**Phenotype Description for study “Performance of phenotype algorithms for the identification of opioid-exposed infants”**

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# Study Description

**Objective**

Observational studies examining outcomes among opioid-exposed infants are limited by phenotype algorithms that may under identify opioid-exposed infants without neonatal opioid withdrawal syndrome (NOWS). We developed and validated the performance of different phenotype algorithms to identify opioid-exposed infants using electronic health record (EHR) data.

**Patients and Methods**

We developed phenotype algorithms for the identification of opioid-exposed infants among a population of birthing person-infant dyads from an academic healthcare system (2010-2022). We derived phenotype algorithms from combinations of 6 unique indicators of in-utero opioid exposure, including those from the infant record (NOWS/opioid-exposure diagnosis, positive toxicology) and birthing person record (opioid use disorder diagnosis, opioid drug exposure record, opioid listed on medication reconciliation, positive toxicology). We determined the positive predictive value (PPV) and 95% confidence interval (CI) for each phenotype algorithm using medical record review as the gold standard.

**Results**

Among 41,047 dyads meeting exclusion criteria, we identified 1,558 infants (3.80%) with evidence of at least one indicator for opioid-exposure and 32 (0.08%) meeting all six indicators of the phenotype algorithm. Among the sample of dyads randomly selected for review (n=600), the PPV for the phenotype requiring only a single indicator was 95.4% (CI: 93.3-96.8) with varying PPVs for the other phenotype algorithms derived from a combination of infant and birthing person indicators (PPV range: 95.4-100.0).

**Conclusions**

Opioid-exposed infants can be accurately identified using EHR data. Our publicly available phenotype algorithms can be used to conduct research examining outcomes among opioid-exposed infants with and without NOWS.

# Phenotype Algorithm Overview

**Population Criteria**

All birthing parent-child dyads from 2010-2022

*AND*

Evidence of live birth confirmation

*AND*

Infant was >=33 weeks gestation

*AND NOT*

(

Evidence of critical illness or respiratory procedures

*OR*

Major congenital malformations at birth

)

**Inclusion Criteria for Opioid-Exposure**

Infant diagnosis of NOWS/opioid-exposure

 *OR*

Infant positive opioid toxicology

 *OR*

Birthing Person Opioid Use Disorder diagnosis from prenatal through 30-days postpartum

 *OR*

Birthing Person outpatient opioid exposure record from 30 to 2 days prior to delivery

*OR*

Birthing Person opioid listed in medication list from 30 to 2 days prior to delivery

 *OR*

Birthing Person positive opioid toxicology

**Exclusion Criteria for Opioid-Exposure**

None

## Phenotype Algorithm Details

Note: the ICD and PCT code Excel file referenced below is available on both [GitHub](https://github.com/Precision-Phenotyping-Core/opioid-exposed-infants) and [PheKB](https://phekb.org/phenotype/opioid-exposed-infants). This file contains the supplementary tables from the published manuscript (URL to be updated upon publication). The file name is AlgorithmValidation\_supplementintotables.xlsx.

### Population Criteria

All birthing parent-child dyads from 2010-2022

* Birthing parent-child dyads were identified using the OMOP RELATIONSHIP table

Evidence of live birth confirmation

* Live birth was defined as existence of certain CPT, ICD9, and ICD10 codes as listed in the file AlgorithmValidation\_supplementintotables.xlsx (Sheet ‘ST1. Live birth codes’) and in Supplementary Table 1 from the manuscript

Infant was >=33 weeks gestation

* Infant gestational age at birth was extracted from the OMOP OBSERVATION table

Evidence of critical illness or respiratory procedures

* Evidence of critical illness was defined as existence of certain CPT, ICD9 procedure, and ICD10 procedure codes as listed in the file AlgorithmValidation\_supplementintotables.xlsx (Sheets ‘ST2. Critical illness codes’ and ‘ST3. Resp proc codes’) and in Supplementary Tables 2 and 3 from the manuscript

Major congenital malformations at birth

* Major congenital malformations at birth were defined as existence of certain ICD9 and ICD10 codes as listed in the file AlgorithmValidation\_supplementintotables.xlsx (Sheet ‘ST4. Congenital malformations’) and in Supplementary Table 4 from the manuscript

### Inclusion Criteria for Opioid-Exposure

Infant diagnosis of NOWS/opioid-exposure

* Diagnosis of NOWS/opioid-exposure was defined as existence of certain ICD9 and ICD10 codes as listed in the file AlgorithmValidation\_supplementintotables.xlsx (Sheet ‘ST5. NOWS-OE diagnosis’) and in Supplementary Table 5 from the manuscript

Infant positive opioid toxicology

* Positive opioid toxicology was defined as presence of opioids or opioid metabolites from relevant labs as listed in the file AlgorithmValidation\_supplementintotables.xlsx (Sheet ‘ST6. Infant opioid lab terms’) and in Supplementary Table 6 from the manuscript

Birthing Person Opioid Use Disorder diagnosis from prenatal through 30-days postpartum

* Diagnosis of opioid use disorder was defined as existence of certain ICD9 and ICD10 codes as listed in the file AlgorithmValidation\_supplementintotables.xlsx (Sheet ‘ST7. Birth parent OUD codes’) and in Supplementary Table 7 from the manuscript

Birthing Person outpatient opioid exposure record from 30 to 2 days prior to delivery

* Opioid exposure was defined as existence of drug search terms in the OMOP DRUG\_EXPOSURE table as listed in the file AlgorithmValidation\_supplementintotables.xlsx (Sheet ‘ST8. Opioid search terms’) and in Supplementary Table 8 from the manuscript

Birthing Person opioid listed in medication list from 30 to 2 days prior to delivery

* Opioid exposure was defined as existence of drug search terms in medication lists found in the OMOP NOTE table as listed in the file AlgorithmValidation\_supplementintotables.xlsx (Sheet ‘ST8. Opioid search terms’) and in Supplementary Table 8 from the manuscript

Birthing Person positive opioid toxicology during birth hospitalization

* Positive opioid toxicology was defined as presence of metabolites for methadone, buprenorphine, norbuprenorphine, or fentanyl from relevant labs as listed in the file AlgorithmValidation\_supplementintotables.xlsx (Sheet ‘ST9. Birth parent lab terms’) and in Supplementary Table 9 from the manuscript

# Code Description

## Data Description

The EHR data used was organized according to Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) (<https://www.ohdsi.org/>).

## Code Availability

All code is available on GitHub at <https://github.com/Precision-Phenotyping-Core/opioid-exposed-infants>.

Code was writing in Python, Spark SQL, and SQL.

Code files are available in two formats: Python-based Jupyter Notebook (\*.ipynb), which can be opened up in most integrated development environment (IDE) software (e.g. Visual Studio Code), and HTML (\*.html), which can be opened in most web browsers (e.g. Chrome).

All the notebooks/files have been edited for public dissemination and are not executable as is.

## Nomenclature

Filenames follow the descriptions described in the published manuscript (see Figure 1).

Within each file, there may be alternative descriptions used. Major examples are listed below:

1. ‘Birthing parent’ may be represented as ‘mom’ or ‘maternal’
2. ‘Child’ may be represented as ‘infant’ or ‘baby’
3. ‘Dyad’ may be represented as ‘pair’, e.g. ‘birthing parent-child dyad’ may be represented as ‘mom-baby pair’
4. ‘Fetal abnormalities’ may be represented as ‘congenital malformations’

## File Descriptions

There are 14 overall notebooks that were used for the implementation of this phenotype algorithm. They listed and described in the order which they are intended to be run.

Additional details and documentation may be found in each notebook/file.

All ICD/CPT codes used can be found in the file AlgorithmValidation\_supplementintotables.xlsx, which is available on both [GitHub](https://github.com/Precision-Phenotyping-Core/opioid-exposed-infants) and [PheKB](https://phekb.org/phenotype/opioid-exposed-infants). This file contains the supplementary tables from the published manuscript (URL to be updated upon publication). Refer to [Chapter 2.1](#_Phenotype_Algorithm_Details) for details on which table should be used for which criteria.

ICD/CPT codes listed in AlgorithmValidation\_supplementintotables.xlsx/Supplementary Tables should supersede any discrepancies in the codes listed in the notebooks/files.

The following is a list and description of notebooks/files in the order of intended execution.

1. 1\_project\_modules.ipynb/.html
	* Called by other notebooks to import necessary libraries, define table names, and define common functions
2. 2\_birthing\_parent\_child\_dyads\_with\_live\_births.ipynb/.html
	* Find birthing parent-child dyads with evidence of live births
3. 3\_birthing\_parent\_child\_dyads\_with\_defined\_hospitalization.ipynb/.html
	* Select birthing parent-child dyads with evidence of live births (from 2\_birthing\_parent\_child\_dyads\_with\_live\_births.ipynb/.html) with a defined birth hospitalization stay, e.g. start and end dates around child date of birth
	* If only have partial birth hospitalization stay information, will impute missing information
4. 4\_estimated\_gestational\_age.ipynb/.html
	* Extract and clean estimated gestational age and only include infants with >=33 weeks gestation
	* Estimated time of conception is also calculated after extracting estimated gestational age using the formula: Baby Date of Birth - estimated gestational age + 14 days
5. 5\_exclusion\_critical\_illness.ipynb/.html
	* Exclude infants with evidence of critical illness based on CPT codes
	* Look for evidence of critical illness during birth hospitalization stay
6. 6\_exclusion\_congenital\_malformations.ipynb/.html
	* Exclude infants with evidence of congenital malformations based on ICD codes
	* Look for evidence of congenital malformations during birth hospitalization stay
7. 7\_exclusion\_respiratory\_procedures.ipynb/.html
	* Exclude infants with evidence of respiratory procedures based on ICD procedure codes
	* Look for evidence of respiratory procedures during birth hospitalization stay
8. 8\_child\_positive\_opioid\_toxicology.ipynb/.html
	* Identify infants with positive opioid toxicology results
9. 9\_birthing\_parent\_opioid\_drug\_exposure\_record.ipynb/.html
	* Identify birthing parents with evidence of outpatient opioid drug exposure from drug exposure data from 30 to 2 days prior to delivery
10. 10\_infant\_NOWS\_opioid\_exposure\_diagnosis.ipynb/.html
	* Identify infants with NOWS or opioid-exposure diagnosis based on ICD codes
11. 11\_birthing\_parent\_opioid\_use\_disorder.ipynb/.html
	* Identify birthing parents with opioid use disorder diagnosis based on ICD codes from estimated time of conception through 30-days after delivery
12. 12\_birthing\_parent\_opioid\_in\_medication\_list.ipynb/.html
	* Identify birthing parents with evidence of opioid drug exposure in medication lists from 30 to 2 days prior to delivery
13. 13\_birthing\_parent\_positive\_opioid\_toxicology.ipynb/.html
	* Identify birthing parents with positive opioid toxicology results during birth hospitalization
14. 14\_create\_final\_table.ipynb/.html
	* Create final output table from phenotype algorithm

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