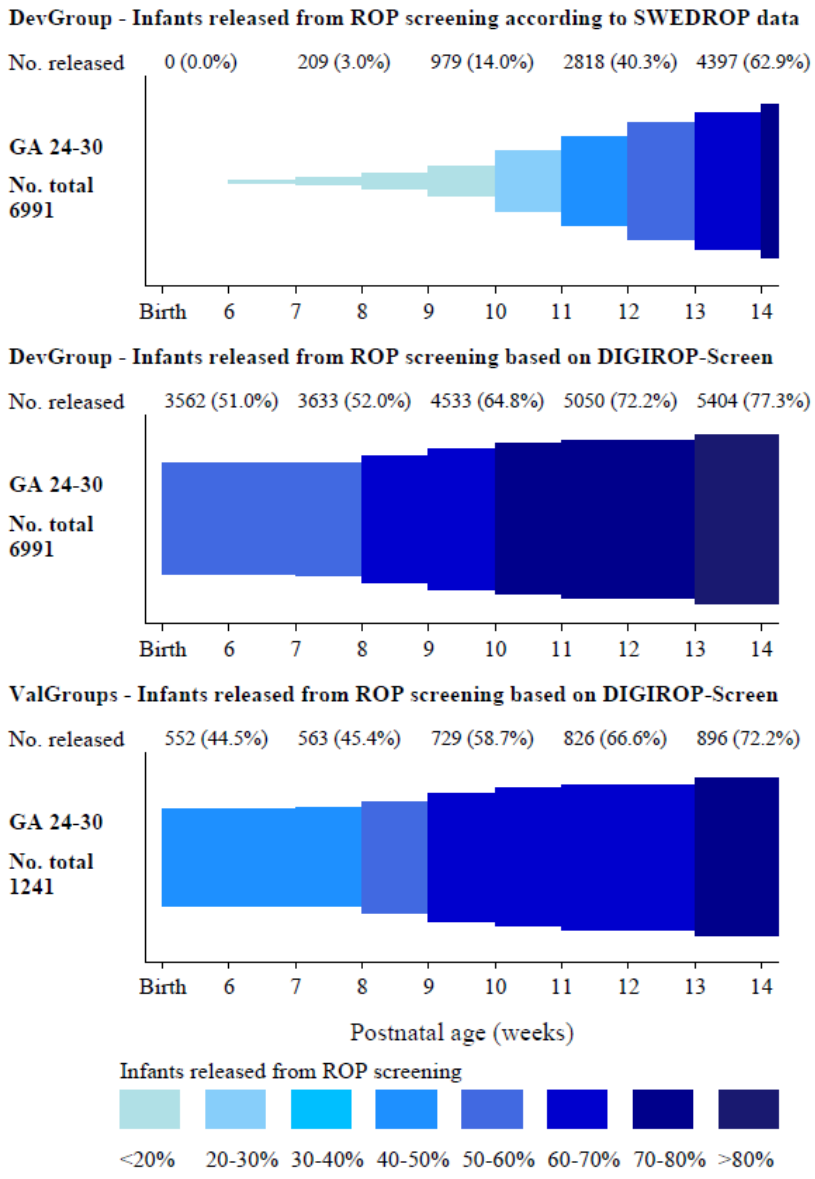


eFigure 7. Infants released from screening for retinopathy of prematurity (ROP) over postnatal ages for infants born 24-30 Weeks of gestational age according to actual ROP screening performed, and risk predictions from DIGIROP-Screen in model development group (DevGroup) and validation groups (ValGroups).

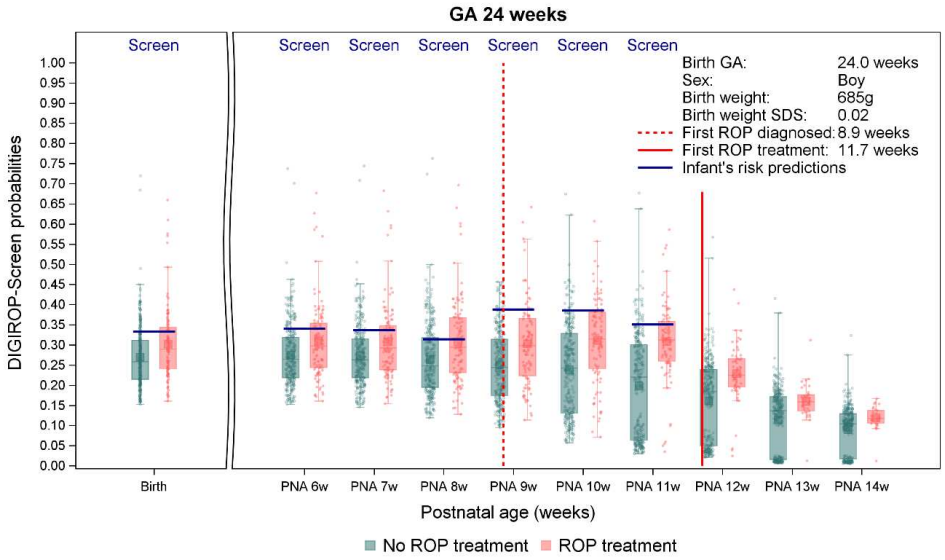
This figure shows the effect of the DIGIROP-Screen prediction tool from birth and applied over the screening process. Comparing to the release from screening based on actual/observed data in SWEDROP, large proportion of infants might be safely released already at birth with the use of DIGIROP-Screen. The n and % are presented for time points: birth, PNA 7, 9, 11, and 13 weeks.



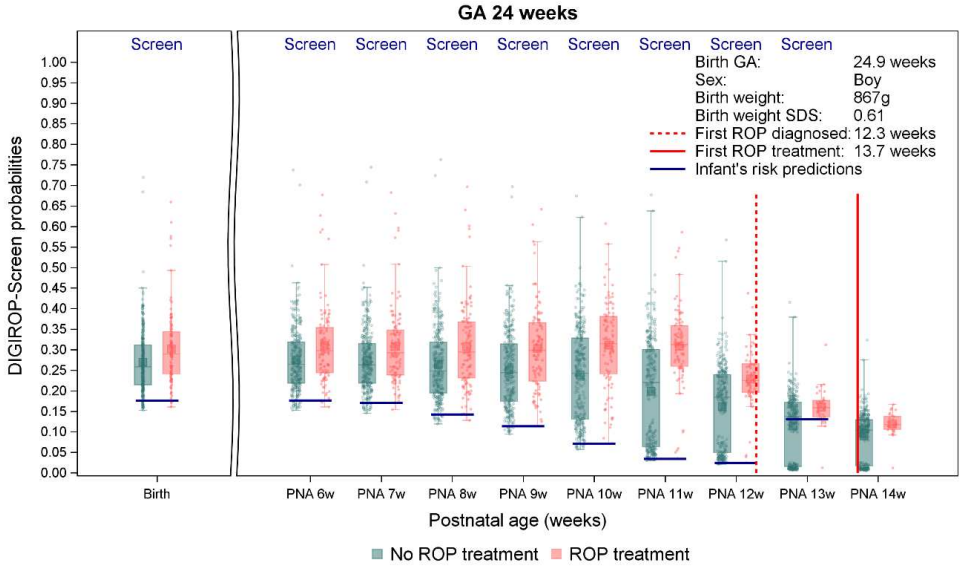
eFigure 8. Follow-up of infants using DIGIROP-Screen

This figures show example infants and the information that might be obtained and showed based on the observed data. Infant's characteristics, the estimated probabilities in relation to probabilities for other infants with reported data in SWEDROP born the same week, and the outcome based on DIGIROP-Screen prediction whether the infant should be screened och released from the screening.

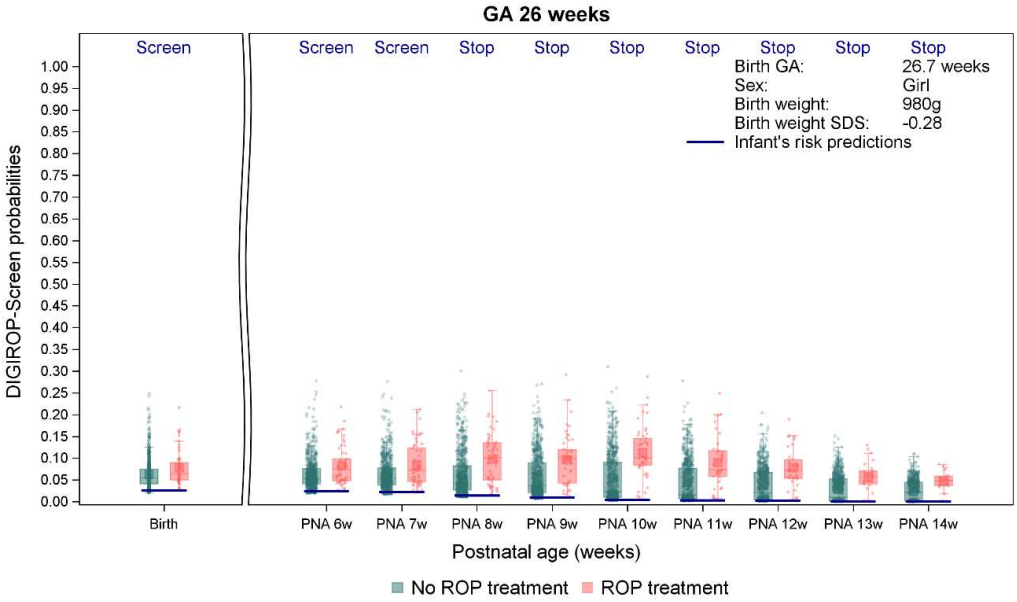
A



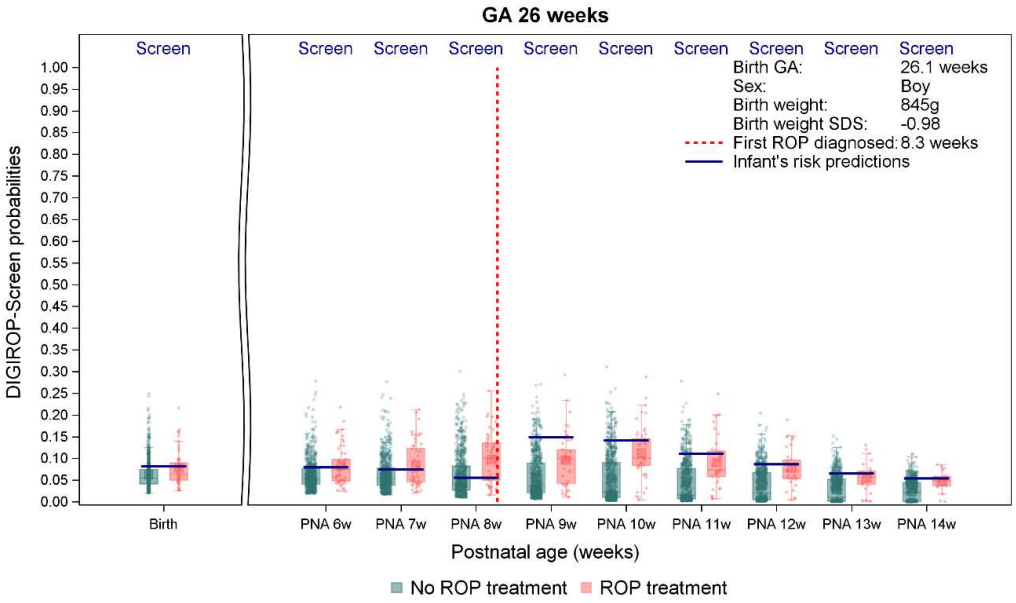
B



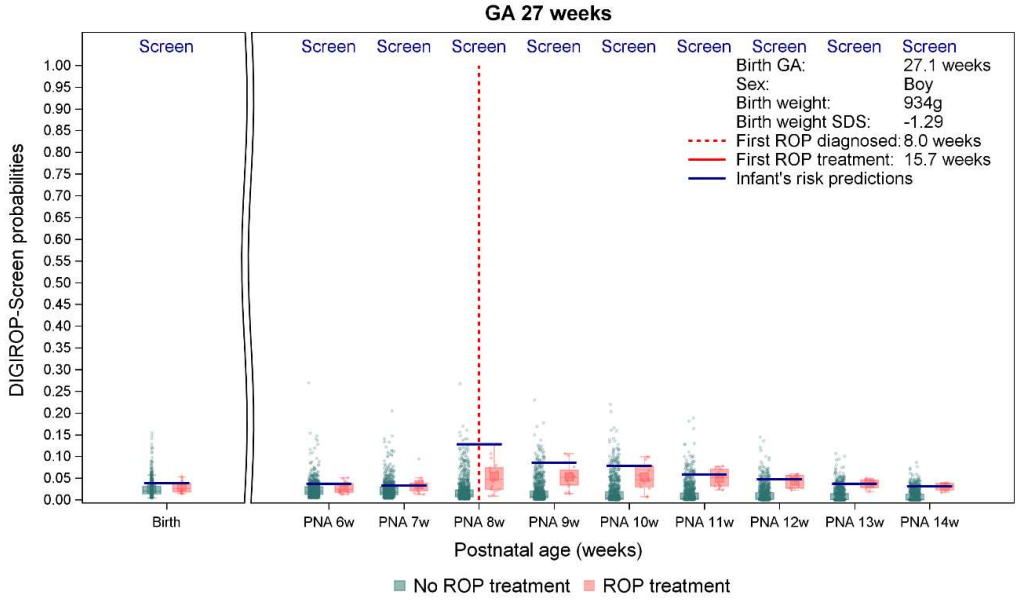
C


GA 26 weeks
Screen
Screen Screen Stop Stop Stop Stop Stop Stop Stop
Birth GA: 26.7 weeks
Sex: Girl
Birth weight: 980g
Birth weight SDS: -0.28
Infant's risk predictions
DIGIROP-Screen probabilities
1.00 0.95 0.90 0.85 0.80 0.75 0.70 0.65 0.60 0.55 0.50 0.45 0.40 0.35 0.30 0.25 0.20 0.15 0.10 0.05 0.00
Birth
PNA 6w PNA 7w PNA 8w PNA 9w PNA 10w PNA 11w PNA 12w PNA 13w PNA 14w
Postnatal age (weeks)
No ROP treatment
ROP treatment

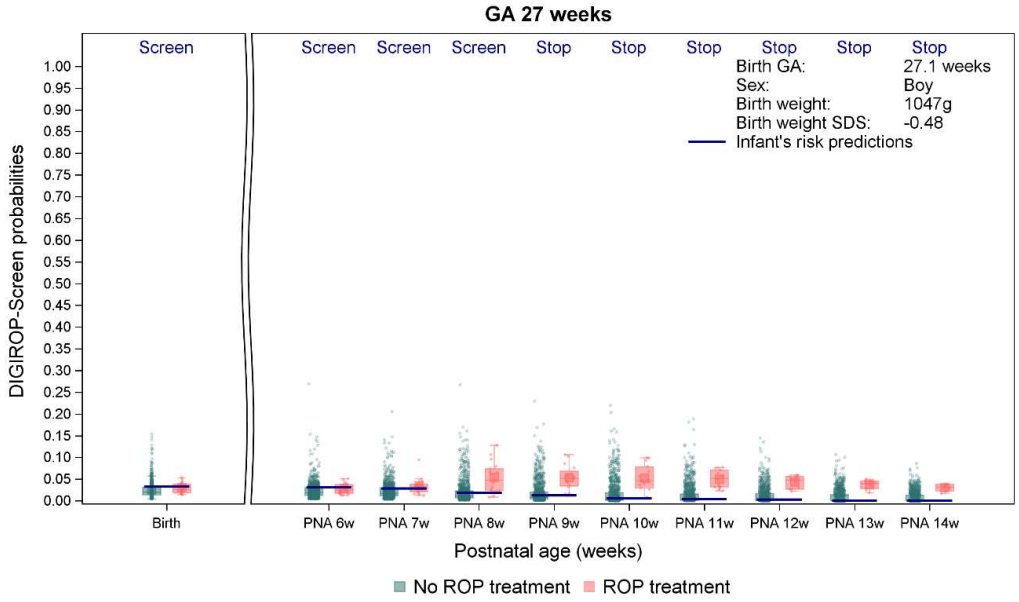
D


GA 26 weeks
Screen
Screen Screen Screen Screen Screen Screen Screen Screen Screen
Birth GA: 26.1 weeks
Sex: Boy
Birth weight: 845g
Birth weight SDS: -0.98
First ROP diagnosed: 8.3 weeks
Infant's risk predictions
DIGIROP-Screen probabilities
1.00 0.95 0.90 0.85 0.80 0.75 0.70 0.65 0.60 0.55 0.50 0.45 0.40 0.35 0.30 0.25 0.20 0.15 0.10 0.05 0.00
Birth
PNA 6w PNA 7w PNA 8w PNA 9w PNA 10w PNA 11w PNA 12w PNA 13w PNA 14w
Postnatal age (weeks)
No ROP treatment
ROP treatment

E


GA 27 weeks
Screen
Screen Screen Screen Screen Screen Screen Screen Screen Screen
Birth GA: 27.1 weeks
Sex: Boy
Birth weight: 934g
Birth weight SDS: -1.29
First ROP diagnosed: 8.0 weeks
First ROP treatment: 15.7 weeks
Infant's risk predictions
DIGIROP-Screen probabilities
1.00 0.95 0.90 0.85 0.80 0.75 0.70 0.65 0.60 0.55 0.50 0.45 0.40 0.35 0.30 0.25 0.20 0.15 0.10 0.05 0.00
Birth PNA 6w PNA 7w PNA 8w PNA 9w PNA 10w PNA 11w PNA 12w PNA 13w PNA 14w
Postnatal age (weeks)
No ROP treatment ROP treatment

F


GA 27 weeks
Screen
Screen Screen Screen Stop Stop Stop Stop Stop Stop
Birth GA: 27.1 weeks
Sex: Boy
Birth weight: 1047g
Birth weight SDS: -0.48
Infant's risk predictions
DIGIROP-Screen probabilities
1.00 0.95 0.90 0.85 0.80 0.75 0.70 0.65 0.60 0.55 0.50 0.45 0.40 0.35 0.30 0.25 0.20 0.15 0.10 0.05 0.00
Birth PNA 6w PNA 7w PNA 8w PNA 9w PNA 10w PNA 11w PNA 12w PNA 13w PNA 14w
Postnatal age (weeks)
No ROP treatment ROP treatment

eTable 1. Infants' characteristics at birth, first sign of retinopathy of prematurity and retinopathy of prematurity treatment for model development group and four external validation cohorts

Variable	Model development group (n=6991)	Temporal (SWEDROP) validation group (n=314)	External (German) validation group (n=322)	External (BIDMC) validation group (n=258)	External (Utah) validation group (n=347)
Sex					
Boys	3833 (54.8%)	158 (50.3%)	178 (55.3%)	126 (48.8%)	172 (49.6%)
Girls	3158 (45.2%)	156 (49.7%)	144 (44.7%)	132 (51.2%)	175 (50.4%)
Gestational age at birth (weeks)	28.3 (1.9) 28.6 (24.0; 30.9) n=6991	28.6 (1.7) 29.0 (24.0; 30.9) n=314	28.1 (1.8) 28.4 (24.0; 30.9) n=322	28.1 (2.0) 28.6 (24.0; 30.9) n=258	27.5 (1.7) 27.9 (24.0; 30.7) n=347
Gestational age (full weeks)					
24	427 (6.1%)	10 (3.2%)	27 (8.4%)	24 (9.3%)	33 (9.5%)
25	597 (8.5%)	24 (7.6%)	27 (8.4%)	22 (8.5%)	41 (11.8%)
26	781 (11.2%)	28 (8.9%)	29 (9.0%)	28 (10.9%)	44 (12.7%)
27	914 (13.1%)	40 (12.7%)	38 (11.8%)	41 (15.9%)	68 (19.6%)
28	1141 (16.3%)	48 (15.3%)	76 (23.6%)	31 (12.0%)	84 (24.2%)
29	1419 (20.3%)	74 (23.6%)	62 (19.3%)	48 (18.6%)	52 (15.0%)
30	1712 (24.5%)	90 (28.7%)	63 (19.6%)	64 (24.8%)	25 (7.2%)
Birth weight (g)	1146 (339) 1135 (307; 3245) n=6991	1175 (332) 1173 (390; 2300) n=314	1036 (309) 1038 (335; 2450) n=322	1076 (338) 1053 (400; 2240) n=258	994 (273) 1000 (410; 1760) n=347
Birth weight SDS (Niklasson & Albertsson-Wikland 2008)	-1.03 (1.37) -0.77 (-8.56; 4.93) n=6991	-1.08 (1.50) -0.76 (-6.93; 2.16) n=314	-1.56 (1.55) -1.25 (-9.92; 2.75) n=322	-1.30 (1.53) -0.99 (-7.30; 2.43) n=258	-1.28 (1.65) -0.97 (-7.61; 2.13) n=347
Birth year					

Variable	Model development group (n=6991)	Temporal (SWEDROP) validation group (n=314)	External (German) validation group (n=322)	External (BIDMC) validation group (n=258)	External (Utah) validation group (n=347)
2006-2007	543 (7.8%)	0 (0.0%)	0 (0.0%)	139 (53.9%)	0 (0.0%)
2008-2009	1331 (19.0%)	0 (0.0%)	0 (0.0%)	119 (46.1%)	0 (0.0%)
2010-2011	1303 (18.6%)	0 (0.0%)	9 (2.8%)	0 (0.0%)	0 (0.0%)
2012-2013	1369 (19.6%)	0 (0.0%)	103 (32.0%)	0 (0.0%)	0 (0.0%)
2014-2015	1445 (20.7%)	0 (0.0%)	118 (36.6%)	0 (0.0%)	131 (37.8%)
2016-2017	1000 (14.3%)	115 (36.6%)	92 (28.6%)	0 (0.0%)	124 (35.7%)
2018-2019	0 (0.0%)	199 (63.4%)	0 (0.0%)	0 (0.0%)	92 (26.5%)
Any ROP	2026 (29.0%)	93 (29.6%)	118 (36.6%)	116 (45.0%)	175 (50.4%)
Postnatal age at first diagnosed ROP (weeks)	8.35 (2.23) 8.14 (3.43; 18.71) n=2026	7.83 (2.32) 7.71 (4.43; 17.57) n=93	8.95 (2.72) 8.36 (4.86; 19.00) n=118	7.81 (1.86) 7.93 (3.86; 13.29) n=116	7.78 (2.85) 7.29 (3.14; 18.29) n=175
ROP treatment	287 (4.1%)	11 (3.5%)	12 (3.7%)	6 (2.3%)	20 (5.8%)
Postnatal age at ROP treatment (weeks)	12.8 (2.8) 12.4 (7.0; 21.9) n=287	13.2 (2.3) 11.9 (10.7; 17.6) n=11	11.6 (1.3) 11.0 (10.0; 14.4) n=12	13.5 (3.3) 13.1 (10.7; 19.6) n=6	12.0 (2.5) 11.5 (7.1; 19.4) n=20

ROP=retinopathy of prematurity; SDS=standard deviation score

For categorical variables n (%) is presented.

For continuous variables Mean (SD) / Median (Min; Max) / n= is presented.

eTable 2. Infants' characteristics at birth, first sign of retinopathy of prematurity and retinopathy of prematurity treatment for model development group and external validation groups for infants with and without retinopathy of prematurity treatment

	Model development group		Validation groups	
	No ROP treatment	**ROP treatment**	**No ROP treatment**	**ROP treatment**
	n=6704	n=287	n=1192	n=49
Sex				
Boys	3656 (54.5%)	177 (61.7%)	604 (50.7%)	30 (61.2%)
Girls	3048 (45.5%)	110 (38.3%)	588 (49.3%)	19 (38.8%)
Gestational age at birth (weeks)	28.4 (1.8) 28.7 (24.0; 30.9) n=6704	25.4 (1.2) 25.1 (24.0; 29.6) n=287	28.2 (1.8) 28.4 (24.0; 30.9) n=1192	25.6 (1.3) 25.1 (24.0; 30.4) n=49
Gestational age (full weeks)				
24	314 (4.7%)	113 (39.4%)	74 (6.2%)	20 (40.8%)
25	510 (7.6%)	87 (30.3%)	100 (8.4%)	14 (28.6%)
26	724 (10.8%)	57 (19.9%)	120 (10.1%)	9 (18.4%)
27	896 (13.4%)	18 (6.3%)	184 (15.4%)	3 (6.1%)
28	1131 (16.9%)	10 (3.5%)	238 (20.0%)	1 (2.0%)
29	1417 (21.1%)	2 (0.7%)	235 (19.7%)	1 (2.0%)
30	1712 (25.5%)	0 (0.0%)	241 (20.2%)	1 (2.0%)
Birth weight (g)	1163 (334) 1155 (307; 3245) n=6704	741 (174) 728 (370; 1700) n=287	1083 (315) 1080 (335; 2450) n=1192	711 (178) 690 (390; 1090) n=49
Birth weight SDS (Niklasson & Albertsson-Wikland 2008)	-1.03 (1.36) -0.77 (-8.56; 4.93) n=6704	-1.16 (1.50) -0.78 (-8.06; 2.84) n=287	-1.29 (1.54) -0.99 (-7.61; 2.75) n=1192	-1.59 (2.27) -1.03 (-9.92; 1.72) n=49
Birth year				
2006-2007	520 (7.8%)	23 (8.0%)	135 (11.3%)	4 (8.2%)
2008-2009	1283 (19.1%)	48 (16.7%)	117 (9.8%)	2 (4.1%)
2010-2011	1243 (18.5%)	60 (20.9%)	8 (0.7%)	1 (2.0%)
2012-2013	1326 (19.8%)	43 (15.0%)	96 (8.1%)	7 (14.3%)
2014-2015	1378 (20.6%)	67 (23.3%)	240 (20.1%)	9 (18.4%)
2016-2017	954 (14.2%)	46 (16.0%)	315 (26.4%)	16 (32.7%)
2018-2019			281 (23.6%)	10 (20.4%)
Any ROP	1739 (25.9%)	287 (100.0%)	453 (38.0%)	49 (100.0%)
Postnatal age for first diagnosed ROP (weeks)	8.30 (2.29) 8.00 (3.43; 18.71) n=1739	8.68 (1.74) 8.43 (4.43; 15.14) n=287	8.12 (2.61) 7.86 (3.14; 19.00) n=453	7.63 (1.99) 7.43 (4.29; 12.14) n=49

	Model development group		Validation groups	
	No ROP treatment	**ROP treatment**	**No ROP treatment**	**ROP treatment**
Postnatal age for ROP treatment (weeks)		12.8 (2.8) 12.4 (7.0; 21.9) n=287		12.3 (2.4) 11.9 (7.1; 19.6) n=49

ROP=retinopathy of prematurity; SDS=standard deviation score

For categorical variables n (%) is presented.
For continuous variables Mean (SD) / Median (Min; Max) / n= is presented.

eTable 3. Final prediction models in model development group for postnatal ages 6-14 weeks (N=6991)

Model for:	n events/N infants	Variables	Estimate (SE)	p-value	Hosmer-Lemeshow goodness-of-fit test p-value
PNA 6 weeks	**287/6991**	**Intercept**	0.0560 (0.1263)	0.66	0.72
		logodds(DIGIROP-Birth)	1.0336 (0.0557)	<.0001	
		FirstROP	5.0363 (4.3698)	0.25	
		FirstROP x FirstROPWeek	-0.7783 (0.7457)	0.30	
		logodds(DIGIROP-Birth) x FirstROP x FirstROPWeek	0.0138 (0.0589)	0.82	
PNA 7 weeks	**287/6991**	**Intercept**	0.0618 (0.1324)	0.64	0.53
		logodds(DIGIROP-Birth)	1.0666 (0.0598)	<.0001	
		FirstROP	1.3407 (1.8188)	0.46	
		FirstROP x FirstROPWeek	-0.1940 (0.2798)	0.49	
		logodds(DIGIROP-Birth) x FirstROP x FirstROPWeek	-0.0343 (0.0264)	0.19	
PNA 8 weeks	**282/6986**	**Intercept**	0.0452 (0.1550)	0.77	0.55
		logodds(DIGIROP-Birth)	1.1899 (0.0763)	<.0001	
		FirstROP	-0.6394 (1.0596)	0.55	
		FirstROP x FirstROPWeek	0.1028 (0.1490)	0.49	
		logodds(DIGIROP-Birth) x FirstROP x FirstROPWeek	-0.0648 (0.0172)	0.0002	
PNA 9 weeks	**265/6969**	**Intercept**	-0.1282 (0.1869)	0.49	0.97
		logodds(DIGIROP-Birth)	1.2439 (0.0939)	<.0001	
		FirstROP	0.9040 (0.7407)	0.22	
		FirstROP x FirstROPWeek	-0.0817 (0.0976)	0.40	
		logodds(DIGIROP-Birth) x FirstROP x FirstROPWeek	-0.0582 (0.0167)	0.0005	
PNA 10 weeks	**252/6956**	**Intercept**	-0.3993 (0.2624)	0.13	1.00
		logodds(DIGIROP-Birth)	1.4012 (0.1410)	<.0001	
		FirstROP	1.2090 (0.5869)	0.039	
		FirstROP x FirstROPWeek	-0.0857 (0.0765)	0.26	
		logodds(DIGIROP-Birth) x FirstROP x FirstROPWeek	-0.0742 (0.0196)	0.0002	
PNA 11 weeks	**209/6913**	**Intercept**	-1.5490 (0.3873)	<.0001	0.59
		logodds(DIGIROP-Birth)	1.1503 (0.1676)	<.0001	
		FirstROP	1.6573 (0.5623)	0.0032	
		FirstROP x FirstROPWeek	-0.0163 (0.0708)	0.82	
		logodds(DIGIROP-Birth) x FirstROP x FirstROPWeek	-0.0361 (0.0218)	0.098	
PNA 12 weeks	**162/6866**	**Intercept**	-1.9017 (0.4772)	<.0001	0.96
		logodds(DIGIROP-Birth)	1.1565 (0.1989)	<.0001	

Model for:	n events/N infants	Variables	Estimate (SE)	p-value	Hosmer-Lemeshow goodness-of-fit test p-value
		FirstROP	2.0944 (0.5740)	0.0003	
		FirstROP x FirstROPWeek	-0.0724 (0.0732)	0.32	
		logodds(DIGIROP-Birth) x FirstROP x FirstROPWeek	-0.0427 (0.0246)	0.082	
PNA 13 weeks	**114/6818**	**Intercept**	-3.3040 (0.7853)	<.0001	1.00
		logodds(DIGIROP-Birth)	1.0138 (0.2733)	0.0002	
		FirstROP	2.4864 (0.7244)	0.0006	
		FirstROP x FirstROPWeek	-0.0179 (0.0860)	0.84	
		logodds(DIGIROP-Birth) x FirstROP x FirstROPWeek	-0.0377 (0.0320)	0.24	
PNA 14 weeks	**90/6794**	**Intercept**	-3.2182 (0.8548)	0.0002	1.00
		logodds(DIGIROP-Birth)	1.1678 (0.3182)	0.0002	
		FirstROP	3.0547 (0.7960)	0.0001	
		FirstROP x FirstROPWeek	-0.1294 (0.0977)	0.19	
		logodds(DIGIROP-Birth) x FirstROP x FirstROPWeek	-0.0599 (0.0366)	0.10	

ROP=retinopathy of prematurity; PNA=postnatal age; logodds(DIGIROP-Birth)=log([DIGIROP-Birth risk estimate]/(1-[DIGIROP-Birth risk estimate])); FirstROP=first ROP diagnosed no(0)/yes(1); FirstROPWeek=postnatal week when first ROP is diagnosed

eTable 4. Gestational age-specific cut-offs (estimated probabilities for retinopathy of prematurity treatment) based on DIGIROP-Screen in model development group (N=6991)

Each column (Birth and PNA 6-14 weeks) represents a separate prediction model

GA at birth	Birth	PNA 6 weeks	PNA 7 weeks	PNA 8 weeks	PNA 9 weeks	PNA 10 weeks	PNA 11 weeks	PNA 12 weeks	PNA 13 weeks	PNA 14 weeks
24	0.05	0.05	0.05	0.05	0.05	0.05	0.034	0.024	0.012	0.011
25	0.05	0.05	0.05	0.037	0.027	0.019	0.011	0.0079	0.05	0.044
26	0.026	0.024	0.021	0.015	0.011	0.0049	0.0071	0.0049	0.0018	0.0012
27	0.014	0.013	0.013	0.0089	0.014	0.0075	0.022	0.022	0.019	0.016
28	0.0054	0.0048	0.004	0.0021	0.0023	0.0017	0.0016	0.0011	0.011	0.0099
29 (and 30)	0.0032	0.0028	0.0023	0.01	0.0069	0.05	0.04	0.032	0.011	0.0099

ROP=retinopathy of prematurity; GA=gestational age; PNA=postnatal age

eTable 5. Area under the receiver operating characteristic curve (AUC) with 95% CI at birth and over postnatal ages 6-14 weeks for model development group (N=6991), internal validation using 10-fold cross-validation (N=6991) and external validation groups (N=1241)

	Model Development Group	Internal Validation	External Validation
AUC (95% CI)	**GA 24-30w**	**GA 24-30w**	**GA 24-30w**
At Birth	0.91 (0.89 - 0.92)	0.91 (0.89 - 0.92)	0.88 (0.84 - 0.93)
At PNA 6 weeks	0.91 (0.89 - 0.92)	0.90 (0.89 - 0.92)	0.90 (0.86 - 0.94)
At PNA 7 weeks	0.91 (0.90 - 0.92)	0.91 (0.89 - 0.92)	0.90 (0.87 - 0.94)
At PNA 8 weeks	0.92 (0.91 - 0.93)	0.92 (0.91 - 0.93)	0.91 (0.89 - 0.94)
At PNA 9 weeks	0.92 (0.91 - 0.93)	0.92 (0.91 - 0.93)	0.92 (0.90 - 0.95)
At PNA 10 weeks	0.93 (0.92 - 0.94)	0.93 (0.92 - 0.94)	0.92 (0.90 - 0.94)
At PNA 11 weeks	0.94 (0.93 - 0.95)	0.94 (0.93 - 0.95)	0.92 (0.90 - 0.94)
At PNA 12 weeks	0.93 (0.92 - 0.94)	0.93 (0.92 - 0.94)	0.92 (0.89 - 0.95)
At PNA 13 weeks	0.93 (0.92 - 0.95)	0.93 (0.92 - 0.94)	0.90 (0.86 - 0.93)
At PNA 14 weeks	0.93 (0.92 - 0.94)	0.93 (0.91 - 0.94)	0.90 (0.85 - 0.95)

AUC=Area under the receiver operating characteristic curve; PNA=postnatal age; GA=gestational age

eTable 6. Specificity and cumulative specificity with 95% CI for 100% sensitivity over postnatal weeks for model development group (N=6991), internal validation using 10-fold cross-validation (N=6991) and external validation groups (N=1241) overall and by gestational age of <28 and ≥28 weeks, and for white and non-white population

	Model development group *			Internal validation**	External validation***				
Specificity (95% CI) min to max	**GA 24-30w N=6991**	**GA 24-27w N=2719**	**GA 28-30w N=4272**	**GA 24-30w N=6991**	**GA 24-30w N=1241**	**GA 24-27w N=524**	**GA 28-30w N=717**	**GA 24-30w White N=177**	**GA 24-30w Non-white N=63**
At Birth	53.1 (51.9 - 54.3)	11.9 (10.6 - 13.3)	76.8 (75.5 - 78.0)	48.0 (46.8 - 49.2) 47.5 to 55.5	46.3 (43.4 - 49.2)	11.3 (8.6 - 14.5)	69.7 (66.2 - 73.1)	54.5 (46.9 - 62.1)	38.3 (26.1 - 51.8)
At PNA 6 weeks	52.4 (51.2 - 53.6)	11.5 (10.2 - 12.8)	75.9 (74.6 - 77.2)	51.4 (50.2 - 52.6) 49.3 to 52.4	44.8 (41.9 - 47.7)	10.3 (7.7 - 13.3)	67.9 (64.4 - 71.3)	52.3 (44.6 - 59.8)	38.3 (26.1 - 51.8)
At PNA 7 weeks	51.2 (50.0 - 52.4)	12.7 (11.4 - 14.1)	73.3 (72.0 - 74.7)	50.4 (49.2 - 51.6) 48.4 to 51.5	41.7 (38.9 - 44.6)	10.9 (8.2 - 14.0)	62.3 (58.7 - 65.9)	49.4 (41.8 - 57.1)	36.7 (24.6 - 50.1)
At PNA 8 weeks	58.4 (57.2 - 59.6)	14.7 (13.3 - 16.2)	83.5 (82.4 - 84.6)	57.5 (56.4 - 58.7) 56.8 to 58.9	49.0 (46.1 - 51.9)	13.2 (10.3 - 16.5)	73.0 (69.6 - 76.2)	56.3 (48.6 - 63.7)	45.0 (32.1 - 58.4)
At PNA 9 weeks	64.9 (63.7 - 66.0)	25.5 (23.8 - 27.3)	87.4 (86.4 - 88.4)	63.7 (62.6 - 64.9) 62.3 to 64.8	55.8 (52.9 - 58.6)	22.2 (18.5 - 26.2)	78.3 (75.1 - 81.3)	58.0 (50.3 - 65.3)	46.7 (33.7 - 60.0)
At PNA 10 weeks	69.5 (68.3 - 70.6)	27.1 (25.4 - 28.9)	93.7 (93.0 - 94.4)	64.7 (63.6 - 65.9) 64.7 to 69.4	61.3 (58.5 - 64.1)	22.0 (18.3 - 26.0)	87.7 (85.0 - 90.0)	60.2 (52.6 - 67.5)	51.7 (38.4 - 64.8)
At PNA 11 weeks	73.0 (72.0 - 74.1)	37.2 (35.2 - 39.1)	93.6 (92.8 - 94.3)	71.9 (70.8 - 73.0) 70.1 to 72.2	65.0 (62.2 - 67.7)	32.0 (27.8 - 36.4)	87.1 (84.4 - 89.5)	63.1 (55.5 - 70.2)	56.7 (43.2 - 69.4)
At PNA 12 weeks	72.9 (71.8 - 73.9)	37.2 (35.2 - 39.1)	93.3 (92.5 - 94.1)	69.7 (68.6 - 70.8) 66.1 to 71.6	64.8 (62.0 - 67.5)	31.8 (27.6 - 36.2)	86.8 (84.1 - 89.2)	62.5 (54.9 - 69.7)	56.7 (43.2 - 69.4)
At PNA 13 weeks	78.6 (77.5 - 79.5)	45.2 (43.2 - 47.2)	97.7 (97.2 - 98.1)	77.0 (76.0 - 78.0) 75.2 to 77.0	72.8 (70.2 - 75.3)	37.7 (33.3 - 42.2)	96.4 (94.7 - 97.6)	67.0 (59.6 - 73.9)	61.7 (48.2 - 73.9)
At PNA 14 weeks	77.8 (76.8 - 78.8)	43.1 (41.2 - 45.1)	97.7 (97.2 - 98.1)	75.3 (74.2 - 76.3) 74.9 to 76.5	72.1 (69.5 - 74.7)	36.0 (31.7 - 40.5)	96.4 (94.7 - 97.6)	66.5 (59.0 - 73.4)	61.7 (48.2 - 73.9)
Cumulatively at PNA 6 weeks	53.3 (52.0 - 54.5)	12.2 (10.9 - 13.6)	76.8 (75.5 - 78.1)	52.3 (51.1 - 53.5) 51.7 to 55.7	46.4 (43.5 - 49.3)	11.3 (8.6 - 14.5)	69.9 (66.4 - 73.2)	54.5 (46.9 - 62.1)	38.3 (26.1 - 51.8)
Cumulatively at PNA 7 weeks	54.2 (53.0 - 55.4)	14.8 (13.4 - 16.2)	76.8 (75.5 - 78.1)	53.4 (52.2 - 54.6) 51.8 to 56.1	47.2 (44.4 - 50.1)	13.4 (10.5 - 16.8)	69.9 (66.4 - 73.2)	55.1 (47.4 - 62.6)	38.3 (26.1 - 51.8)
Cumulatively at PNA 8 weeks	60.5 (59.3 - 61.7)	17.1 (15.7 - 18.7)	85.4 (84.3 - 86.4)	60.0 (58.8 - 61.1) 59.6 to 61.6	53.5 (50.6 - 56.4)	15.9 (12.7 - 19.5)	78.7 (75.5 - 81.7)	60.2 (52.6 - 67.5)	45.0 (32.1 - 58.4)

	Model development group *			Internal validation**	External validation***				
Specificity (95% CI) min to max	**GA 24-30w N=6991**	**GA 24-27w N=2719**	**GA 28-30w N=4272**	**GA 24-30w N=6991**	**GA 24-30w N=1241**	**GA 24-27w N=524**	**GA 28-30w N=717**	**GA 24-30w White N=177**	**GA 24-30w Non-white N=63**
Cumulatively at PNA 9 weeks	67.6 (66.5 - 68.7)	28.6 (26.8 - 30.4)	90.0 (89.1 - 90.9)	66.5 (65.3 - 67.6) 65.5 to 68.0	61.2 (58.3 - 63.9)	25.1 (21.3 - 29.2)	85.3 (82.5 - 87.8)	63.6 (56.1 - 70.7)	48.3 (35.2 - 61.6)
Cumulatively at PNA 10 weeks	72.1 (71.0 - 73.2)	31.3 (29.5 - 33.2)	95.5 (94.8 - 96.1)	68.6 (67.5 - 69.7) 68.6 to 72.2	65.9 (63.1 - 68.5)	26.2 (22.3 - 30.3)	92.4 (90.2 - 94.3)	65.3 (57.8 - 72.3)	51.7 (38.4 - 64.8)
Cumulatively at PNA 11 weeks	75.3 (74.3 - 76.4)	40.1 (38.1 - 42.1)	95.5 (94.9 - 96.1)	74.3 (73.2 - 75.3) 73.8 to 75.2	69.3 (66.6 - 71.9)	34.7 (30.5 - 39.2)	92.4 (90.2 - 94.3)	65.9 (58.4 - 72.9)	56.7 (43.2 - 69.4)
Cumulatively at PNA 12 weeks	75.5 (74.5 - 76.5)	40.6 (38.6 - 42.6)	95.5 (94.9 - 96.1)	74.9 (73.9 - 75.9) 74.4 to 75.6	69.6 (66.9 - 72.2)	35.4 (31.1 - 39.8)	92.6 (90.4 - 94.4)	65.9 (58.4 - 72.9)	56.7 (43.2 - 69.4)
Cumulatively at PNA 13 weeks	80.6 (79.6 - 81.5)	49.3 (47.3 - 51.3)	98.6 (98.2 - 98.9)	80.0 (79.0 - 80.9) 79.3 to 80.0	75.2 (72.6 - 77.6)	41.8 (37.4 - 46.4)	97.5 (96.0 - 98.5)	68.8 (61.3 - 75.5)	63.3 (49.9 - 75.4)
Cumulatively at PNA 14 weeks	80.6 (79.7 - 81.6)	49.3 (47.3 - 51.3)	98.6 (98.2 - 98.9)	80.1 (79.2 - 81.1) 79.8 to 80.3	75.2 (72.6 - 77.6)	41.8 (37.4 - 46.4)	97.5 (96.0 - 98.5)	68.8 (61.3 - 75.5)	63.3 (49.9 - 75.4)

CI=confidence interval; PNA=postnatal age; GA=gestational age; w=weeks

Model development group includes data from Swedish national registry for retinopathy of prematurity, born at gestational age of 24-30 weeks (2007-2017).

Validation groups consist of four external validation cohorts, one from Sweden (later time period than in model development group), one from Germany and two from the United States.

Specificity is obtained from each PNA-model applying cut-offs based on estimated probabilities for 100% sensitivity in model development group.

Cumulative specificity at a certain PNA is calculated as a union of specificities up to and including that certain PNA.

*Cut-offs selected in model development group for sensitivity 100%.

**For internal validation same models were run applying 10-fold cross-validation and cut-offs based on those estimates retrieved. The range (min to max) obtained using 10 randomly selected seeds expresses the uncertainty of the internal validation.

***For validation groups, cut-offs obtained from model development group are applied. Sensitivity 100% for all postnatal weeks except for 1 infant at birth, and PNA 6 and 7 weeks (sensitivity 48/49 at those time points), with severe comorbidity profile.

eTable 7. Distribution of maximum retinopathy of prematurity stage for infants not needing and needing retinopathy of prematurity screening according to DIGIROP-Screen (N=6991)

Need for ROP Screening acc. to DIGIROP-Screen	No ROP (n=4965)	Max stage 1 (n=661)	Max stage 2 not treated (n=771)	Max stage 3 not treated (n=307)	Treated ROP (n=287)
Risk flag at Birth					
No	3179 (64.0%)	202 (30.6%)	137 (17.8%)	44 (14.3%)	0 (0.0%)
Yes	1786 (36.0%)	459 (69.4%)	634 (82.2%)	263 (85.7%)	287 (100.0%)
Risk flag cumulatively up to PNA 8 weeks					
No	3630 (73.1%)	227 (34.3%)	152 (19.7%)	47 (15.3%)	0 (0.0%)
Yes	1335 (26.9%)	434 (65.7%)	619 (80.3%)	260 (84.7%)	287 (100.0%)
Risk flag cumulatively up to PNA 12 weeks					
No	4503 (90.7%)	287 (43.4%)	215 (27.9%)	57 (18.6%)	0 (0.0%)
Yes	462 (9.3%)	374 (56.6%)	556 (72.1%)	250 (81.4%)	287 (100.0%)

ROP=retinopathy of prematurity; PNA=postnatal age

For categorical variables n (%) is presented.

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