MarketScan

WHITEPAPER

Post-marketing surveillance: Addressing pregnancy safety and regulatory requirements with real-world data

merative™

Evaluating prenatal exposures and outcomes using real-world data.

Regulatory bodies and other stakeholders increasingly see the value of and need for real-world data and evidence when making critical decisions about drugs and other biological products. Strategic use of real-world data for post-authorization studies can help life sciences organizations demonstrate the safety of their products and adhere to regulatory requirements. This white paper, written by Merative epidemiology experts, demonstrates the use of the Merative™ MarketScan® Research Databases for pregnancy safety studies.

Merative researchers have decades of experience conducting and consulting on research across a wide range of therapeutic areas using a variety of advanced methodologies backed by robust data assets. With direct access to Merative MarketScan Research Databases and the ability to link mothers to their infants using these data, Merative researchers can conduct studies to evaluate the safety of products used during pregnancy.

Using the Merative MarketScan Research Databases to describe prenatal exposures and assess pregnancy and infant outcomes

Introduction

There are over 75 million women of reproductive age in the United States, many living with chronic conditions treated with medications or biological products (Admon et al. 2017, Monte & Ellis 2014). Nearly 6 million pregnancies occur annually and many of these pregnancies are unintended (Curtain et al. 2015). Even among intended pregnancies, women may not know they are pregnant until several weeks have elapsed into the pregnancy. Therefore, many pregnancies may have inadvertent or planned exposure to medications or biological products for which the risk of adverse pregnancy outcomes or major congenital malformations is not well understood and frequently, there are limited human data to inform the safety of these medications or biological products during pregnancy.

Regulatory agencies have historically relied on pregnancy exposure registries to monitor safety of medications or biological products. However, registries may have limited power to detect rare pregnancy outcomes or major congenital malformations and identification of an appropriate comparator group may be a challenge. In addition, data generated from these types of studies may not be sufficient to assess a product's safety during pregnancy. Recently, the US Food and Drug Administration (FDA) issued guidance related to pregnancy safety studies and also included other types of epidemiologic studies such as post-authorization safety studies (PASS) utilizing real-world data to assess pregnancy outcomes in women with prenatal exposure to drugs and other biological products to corroborate registry findings (FDA 2019).
The MarketScan Research Databases reflect the combined healthcare service use of individuals covered by Merative clients nationwide. Merative researchers have successfully used these databases to assess pregnancy and infant outcomes. In order to successfully conduct pregnancy research in claims data, Merative researchers have developed methods to:

- Estimate date of last menstrual period (LMP) and gestational age using data from administrative claims data to evaluate prenatal exposures and pregnancy outcomes
- Perform linkage of infants to their mothers in order to describe infant outcomes based on maternal exposures or comorbidities

This document describes selected research projects that Merative researchers have undertaken to study pregnancy and infant outcomes utilizing MarketScan Research Databases.

Merative MarketScan Research Databases

Cited in over 2,700 peer-reviewed publications, the Merative MarketScan Research Databases are a family of research data sets that integrate de-identified patient-level health data (medical, drug and dental), productivity (workplace absence, short- and long-term disability and workers' compensation), laboratory results, health risk assessments (HRAs), hospital discharges and electronic medical records (EMRs) into data sets available for healthcare research. The MarketScan family consists of three core claims databases, a hospital discharge database, as well as several linked databases, data sets and files that combine claims data with other patient and employee data at the patient level.

Estimating Gestational Age at Time of Prenatal Exposure

Merative researchers utilized a validated claims-based algorithm (Ailes et al. 2016, Devine et al. 2010, Moll et al. 2020), to estimate gestational age based on the diagnosis and procedure codes present at the time of the pregnancy end date. Pregnancies for women age 15-44 with claims related to pregnancy end were identified if the pregnancy end date was between January 1, 2010 and April 30, 2017 in the MarketScan Commercial and Multi-State Medicaid databases. The date of LMP was estimated as the pregnancy end date less the gestational age at pregnancy end and continuous enrollment in the database was required from six months prior to LMP through 60 days following the pregnancy end date. The presence of influenza and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination during pregnancy were identified using procedure codes on medical claims or NDC on drug claims. Gestational age at vaccination was estimated using gestational weeks between the estimated LMP date and the vaccination service date (Ghaswalla 2019).

Merative MarketScan Commercial Database

The Merative MarketScan Commercial Database consists of medical and drug data from employers and health plans for over 203 million individuals annually, encompassing employees, their spouses and dependents who are covered by employer-sponsored private health insurance in the US.

Merative MarketScan Multi-State Medicaid Database

The Merative MarketScan Multi-State Medicaid Database contains the medical, surgical and prescription drug experience of more than 48 million enrollees from multiple states, including records of inpatient services and admissions, outpatient services and prescription drugs.

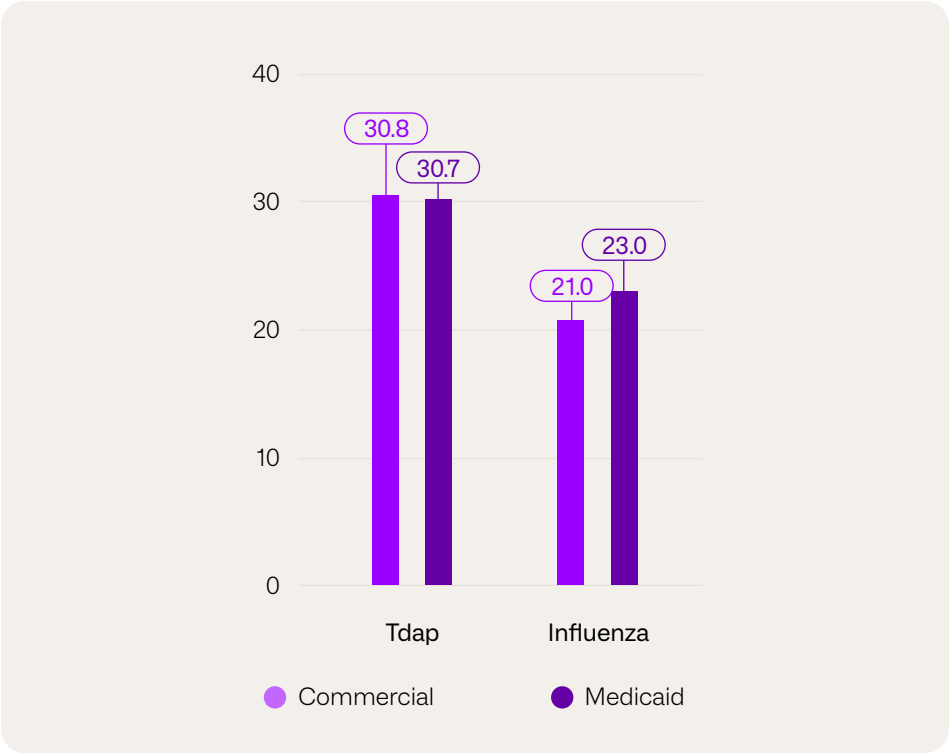

Figure 1. Mean Gestational Age at Tdap and Influenza Vaccination: Commercial and Medicaid Pregnancies Ending 2010-2017

Observations

In total 1,852,705 pregnancies in the Commercial cohort and 628,079 pregnancies in the Medicaid cohort were eligible for the study and influenza vaccination coverage and gestational age at influenza vaccination was analyzed in this cohort. For Tdap vaccination outcomes, pregnancies were restricted to those with gestational age of at least 23 weeks at pregnancy end (1,421,452 Commercial; 523,623 Medicaid). Mean gestational age at Tdap and influenza vaccination for those who received either a Tdap or influenza vaccination is provided separately for the Commercial and Medicaid cohorts in Figure 1. Mean gestational age at Tdap vaccination was similar in the Commercial (30.8, SD: 5.3) and Medicaid cohorts (30.7, SD: 5.4). In addition, most pregnancies received a Tdap vaccination within the recommended time (CDC 2012), between 27 and 36 weeks gestation (Commercial: 89.1%, Medicaid 88.8%). Mean gestational age at time of influenza vaccination was shorter; 21.0 weeks (SD: 10.6) in the Commercial cohort and 23.0 weeks (SD: 10.0) in the Medicaid cohort.

Linkage of Infants to Mothers to Evaluate Impact of Maternal Prenatal Exposure or Comorbidity

Merative researchers are able to identify fetal exposures occurring during pregnancy, link mothers to their infants and examine infant outcomes that may be related to the pregnancy exposures. In one analysis, women aged 15-50 with live birth singleton deliveries between January 1, 2010 and September 30, 2015 in the Merative MarketScan Commercial Database were linked to their infants. Maternal pre-eclampsia and gestational diabetes mellitus (GDM) were identified by presence of a diagnosis for these conditions during the pregnancy and prior to the delivery date (Packnett et al. 2020) and maternal post-partum depression (PPD) was identified if the mother was diagnosed with PPD between 15 and 365 days after the date of delivery (Moore Simas et al. 2019).

Observations

A total of 557,481 mother-infant pairs were identified that met all of the patient selection criteria. To compare infant outcomes based on maternal pre-eclampsia and GDM, infant outcomes were identified at the time of birth and in the 12 months following birth. For the comparison of infant outcomes based on presence of maternal PPD, infant outcomes were identified at the time of birth and in the 24 months following birth. All of these analyses compared infants with mothers who were diagnosed with either pre-eclampsia, GDM or PPD to infants with mothers who did not have the specific condition. Infant clinical outcomes were assessed by the presence of diagnosis codes on medical claims during the follow-up period.

Figure 2 shows the prevalence of selected infant clinical outcomes in the first year of life in infants with and without maternal pre-eclampsia exposure. Feeding problems, congenital anomalies, low birthweight, vomiting, and fussiness/excessive crying were the most common outcomes in the first year of life. Each clinical outcome was significantly more common when comparing infants with pre-eclampsia exposure to those without (p<0.001 for all).

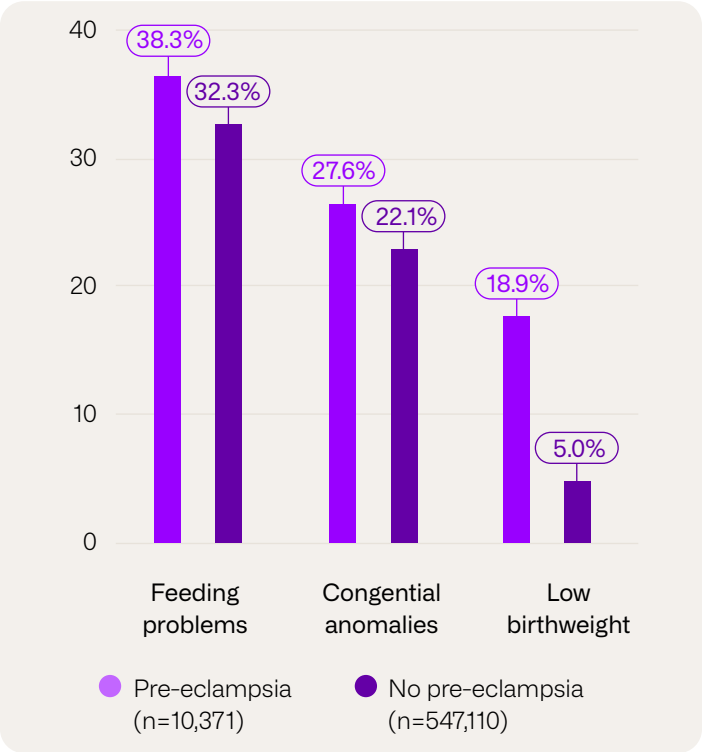

Figure 2. Infant Clinical Outcomes in the First Year of Life by Presence of Maternal Pre-eclampsia
p<0.001 for all when comparing pre-eclampsia vs. no pre-eclampsia for all outcomes shown.

The prevalence of selected infant clinical outcomes with and without maternal GDM exposure is shown in Figure 3. Feeding problems, congenital anomalies, fussiness/excessive crying, vomiting, and low birthweight were the most common outcomes in the first year of life. Though each clinical outcome was significantly more common when comparing infants with GDM exposure to those without (p<0.001 for all), the absolute differences between the groups were small.

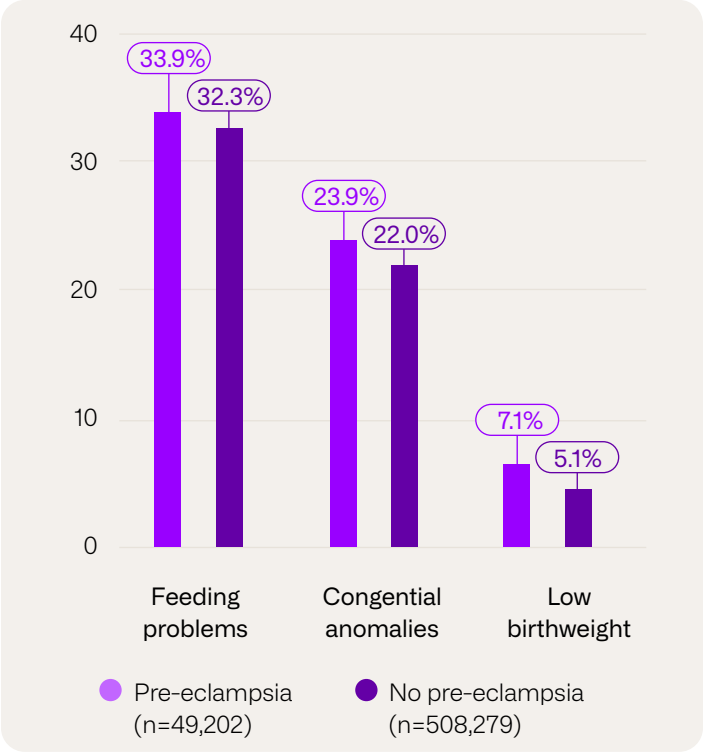

Figure 3. Infant Clinical Outcomes in the First Year of Life by Presence of Maternal GDM
p<0.001 for all when comparing GDM vs. no GDM for all outcomes shown.

Figure 4 shows the prevalence of selected infant clinical outcomes in the first two years of life in infants with maternal PPD exposure and matched infants without maternal PPD exposure. Similar to the pre-eclampsia and GDM cohorts, feeding problems, congenital anomalies, vomiting, fussiness/excessive crying, and low birthweight were the most common clinical outcomes in the first two years of life. Each clinical outcome was significantly more common when comparing infants with pre-eclampsia exposure to those without ($p<0.001$), except for low birthweight ($p=1.00$). No differences in low birthweight were observed because infants were matched on presence of maternal diagnosis of pre-term birth.

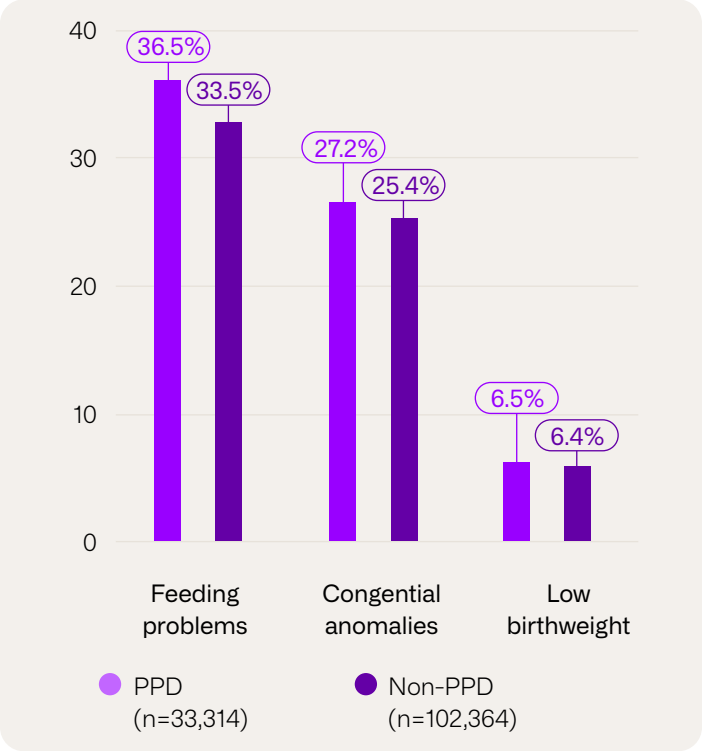

Figure 4. Infant Clinical Outcomes in the First Year of Life by Presence of Maternal PPD

Validation of Pregnancy and Infant Outcomes

Pregnancy outcomes

Merative researchers conducted a validation study to develop a claims-based algorithm to identify pregnancy outcomes of live birth, spontaneous abortion, pre-term birth and stillbirth and estimate gestational age. Diagnosis and procedure codes on insurance claims for women aged 12–55 years in the 2016–2018 IBM MarketScan Explorys® Claims-EMR Data Set (CED) were utilized to classify the outcomes and assign an estimated gestational age (Moll et al. 2020). Physician reviewers then reviewed the EMR data associated with a sample of the pregnancies identified in the claims data as having stillbirth, full-term and preterm live births, and spontaneous abortions. The physician reviewers assigned a level of certainty to each outcome based on Global Alignment of Immunization safety Assessment in pregnancy (GAIA) case definitions. Percentage positive agreement (PPA) was calculated, comparing results from the algorithms and adjudication.

Mertative MarketScan Explorys Claims-EMR Data Set

The Merative MarketScan Explorys Claims-EMR Data Set is a longitudinal, patient-level linked claims and EMR data set containing over 6 million patient lives. It can be used to conduct research studies that involve both clinical and cost information.

Observations

A total of 34,204 pregnancies were identified using medical claims in CED and gestational age at pregnancy end was estimated at outcome. EMR data were available for 10% of the pregnancy episodes, and the demographic and clinical characteristics of the pregnancies with and without EMR data were similar (most standardized mean differences <0.2). Physician reviewers classified each outcome and assigned a gestational age at outcome and indicated GAIA levels of certainty of 1–3 for 93 preterm births, 92 full term births, 75 spontaneous abortions, and 24 stillbirths. Figure 5 shows the PPA for pregnancy outcomes and gestational age among the sampled pregnancies. The PPA on pregnancy outcome was 98% for full term births, 62% for preterm births, 100% for spontaneous abortions, and 71% for stillbirths. The PPA on gestational age within 7 and 14 days, respectively, was 86% and 99% for full term births, 82% and 93% for preterm births, 61% and 81% for spontaneous abortions, and 67% and 79% for stillbirths. The claims-based pregnancy outcome algorithms were developed and validated with a high level of agreement.

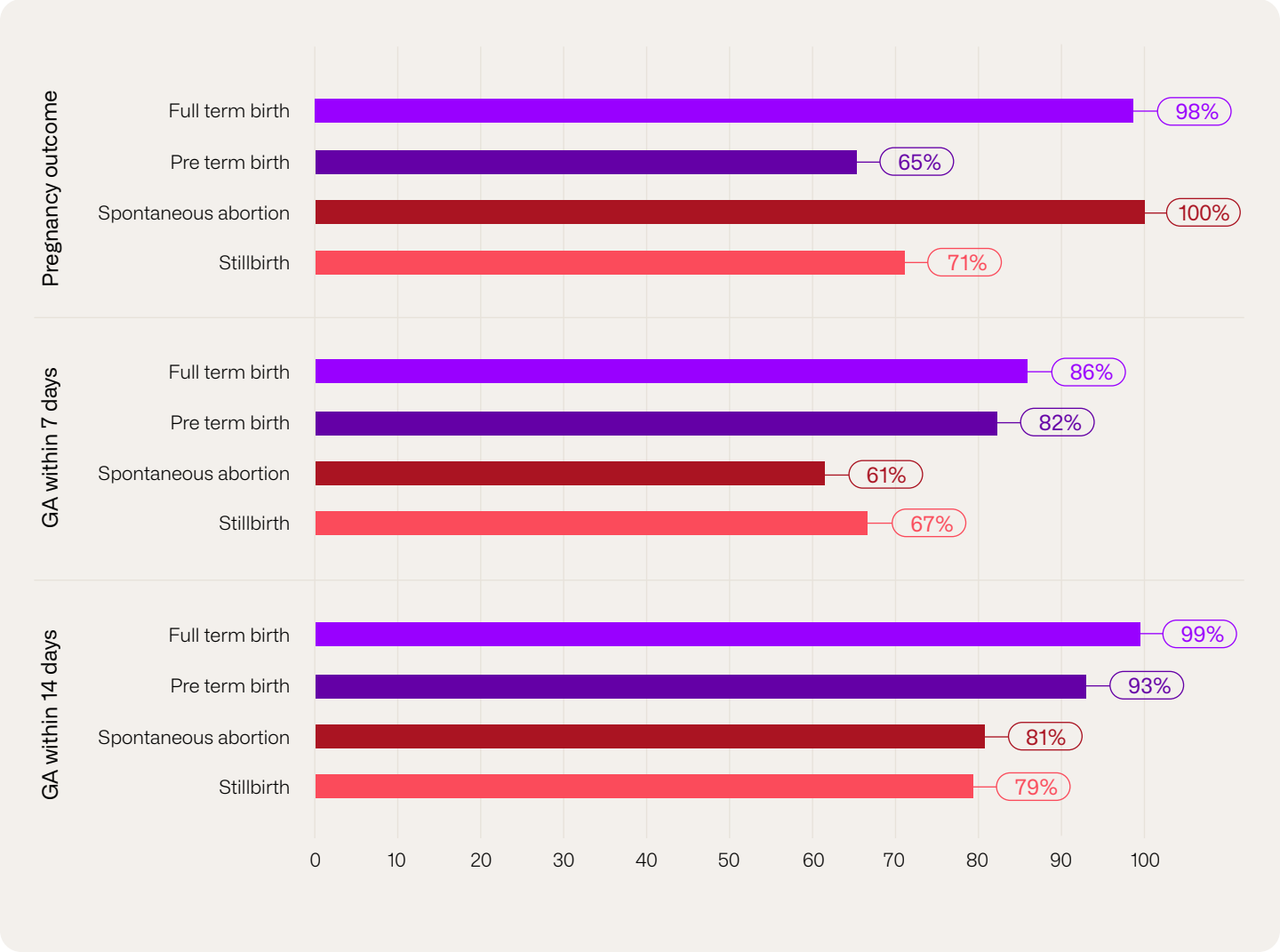

Figure 5. Percent Positive Agreement between Claims-based Algorithm and Physician Review for Pregnancy Outcomes and Gestational Age at Outcome

Congenital Malformations in Infants

Merative researchers identified infants with insurance claims for live births and aged <1 year in the 2002–2018 Merative MarketScan Explorys Claims-EMR Data Set (CED). Infants with specific congenital heart defects were identified if they had two or more medical claims on separate days for ventricular septal defects or patent ductus arteriosis in the first year of life. Among infants with evidence of either one of these defects in insurance claims, the subset with EMR records were identified and the records were reviewed to determine if the infant had the specified congenital heart defect. Proportion positive agreement (PPA) between the insurance claims and EMR was assessed in the first year following the birth (data on file, Merative 2020).

Observations

In total 32,853 infants were identified in the linked claims-EMR database and 270 (0.8%) had two or more insurance claims for ventricular septal defects and 203 (0.6%) had two or more insurance claims for patent ductus arteriosis in the first year of life. Among the infants with insurance claims for ventricular septal defects 66 (24.4%) had EMR records available for analysis during their first year of life; 57(28.0%) infants with patent ductus arteriosis had EMR records available for analysis during their first year of life.

Figure 6 shows the PPA between diagnosis for congenital heart malformation found in the claims data and specified congenital heart malformations found in the EMR records. PPA for infants with ventricular septal defects was 85% and 81% in infants with patent ductus arteriosis. These results are based solely on the presence of diagnoses codes in both databases. A more complete records review beyond just diagnoses codes in the EMR may produce higher estimates of PPA.

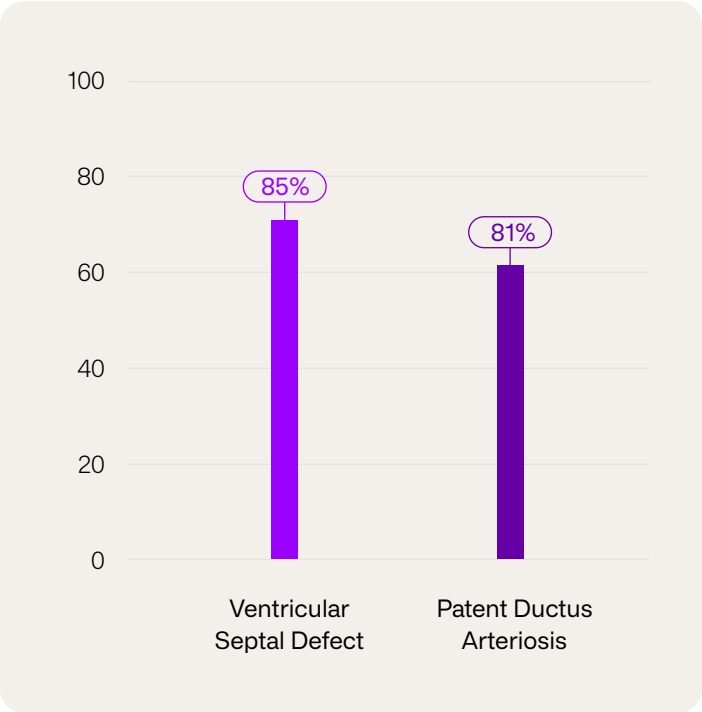

Figure 6. Percent Positive Agreement between Insurance Claims and EMR Data Review for Cardiac Malformations

Conclusions

Insurance claims data in the MarketScan Research Databases can be used to identify pregnancy outcomes, estimate gestational age at the time the pregnancy ends and also estimate gestational age at the time of prenatal exposures. Pregnancies identified in these databases can also be linked to infants to describe infant outcomes, such as congenital malformations, in the context of prenatal exposures and the timing of prenatal exposures. Infants can be linked to their mothers utilizing both the MarketScan Commercial and Multi-State Medicaid databases with approximately 70% of live birth pregnancy outcomes in the Commercial database and 40% of live birth pregnancy outcomes in the Multi-State Medicaid database. Overall, these analyses demonstrated that data from insurance claims in the MarketScan Research Databases can be leveraged to describe pregnancy and infant outcomes, including congenital malformations, in the context of presence of prenatal maternal exposures and timing and duration of these exposures.

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Ms. Packnett has over 10 years of research experience in the development, coordination, and execution of observational epidemiologic studies. She has extensive expertise working with large healthcare encounter databases including inpatient, outpatient, and pharmaceutical data to conduct observational studies. She has integrated healthcare encounter, administrative, and personnel data to conduct retrospective observational studies to support the development of evidence-based policy. The results of her research have appeared in numerous peer-reviewed publications related to maternal and child health, behavioral health, vaccination coverage and completion, and respiratory disorders. Since joining Merative she has led several studies assessing prenatal exposure and linking infants to their mothers to describe infant outcomes based on maternal exposure. Before joining Merative, Ms. Packnett spent nine years as an epidemiologist at the Walter Reed Army Institute of Research, designing and conducting epidemiology and surveillance studies. She holds an MPH in epidemiology from the University of Michigan School of Public Health.

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Merative Life Sciences Research Services

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