

Outcomes and Management of Pregnancies Screening Positive for Microdeletions 22q11.2, 15q11.2, 1p36, 4p, or 5p: A Retrospective Cohort Study

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Purpose: To compare pregnancy outcomes and management between patients screening positive for five microdeletions (microdeletion screen-positive, MDS+) and patients screening negative (microdeletion screen-negative, MDS-).

Patients and Methods: Patients who received a prenatal cell-free DNA (pcfDNA) test that screens for microdeletions 22q11.2, 15q11.2, 1p36, 4p, and 5p and results were linked to de-identified insurance claims. Diagnosis and procedure codes were used to assess outcomes. Logistic and Poisson regression with adjustment for prior high-risk pregnancy and payer type were used to compare pregnancy outcomes and management in those with MDS+ and MDS- results.

Results: A total of 119 MDS+ patients and 287,169 MDS- patients were eligible for analysis. During pregnancy, MDS+ patients were more likely than MDS- patients to have polyhydramnios (18.5% in MDS+ vs. 3.4% in MDS-; OR=6.3 [95% CI: 3.8–10.1]; $p<0.001$) and fetal growth restriction (22.2% in MDS+ vs. 10.4% in MDS-; OR=2.4 [95% CI: 1.5–3.7]; $p<0.001$). MDS+ patients were more likely to experience pregnancy loss (OR=3.2; 95% CI: 1.3–6.3; $p=0.004$) or terminate the pregnancy (OR=22.2 [95% CI: 8.6–46.8]; $p<0.001$). Among patients with a live birth, MDS+ were more likely to have a preterm delivery (25.0% in MDS+ vs. 15.4% in MDS-; OR=1.8 [95% CI: 1.0–3.0]; $p=0.04$). MDS+ patients had increased pregnancy management, including more invasive diagnostic testing (13.4% in MDS+ vs. 0.5% in MDS-; OR=31.0 [95% CI: 17.5–51.1]; $p<0.001$) and more frequent echocardiograms (RR=1.5 [95% CI: 1.2, 1.9]; $p<0.001$) compared to MDS- pregnancies.

Conclusion: MDS+ pregnancies had elevated rates of ultrasound abnormalities, pregnancy loss, preterm birth, and pregnancy management as compared to an MDS- control group. These findings support the clinical utility of microdeletion screening in prenatal care.

Keywords: microdeletions, prenatal cfDNA, prenatal diagnosis, microdeletion 22q11.2, microdeletion 15q11.2

Introduction

Microdeletion syndromes result from subchromosomal deletions, the most common being 22q11.2 (DiGeorge/velocardiofacial syndrome), 15q11.2 (Prader-Willi/Angelman syndrome), 1p36 deletion syndrome, 4p (Wolff-Hirschhorn syndrome), and 5p (Cri-du-chat syndrome). The prenatal prevalences of these syndromes range from approximately 1 in 3500 for 22q11.2 deletion syndrome to 1 in 50,000 for 4p and 5p deletion syndromes.^{1,2}

In children and adults, these syndromes are associated with a wide range of neurodevelopmental disorders, including intellectual disability, autism spectrum disorder, epilepsy, and psychiatric illnesses.³ During pregnancy, affected fetuses may display ultrasound abnormalities such as heart defects, craniofacial anomalies, polyhydramnios, oligohydramnios, and fetal growth restriction (FGR).^{4–8} Substantial phenotypic heterogeneity across and within microdeletion syndromes is common, and microdeletion phenotypes may have variable penetrance and expressivity such that not all affected fetuses display the same type or severity of symptoms.^{1,3} Due to their low prevalence and high rates of termination,^{5,8–10}

pregnancy complications, outcomes, and management in microdeletion-affected pregnancies are challenging to characterize. In particular, little is known about how affected pregnancies are managed clinically, including the frequency of additional testing and monitoring.

Recent technological advancements have enabled detection of microdeletions in pregnancies as early as 10 weeks gestational age using prenatal cell-free DNA (pcfDNA) screening.^{11–13} Although early diagnosis may improve pregnancy outcomes and prognosis of these syndromes,^{1,14} current guidelines are mixed on whether microdeletion screening should be offered to pregnant patients. While the American College of Obstetricians and Gynecologists (ACOG) does not currently recommend routine screening for microdeletions,¹⁵ the American College of Medical Genetics (ACMG) recommends offering screening for 22q11.2 microdeletion, but not other microdeletions.¹⁶ Both ACOG and ACMG cite a lack of clinical evidence supporting screening, including low or unknown positive predictive value for non-22q11.2 microdeletions (clinical validity) and few studies demonstrating that screening improves management and outcomes (clinical utility). However, guidelines acknowledge that microdeletions are relatively common collectively and the risk is independent of maternal age.^{15,16}

To address these evidence gaps, we linked pcfDNA screening results to de-identified claims data to compare (1) pregnancy complications and end-of-pregnancy outcomes for 22q11.2, 15q11.2, 1p36, 4p, or 5p microdeletion screen-positive (MDS+) versus microdeletion screen-negative (MDS-) pregnancies, and (2) pregnancy management for MDS+ versus MDS- pregnancies. Administrative claims data provide longitudinal, real-world insights into healthcare utilization, offering a unique opportunity to follow a large cohort of pregnant patients after screening. To our knowledge, this is the first cohort study using linked pcfDNA and claims data to assess both pregnancy outcomes and management in microdeletion-screen positive pregnancies compared to a control group.

Materials and Methods

Data Sources

This retrospective observational cohort study used a linked dataset that combined US administrative claims data from the Komodo Healthcare MapTM (Komodo Health, New York, NY, USA) with pcfDNA screening results and clinical data from the Prequel[®] Prenatal Screen (Myriad Genetics, Inc., Salt Lake City, UT, USA). The Komodo Healthcare MapTM integrates various sources of both open and closed claims data to map longitudinal healthcare journeys for over 325 million patients across the US.¹⁷ Open claims typically come from multiple sources (including clearinghouses, pharmacies, and hospital systems) over an open-ended period while closed claims are usually sourced directly from the payer and include a more limited but clearly defined enrollment period for each patient.¹⁸ Prequel is a whole-genome sequencing based pcfDNA screening test that incorporates fetal fraction amplification and includes screening for microdeletions 22q11.2, 15q11.2, 1p36, 4p, and 5p.^{19–22} An encrypted tokenization process (Datavant, Phoenix, AZ, USA) was used to link the two datasets and to protect patient privacy in each dataset.²³ Expert determination was conducted to reduce the risk of re-identification from the linked dataset. The data used for this study were de-identified and did not meet the US Health and Human Services definition of human subjects research (HHS 46.102); therefore, this study did not require Institutional Review Board approval.

Study Population

The study population included patients who received pcfDNA screening from July 27, 2020, through January 31, 2023. Patients, who were under age 18 received testing in New York State or opted out of research, were excluded prior to linking with the Komodo Healthcare MapTM (Figure 1). After linking, patients with a multiple gestation pregnancy or an estimated pregnancy start date after October 31, 2022, were excluded. Continuous enrollment is a common inclusion criteria applied in closed claims-based studies to ensure complete capture of claims during the study period. Because this study consists of both closed and open claims, a proxy was used to increase the likelihood that study patients were enrolled in insurance for the entire duration of pregnancy and during the baseline period (see Figure 1 for details). Finally, patients with evidence of cancer during baseline or bone marrow or organ transplant any time before the current

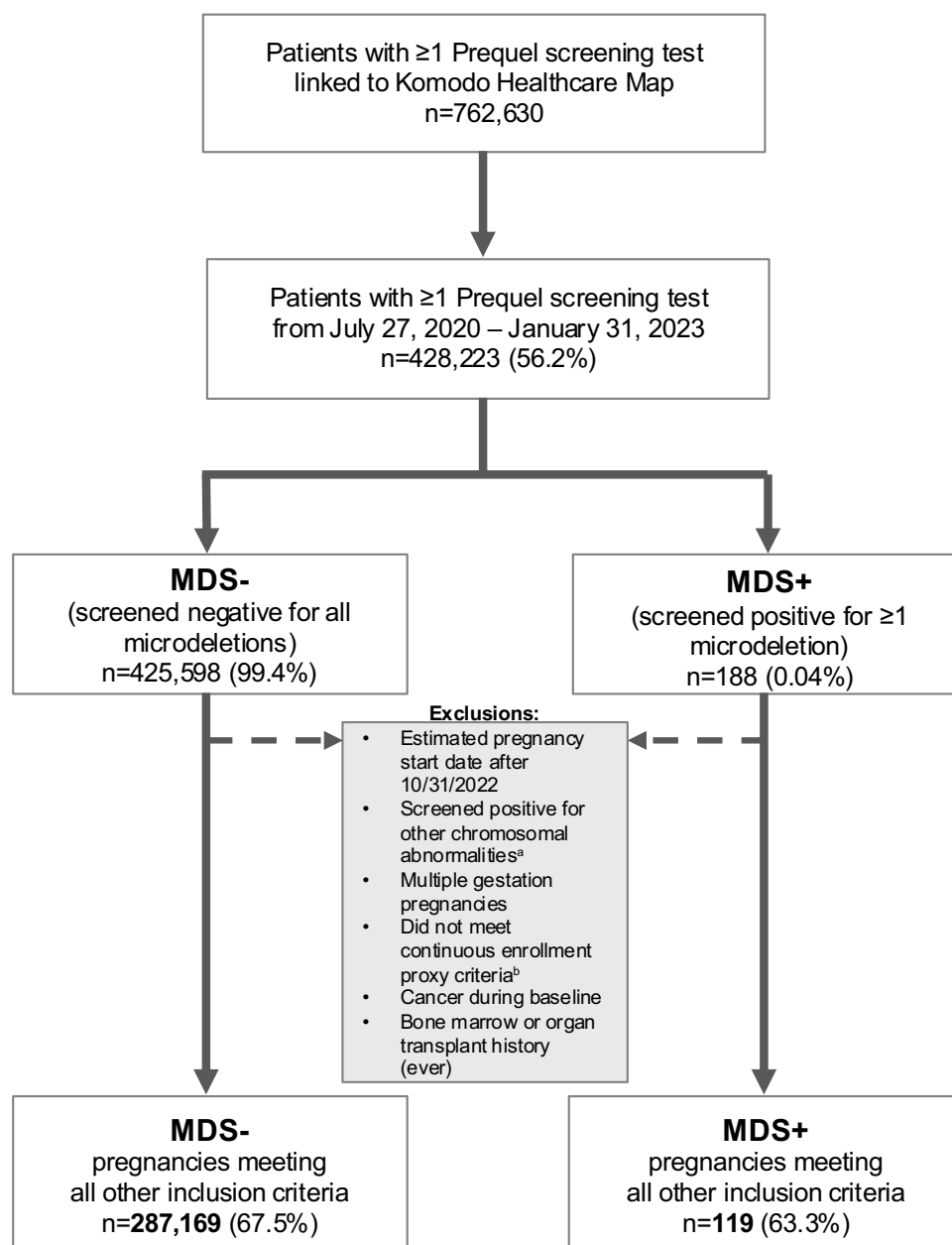


Figure 1 Cohort diagram and study exclusion criteria. ^aOther chromosomal abnormalities included monosomy or trisomy results for any autosomal chromosomes (1–22) or any sex chromosome abnormalities. In the MDS+ group, patients screening positive for multiple microdeletions were also excluded in this step. ^bFor the continuous enrollment proxy, we required: 1) at least one medical or pharmacy claim from 24 months prior to index date (baseline period) to 8 weeks after index date, and 2) at least one medical or pharmacy claim $\pm$ 4 weeks around Prequel test date, and 3) at least one pregnancy-related claim from index date to 42 weeks after index date (follow-up period). This was to ensure we were capturing most claims occurring during the study period.

Abbreviations: MDS+, microdeletion screen-positive; MDS-, microdeletion screen-negative.

pregnancy were excluded. Only one pregnancy per patient was included; if a patient had pcfDNA results from multiple pregnancies, the MDS+ pregnancy was selected or the first occurring pregnancy if all results were MDS-.

Patients were considered MDS+ if they screened positive for any microdeletion on the pcfDNA screen (22q11.2, 15q11.2, 1p36, 4p, or 5p). Patients were considered MDS- if they did not screen positive for any microdeletion. Patients with any other abnormal screening results (including autosomal or sex chromosome aneuploidies) on the pcfDNA screen were excluded from both groups. Of note, the microdeletion panel was run on all patients, but providers had to opt in to receive the results, so not all patients were informed of their screen status.

Study Period

The follow-up period used to determine study eligibility and outcomes was the estimated pregnancy period corresponding to each pcfDNA result. The start of pregnancy was estimated from the gestational age given by the provider on the pcfDNA test request form. The end of the follow-up period was the date of the first end-of-pregnancy event (code for delivery, birth, loss, or termination) occurring after the test date but no later than 42 weeks after the estimated pregnancy start. If there was no end-of-pregnancy event, the date of the last pregnancy-related claim within 42 weeks was used.

Baseline Characteristics

Patient demographics and clinical characteristics were captured on the test request form on the date of pcfDNA testing or were based on patient enrollment data in the Komodo Healthcare Map™ ([Supplementary Table S1](#)). The Charlson comorbidity index (CCI) and other comorbidities were determined from diagnosis and procedure codes in the 24-month baseline period.²⁴ Pregnancy history characteristics were determined using all available claims data prior to the current pregnancy ([Supplementary Table S1](#)).

Outcomes

The main outcomes of interest for this study were ultrasound findings, pregnancy complications, end-of-pregnancy events, and pregnancy management metrics in MDS+ and MDS- patients ([Supplementary Table S1](#)). Outcomes were determined during the follow-up period using diagnosis and procedure codes used in a previous claims-based study.²⁵ The following ultrasound findings were assessed using diagnosis codes referencing “maternal care” for the condition: suspected fetal congenital anomaly, suspected fetal chromosome abnormality, hydrops fetalis, abnormal ultrasound findings, inconclusive fetal viability, decreased fetal movements, abnormal heart rate/rhythm, other or unspecified fetal problems. Pregnancy complications identified for this study were gestational diabetes, preeclampsia, polyhydramnios, oligohydramnios, and FGR.

End-of-pregnancy events included elective termination, loss (miscarriage, stillbirth, intrauterine fetal demise, ectopic pregnancy, or molar pregnancy), live birth, or “unspecified pregnancy end”. The outcome was considered “unspecified pregnancy end” when a code indicated a delivery had taken place but was not specific enough to indicate the type of delivery, such as live birth or loss, and no other specific events were coded. In other cases, no claims or codes indicated a pregnancy end or delivery; these cases were considered unknown end-of-pregnancy events and were excluded from models. End-of-pregnancy outcomes were considered mutually exclusive, and if multiple events were coded during follow-up, the most specific event or the event coded first was typically used, except when that event was not medically probable (such as a live birth occurring before 20 weeks gestation). Separately, delivery type (vaginal or cesarean section) was also reported.

Pregnancy management metrics included ultrasounds, echocardiograms, Doppler studies, nonstress testing, prenatal visits, pcfDNA screening, stress testing, invasive diagnostic testing, specimen testing, and supervision of high-risk pregnancy ([Supplementary Table S1](#)).

Statistical Analyses

Descriptive statistics were reported as means, standard deviations (SDs), medians, and quartiles for continuous variables and as frequencies and proportions for categorical variables. The Comorbidity R package was used to determine the CCI for each patient.²⁶

For the primary analyses, we compared outcomes in MDS+ patients versus MDS- patients. Binary outcomes were modeled using logistic regression, and count outcomes (such as ultrasound counts) were modeled using Poisson regression with an offset (natural log of each individual’s follow-up time) to account for variable follow-up time and length of pregnancy by patient. Baseline characteristics that differed significantly (based on *t*-test or Fisher’s exact test) between MDS+ and MDS- were adjusted for in all multivariable models, which included history of high-risk pregnancy (yes, no, or no known history of prior pregnancy) and payer type (Commercial, Medicaid, Medicare, or Other).

Rates of pregnancy complications and end-of-pregnancy events were reported and modeled only among patients eligible for the event or where an end-of-pregnancy event was apparent. For example, complications such as gestational diabetes and preeclampsia are not typically screened or diagnosed before 20 weeks of gestation, so these outcomes were only modeled among the subset of patients whose pregnancy continued through at least 20 weeks. End-of-pregnancy events were only modeled among patients who had a known end-of-pregnancy event. Preterm birth models only included patients who had a known live birth event.

An exploratory subgroup analysis was conducted in the MDS+ group comparing pregnancy complications and outcomes among patients with 22q11.2 versus other microdeletions to understand the clinical significance of the other four, less studied microdeletions. For this analysis, p-values were calculated using *t*-tests for continuous variables or Fisher's exact tests for categorical variables, due to small sample size.

P-values < 0.05 were considered statistically significant. No corrections for multiple testing were imposed in this analysis. Analyses were conducted in R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). To preserve patient privacy, patient counts, percentages, and corresponding unadjusted odds ratios were masked if there were fewer than 11 patients with the condition.

Results

Cohort Characteristics

After exclusions, the study population included 119 MDS+ patients and 287,169 MDS- patients (Figure 1). The screen-positive rate for the five microdeletions included in the study was 0.04%. Of the 119 MDS+ patients, 59 (49.6%) screened positive for 22q11.2, 20 (16.8%) for 15q11.2, 15 (12.6%) for 1p36, 12 (10.1%) for 4p, and 13 (10.9%) for 5p.

At baseline, MDS+ and MDS- patients were similar in age, region, ethnicity, and comorbidities (Table 1). The two groups differed in the distribution of payer types ($p=0.03$) and the prevalence of previous high-risk pregnancy ($p=0.028$).

Table 1 Demographic and Clinical Characteristics by Microdeletion Screening Result Status

Characteristic	MDS-	MDS+	P-value
Total N	287,169	119	–
Baseline characteristics			
Maternal age at expected delivery date (years)			
Mean (SD)	30.9 (5.8)	30.9 (5.6)	0.986
Median (Q1 - Q3)	31.0 (27.0–35.0)	32.0 (26.5–35.0)	
Advanced maternal age			
Yes	84,101 (29.4%)	34 (28.6%)	0.920
No	201,650 (70.6%)	85 (71.4%)	
Missing	1,418	0	
Region			
Midwest	64,514 (23.1%)	26 (21.8%)	0.582
South	131,936 (47.2%)	58 (48.7%)	
West	42,647 (15.3%)	22 (18.5%)	
Northeast	40,531 (14.5%)	13 (10.9%)	
Missing	7,541	0	
Payer			
Commercial	200,493 (69.8%)	>59 (>49.6%)	0.030
Medicaid	80,742 (28.1%)	38 (31.9%)	
Medicare	1,690 (0.6%)	<11 (<9.2%)	
Other	4,244 (1.5%)	<11 (<9.2%)	

(Continued)

Table 1 (Continued).

Characteristic	MDS-	MDS+	P-value
Ethnicity			
African or African American	35,868 (12.5%)	15 (12.6%)	0.455
Ashkenazi Jewish	2,386 (0.8%)	0 (0%)	
Asian/Pacific Islander	13,430 (4.7%)	<11 (<9.2%)	
European	28,420 (9.9%)	12 (10.1%)	
French Canadian or Cajun	376 (0.1%)	0 (0%)	
Hispanic	32,529 (11.3%)	18 (15.1%)	
Middle Eastern	2,197 (0.8%)	<11 (<9.2%)	
Native American	1,304 (0.5%)	0 (0%)	
Other/Mixed White	100,811 (35.1%)	>31 (>26.1%)	
Unknown	69,848 (24.3%)	21 (17.6%)	
CCI categories			
0	252,825 (88.0%)	>94 (>79.0%)	0.301
1	26,546 (9.2%)	14 (11.8%)	
2+	7,798 (2.7%)	<11 (<9.2%)	
Other comorbidities			
Congenital heart defects	1,547 (0.5%)	<11 (<9.2%)	0.474
Hypertension	15,080 (5.3%)	<11 (<9.2%)	0.411
Uterine fibroids	5,887 (2.1%)	<11 (<9.2%)	0.738
PCOS	11,210 (3.9%)	<11 (<9.2%)	1
Pregnancy history			
Previous pregnancy	157,750 (54.9%)	67 (56.3%)	0.783
Non-elective pregnancy loss	49,506 (31.4%)	20 (29.9%)	0.895
Elective termination	6,110 (3.9%)	0 (0%)	0.116
Preeclampsia	10,647 (6.7%)	<11 (<16.4%)	0.459
Gestational diabetes	12,291 (7.8%)	<11 (<16.4%)	0.648
High-risk pregnancy	133,101 (84.4%)	>56 (>83.5%)	0.028
Fetal growth restriction	16,370 (10.4%)	11 (16.4%)	0.108
Multiple gestation	3,041 (1.9%)	0 (0%)	0.642
Pregnancy complications	12,090 (7.7%)	<11 (<16.4%)	0.818
Previous delivery	110,551 (38.5%)	56 (47.1%)	0.060
Preterm birth	7,917 (7.2%)	<11 (<19.6%)	0.120
Characteristics at pcfDNA testing			
Year of test			
2020	46,249 (16.1%)	31 (26.1%)	0.013
2021	117,979 (41.1%)	>42 (>35.3%)	
2022	115,977 (40.4%)	35 (29.4%)	
2023	6964 (2.4%)	<11 (<9.2%)	
Gestational age (weeks)			
Mean (SD)	13.0 (3.7)	14.3 (5.0)	0.009
Median (Q1 - Q3)	12.0 (10.9–13.4)	12.6 (11.0–15.3)	
BMI			
Mean (SD)	29.0 (7.4)	29.6 (6.6)	0.456
Median (Q1 - Q3)	27.5 (23.5–33.3)	28.2 (24.7–33.9)	
Missing	99,284 (34.6%)	38 (31.9%)	

(Continued)

Table 1 (Continued).

Characteristic	MDS-	MDS+	P-value
BMI category			
Underweight	4,470 (1.6%)	<11 (<9.2%)	0.689
Healthy weight	64,959 (22.6%)	24 (20.2%)	
Overweight	55,943 (19.5%)	29 (24.4%)	
Obese	85,970 (29.9%)	37 (31.1%)	
Unknown	75,827 (26.4%)	>18 (>15.1%)	
Pregnancy conceived using IVF			
No	281,127 (97.9%)	>108 (>90.8%)	1
Yes	6,042 (2.1%)	<11 (<9.2%)	
Include microdeletion report results			
No	248,209 (86.4%)	81 (68.1%)	<0.001
Yes	38,960 (13.6%)	38 (31.9%)	
Testing indication(s) [†]			
Advanced maternal age	51,142 (17.8%)	18 (15.1%)	0.549
Abnormal ultrasound	5,151 (1.8%)	<11 (<9.2%)	0.001
Abnormal maternal serum screen	1,592 (0.6%)	0 (0%)	1
Chromosome abnormality suspected	1,377 (0.5%)	<11 (<9.2%)	0.436
Previous pregnancy/child with chromosome abnormality	1,854 (0.6%)	<11 (<9.2%)	0.180
Family history	2,715 (0.9%)	0 (0%)	0.633
Supervision of other high-risk pregnancy	27,642 (9.6%)	20 (16.8%)	0.012
Supervision of normal pregnancy	101,111 (35.2%)	29 (24.4%)	0.013
Missing indication	103,616 (36.1%)	48 (40.3%)	0.341
Fetal fraction			
Mean (SD)	0.21 (0.08)	0.20 (0.08)	0.223
Median (Q1 - Q3)	0.20 (0.15–0.25)	0.19 (0.14–0.23)	

Notes: P-values were calculated using t-test for continuous numeric variables and Fisher's exact test for categorical variables. Cell sizes <11 were masked to protect patient privacy. [†] Providers could select multiple testing indications when placing the pcfDNA testing order.

Abbreviations: MDS-, microdeletion screen-negative; MDS+, microdeletion screen-positive; SD, standard deviation; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile); PCOS, polycystic ovary syndrome; pcfDNA, prenatal cell-free DNA; BMI, body mass index; IVF, in vitro fertilization.

At testing, MDS+ patients were more likely to have a testing indication related to abnormal ultrasound ($p=0.001$) or supervision of high-risk pregnancy ($p=0.012$), and more likely to have opted in to receiving microdeletion results ($p<0.001$) compared to MDS- patients (Table 1).

Pregnancy Complications and End-of-Pregnancy Events

During pregnancy, MDS+ patients were more likely to have polyhydramnios (18.5% vs. 3.4%; odds ratio [OR]=6.3 [95% CI: 3.8–10.1]; $p<0.001$), and FGR (22.2% vs. 10.4%; OR=2.4 [95% CI: 1.5–3.7]; $p<0.001$) compared to MDS- patients, but did not have higher odds of gestational diabetes or preeclampsia (Figure 2). Among patients with an end-of-pregnancy event, MDS+ patients were significantly more likely to experience pregnancy loss (OR=3.2 [95% CI: 1.3–6.3]; $p=0.004$), terminate the pregnancy (OR=22.2 [95% CI: 8.6–46.8]; $p<0.001$), and deliver by caesarean section (OR=1.6 [95% CI: 1.1–2.4]; $p=0.02$) compared to MDS- patients. MDS+ patients were also more likely to have an unspecified pregnancy end, ie, a delivery/childbirth-related code without specification of the birth outcome ($p=0.048$). MDS+ patients were less likely to have live births, and among those with a live birth, were more likely to have a preterm delivery (25.0% vs. 15.4%; OR=1.8 [95% CI: 1.0–3.0]; $p=0.04$) compared to MDS- (Figure 2).

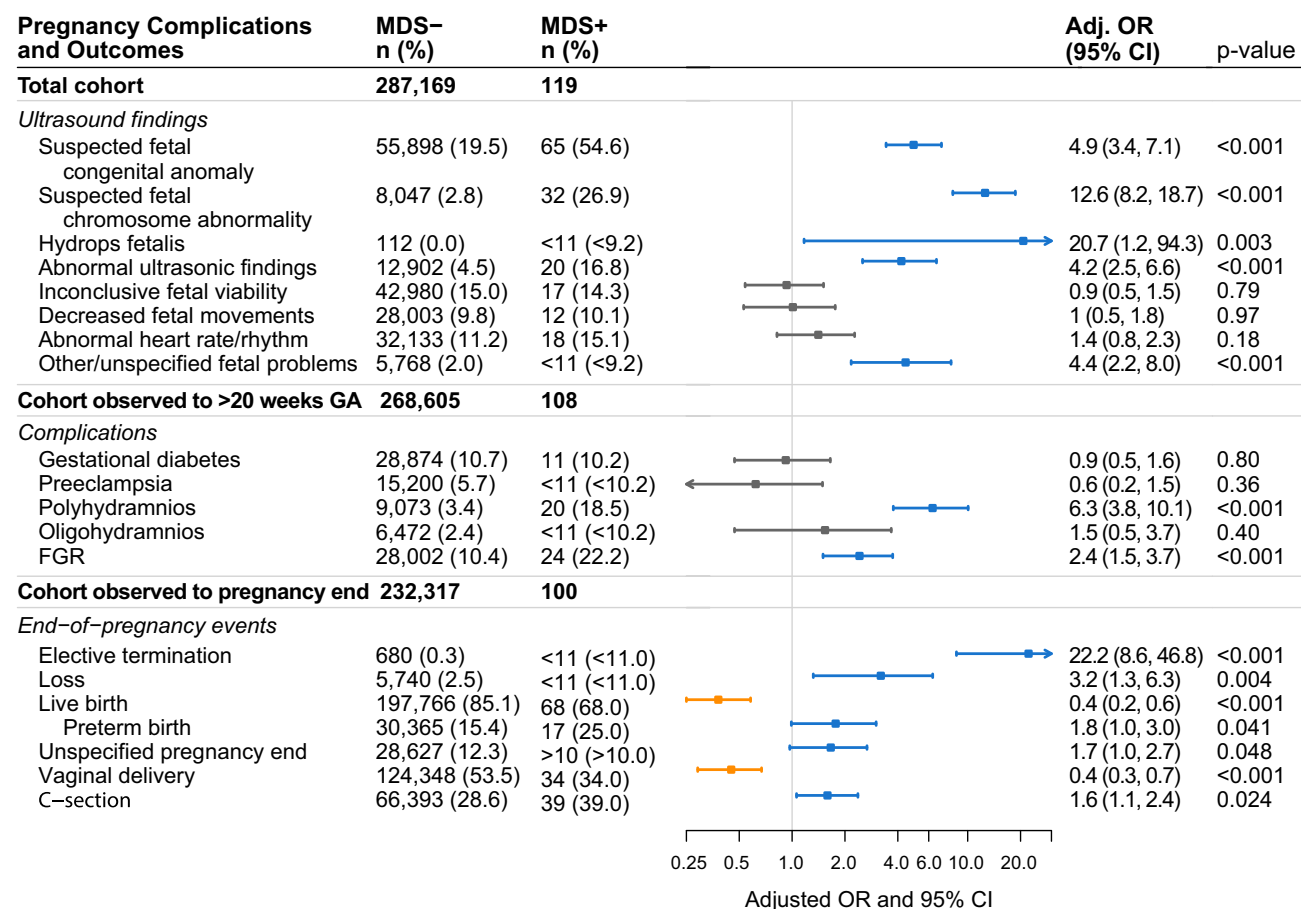


Figure 2 Logistic regression modeling results comparing odds of outcomes and complications in MDS+ versus MDS- pregnancies.

Abbreviations: MDS-, microdeletion screen-negative; MDS+, microdeletion screen-positive; GA, gestational age; Adj. OR, adjusted odds ratio; CI, confidence interval; FGR, fetal growth restriction.

Pregnancy Management

MDS+ patients were more likely to have at least one Doppler study, echocardiogram, and prenatal visit during pregnancy compared to MDS- patients (Table 2). MDS+ patients were also more likely to have invasive diagnostic testing

Table 2 Pregnancy Management by Microdeletion Screening Result Status

Pregnancy Management Outcomes	MDS-	MDS+	Adjusted OR or RR (95% CI)	P-value
Total cohort	287,169	119		
Follow-up time, weeks				
Mean (SD)	35.8 (7.0)	33.1 (7.8)		
Median (Q1 - Q3)	38.4 (36.4–39.3)	36.9 (26.7–38.7)		
Total person-weeks	10,300,000	3,940		
Ultrasounds				
N (%) with at least one	236,263 (82.3%)	103 (86.6%)	1.32 (0.80, 2.34)	0.300
Counts during follow-up				
Mean (SD)	5.0 (3.5)	6.2 (4.1)		
Median (Q1 - Q3)	4.0 (3.0–7.0)	5.0 (3.0–8.0)		
Total counts	1,180,000	634		
Follow-up time for those with ultrasounds	8,594,967	3,462		
Rate per 10 person-weeks	1.37	1.83	1.33 (1.23, 1.43)	<0.001

(Continued)

Table 2 (Continued).

Pregnancy Management Outcomes	MDS-	MDS+	Adjusted OR or RR (95% CI)	P-value
Echocardiograms				
N (%) with at least one	22,301 (7.8%)	37 (31.1%)	5.34 (3.58, 7.82)	<0.001
Counts during follow-up				
Mean (SD)	1.4 (1.5)	1.9 (1.3)		
Median (Q1 - Q3)	1.0 (1.0–1.0)	1.0 (1.0–2.0)		
Total counts	30,200	71		
Follow-up time for those with echocardiograms	816,854	1,290		
Rate per 10 person-weeks	0.37	0.55	1.49 (1.17, 1.86)	<0.001
Doppler studies				
N (%) with at least one	40,811 (14.2%)	46 (38.7%)	3.76 (2.58, 5.42)	<0.001
Counts during follow-up				
Mean (SD)	2.9 (3.1)	3.4 (2.9)		
Median (Q1 - Q3)	1.0 (1.0–4.0)	2.0 (1.0–4.0)		
Total counts	119,000	154		
Follow-up time for those with Doppler studies	1,509,365	1,573		
Rate per 10 person-weeks	0.79	0.98	1.23 (1.04, 1.43)	0.011
Nonstress tests				
N (%) with at least one	136,320 (47.5%)	59 (49.6%)	1.06 (0.74, 1.52)	0.762
Counts during follow-up				
Mean (SD)	3.8 (3.5)	5.6 (4.6)		
Median (Q1 - Q3)	3.0 (1.0–5.0)	4.0 (2.0–8.5)		
Total counts	523,000	329		
Follow-up time for those with nonstress test	5,172,105	2,185		
Rate per 10 person-weeks	1.01	1.51	1.48 (1.33, 1.65)	<0.001
Prenatal visits [†]				
N (%) with at least one	246,004 (85.7%)	95 (79.8%)	0.62 (0.40, 1.00)	0.039
Counts during follow-up				
Mean (SD)	6.9 (5.2)	7.4 (6.2)		
Median (Q1 - Q3)	6.0 (3.0–10.0)	6.0 (3.0–10.0)		
Total counts	1,700,000	710		
Follow-up time for those with visits	8,927,911	3,169		
Rate per 10 person-weeks	1.90	2.24	1.15 (1.07, 1.24)	<0.001
Other pregnancy management metrics, N (%)				
Fetal stress test	205 (0.1%)	0 (0%)	-	-
Specimen testing	2,713 (0.9%)	17 (14.3%)	17.78 (10.25, 28.95)	<0.001
Supervision of high-risk pregnancy	139,331 (48.5%)	60 (50.4%)	1.03 (0.72, 1.49)	0.869
Invasive diagnostic testing	1,477 (0.5%)	16 (13.4%)	30.96 (17.54, 51.11)	<0.001

Notes: Binary outcomes were modeled using logistic regression, resulting in odds ratio estimates and corresponding p-values. Rates were modeled using Poisson regression with an offset to account for unequal follow-up time across patients, resulting in rate ratio estimates and corresponding p-values. Person-weeks, which is a summation of all the eligible person-time in which an outcome could have occurred, was used as the denominator for Poisson regression models. Only patients with counts >0 were included in the Poisson regression models. All models were adjusted for payer type and history of high-risk pregnancy. [†]Prenatal visits defined as encounters with a diagnosis code of either Z34.xx (Supervision of normal pregnancy) or O09.xx (Supervision of high-risk pregnancy).

Abbreviations: MDS-, microdeletion screen-negative; MDS+, microdeletion screen-positive, OR, odds ratio; RR, rate ratio; CI, confidence interval; SD, standard deviation; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile).

procedures during pregnancy (13.4% vs. 0.5%; OR=30.96 [95% CI: 17.54–51.11]; p<0.001) and specimen testing (14.3% vs. 0.9%; OR=17.78 [95% CI: 10.25–28.95]; p<0.001). Additionally, the rates of ultrasounds, echocardiograms, Doppler studies, nonstress tests, and prenatal visits were all significantly higher in MDS+ pregnancies compared to MDS- pregnancies when accounting for variable follow-up time (Table 2). In particular, MDS+ patients had an approximately

50% higher rate of both echocardiograms (risk ratio [RR]=1.49 [95% CI: 1.17, 1.86]; $p<0.001$) and nonstress tests (RR=1.48 [95% CI: 1.33, 1.65]; $p<0.001$) compared to MDS- patients.

Subgroup Analysis

Among MDS+ patients, 31/59 (52.5%) of the 22q11.2 group and 37/60 (61.7%) of the other microdeletions group had evidence of live birth, which was not significantly different (Table 3). Though sample sizes were small, statistical testing indicated patients screening positive for 22q11.2 were not more or less likely to experience polyhydramnios, FGR, pregnancy loss, termination, C-section, or preterm birth compared to the other microdeletions.

Table 3 Pregnancy Complications and Outcomes by Microdeletion Type

Pregnancy Complications and Outcomes	22q11.2	Other (15q11.2, 1p36, 4p, 5p)	P-value
Total cohort	59	60	
Length of follow-up time, weeks			
Mean (SD)	31.8 (8.4)	34.4 (6.9)	0.061
Median (Q1 - Q3)	35.6 (24.4–38.6)	37.6 (32.3–39.0)	
Ultrasound findings			
Suspected fetal congenital anomaly	36 (61.0%)	29 (48.3%)	0.199
Suspected fetal chromosome abnormality	16 (27.1%)	16 (26.7%)	1
Hydrops fetalis	0 (0%)	<11 (<18.3%)	1
Abnormal ultrasound findings	~	~	0.053
Inconclusive fetal viability	~	~	0.114
Decreased fetal movements	~	~	0.125
Abnormal heart rate/rhythm	~	~	0.799
Other/unspecified fetal problems	~	~	0.054
Cohort observed to ≥ 20 weeks GA	~	~	
Complications of pregnancy			
Gestational diabetes	~	~	1
Preeclampsia	~	~	0.334
Polyhydramnios	~	~	0.217
Oligohydramnios	~	~	1
FGR	<11 (<22.0%)	>13 (>22.4%)	0.649
Cohort observed to end of pregnancy	~	~	
GA at end of pregnancy, weeks			
Mean (SD)	32.9 (8.0)	34.8 (6.8)	0.213
Median (Q1 - Q3)	36.8 (30.4–38.7)	37.7 (34.8–39.0)	
End-of-pregnancy events			
Elective termination	~	~	0.410
Loss	~	~	0.7
Live birth	31	37	1
Unspecified pregnancy end	~	~	0.448
Delivery type			
Vaginal delivery	12	22	0.142
C-section	20	19	0.418

(Continued)

Table 3 (Continued).

Pregnancy Complications and Outcomes	22q11.2	Other (15q11.2, 1p36, 4p, 5p)	P-value
Live birth cohort	31	37	
Preterm birth	~	~	0.265
Gestational age at live birth, weeks			
Mean (SD)	37.2 (3.4)	37.8 (2.7)	0.419
Median (Q1 - Q3)	38.3 (36.8–38.9)	38.3 (37.4–39.4)	

Notes: P-values were calculated using t-tests for continuous variables and Fisher's exact test for categorical variables. Cell sizes <11 and cells that allow for back-calculation of those <11 were masked with "~" to protect patient privacy.

Abbreviations: MDS-, microdeletion screen-negative; MDS+, microdeletion screen-positive; FGR, fetal growth restriction; GA, gestational age; SD, standard deviation; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile).

Discussion

This study linked pcfdNA screening results data with de-identified claims data to compare pregnancy outcomes and management in a cohort of 119 MDS+ patients compared to 287,169 MDS- patients. Consistent with previous studies, we found that MDS+ patients had high rates of ultrasound abnormalities, pregnancy loss, and preterm birth. Further, we showed that these rates are significantly elevated when compared to an MDS- control group. Additionally, we demonstrated that MDS+ patients experienced increased pregnancy management compared to MDS- patients, a result that has not been previously reported.

Microdeletions 22q11.2, 15q11.2, 1p36, 4p, or 5p are associated with severe outcomes, including congenital heart defects (common in 22q11.2 deletion syndrome),^{5,27} craniofacial abnormalities (common in 4p deletion syndrome),^{8,28} and cerebellar hypoplasia (common in 5p deletion syndrome).^{4,9,29} Consistent with these observations, patients screening positive for microdeletions 22q11.2, 15q11.2, 1p36, 4p, or 5p in our study were significantly more likely to have diagnosis codes for hydrops fetalis, abnormal ultrasound findings, suspected fetal congenital anomaly, or chromosome abnormality compared to screen-negative patients after adjustment for relevant covariates, suggesting that our claims-based approach adequately captured associated outcomes.

Polyhydramnios has been frequently reported in microdeletion-affected pregnancies, particularly those with 22q11.2 deletion, with reported rates ranging from 9.2% to 38.1%.^{5,13,27,30} In our study, 18.5% of MDS+ patients experienced polyhydramnios, corresponding to 6.3-fold higher odds when compared to MDS- patients. Oligohydramnios has been frequently reported in both 4p and 15q11.2 deletions.^{8,31} While we did observe a higher rate of oligohydramnios in MDS+ patients compared to MDS-, the difference between the groups was not statistically significant.

FGR is one of the most commonly reported ultrasound findings among 22q11.2, 1p36, 4p, and 5p, with reported rates ranging from 8.5% in a literature review of 47 5p deletion cases⁴ to over 75% in a review of 118 cases of 4p deletion.⁸ We observed a diagnosis of FGR in 22.2% of MDS+ patients, corresponding to a 2.4-fold increase in odds compared to MDS- patients.^{4,8} Similarly, a recent clinical validation study focused on 22q11.2 screen-positive patients that partially overlapped with those in this study cohort reported an FGR rate of 10/53 (18.9%).¹³ The 22q11.2 region contains multiple genes crucial for embryonic development, like *TBX1*,³² which may help explain the FGR findings. In this study, cases of FGR were observed across all microdeletion types except 1p36.

Pregnancy loss and elective termination may be under-captured in claims data since both sometimes occur without insurance billing. Despite this limitation, we observed that MDS+ patients had significantly higher odds of pregnancy loss (a three-fold increase) and elective termination (over 20-fold increase) compared to MDS- patients. Pregnancy loss, including miscarriage and stillbirth, has been documented in some microdeletion-affected pregnancies. The pregnancy loss rate was 9.1% in a recent study of 22q11.2 microdeletion screen-positive patients with outcomes available,¹³ and 4% in a 2018 study of 22q11.2, 15q11.2, 1p36, and 5p microdeletions.³³ While the rate of loss in our study was <11% among pregnancies with a known endpoint, the subgroup analysis showed the frequency of loss in the 22q11.2 screen-positive group was not significantly different compared to the group combining the four other microdeletions. High rates of

termination across microdeletion-affected pregnancies have been widely reported, in some studies >50%, particularly outside of the US.^{5,8–10} This is a complicating factor when determining how many pregnancies would have resulted in miscarriage or stillbirth.

We also found that 25% of MDS+ live births were preterm. Preterm birth has been reported in 22q11.2 and 15q11.2 deletions, with rates of 16–18%.^{13,31} In the US general population, preterm birth accounts for about 10% of live births,³⁴ yet our study found an elevated preterm birth rate of 15.4% in the screen-negative control group. Nonetheless, among patients with live births, MDS+ patients had significantly higher odds (OR=1.8) of preterm birth compared to the control group after adjustment for history of high-risk pregnancy and payer type.

A large but comparable proportion of patients in each group had no known pregnancy end or outcome captured in the claims data (19.1% of MDS- and 16.0% of MDS+). This is likely due to the use of an open claims dataset, which may be missing claims if deliveries or other pregnancy-ending events occurred at facilities not captured in the Komodo Healthcare MapTM. Among patients with a known pregnancy end, another significant portion had an “unspecified pregnancy end”. This outcome was more common in the MDS+ group. Interestingly, billing guidance by ACOG suggests that both spontaneous and induced abortions occurring after 20 weeks gestation be reported using a non-specific delivery code,³⁵ and therefore late pregnancy losses and terminations may be overrepresented in this outcome category.

In the pregnancy management analysis, we found that MDS+ patients had higher rates of echocardiograms, which may be due to the association between 22q11.2 microdeletion and congenital heart defects.^{4–6,10} Additionally, MDS+ patients had higher rates of ultrasounds, nonstress tests, and prenatal visits, suggesting these pregnancies received increased monitoring. MDS+ patients were also more likely to receive additional diagnostic and specimen testing procedures. Of note, only about 32% of MDS+ patients were informed of their screen-positive status on the pcfDNA screening test, ie, the provider specifically requested microdeletion results when ordering the test. While some increased management may be due to receipt of positive pcfDNA results, other apparent abnormalities detected during pregnancy care may have led to further testing and monitoring.

In 2022, ACMG published guidelines conditionally recommending that pcfDNA screening for 22q11.2 deletion be offered to all patients, but stated that evidence was insufficient to recommend routine screening for other microdeletions.¹⁶ ACOG does not currently recommend pcfDNA screening for microdeletions, citing a lack of clinical validity, including low positive predictive value for these disorders.¹⁵ However, a recent study on 22q11.2 detected by the same pcfDNA screen used in this study demonstrated a positive predictive value of 100.0%.¹³ Given that both ACMG and ACOG cite the lack of clinical validity for microdeletions other than 22q11.2, the data presented in this study showing that patients screening positive for any of five microdeletions experienced elevated rates of complications including polyhydramnios, FGR, pregnancy loss, and preterm birth is particularly compelling. Our exploratory analysis comparing complication rates in 22q11.2 versus other microdeletions showed no significant differences between the two groups, suggesting that complication rates for other microdeletions may be comparable to that of 22q11.2.

Strengths and Limitations

This study took a novel approach to investigate microdeletions using claims data, resulting in over 100 screen-positive patients followed longitudinally to characterize the entire clinical journey of their pregnancy. This study also included a control group of over 287,000 screen-negative patients, establishing benchmark rates of pregnancy complications, outcomes, and management for the population of patients who received pcfDNA screening from 2020 to 2023. This study was large compared to previous microdeletion studies, which are often case series or have no control group available for hypothesis testing with adjustment for confounders. Additionally, this was the first microdeletion study that investigated pregnancy management beyond additional diagnostic testing.

This study had several limitations. First, because pcfDNA screening is typically offered beginning at 10 weeks of gestation, pregnancies ending prior to screening were not included, therefore the true rate of pregnancy loss is likely underestimated. However, this limitation is present in most pregnancy studies. Second, we were unable to confirm that the microdeletion screen-positive pregnancies were true positives, as few patients underwent invasive diagnostic testing,

and the results of further testing are not available in claims data. However, the distribution of fetal fraction in MDS+ was favorable, with at least 75% of samples having fetal fraction $\geq 14\%$. Even without confirmation of true positives, results of this study are clinically actionable because they suggest that simply screening positive for a microdeletion on pcfDNA, independent of other risk factors, is associated with increased risk of pregnancy complications and adverse outcomes.

The nature of insurance claims data presents additional challenges. We were unable to link mother and infant records, so we could not evaluate infant outcomes after delivery. Billing codes may be misused or lack necessary specificity, potentially leading to misclassification of clinical characteristics and outcomes.³⁶ Privacy restrictions prevented the reporting of any cell sizes <11 , which made it difficult to report rare outcomes or examine differences between individual microdeletions. Additionally, terminations and pregnancy losses may be coded similarly in claims, or may be less accurately coded than live births.^{37,38} In some cases, these outcomes may not be coded if they happened early at home (in the case of some miscarriages) or were paid for out-of-pocket (in the case of some terminations).

Conclusions

In this administrative claims-based study, pregnant patients screening positive for microdeletions 22q11.2, 15q11.2, 1p36, 4p, or 5p on pcfDNA had higher rates of ultrasound abnormalities, including polyhydramnios and FGR, and experienced higher rates of pregnancy loss and preterm birth compared to patients screening negative for all chromosomal abnormalities. MDS+ pregnancies were also more closely monitored, undergoing higher rates of prenatal visits, invasive testing, ultrasounds, echocardiograms, and nonstress tests. Results from this study suggest that screening for microdeletions has clinical utility.

Abbreviations

ACMG, American College of Medical Genetics; ACOG, American College of Obstetricians and Gynecologists; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; FGR, fetal growth restriction; GA, gestational age; IVF, in vitro fertilization; MDS+, microdeletion screen-positive; MDS-, microdeletion screen-negative; OR, odds ratio; pcfDNA, prenatal cell-free DNA; PCOS, polycystic ovary syndrome; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile); RR, rate ratio; SD, standard deviation.

Data Sharing Statement

The underlying data that support the findings of this study were sourced from Myriad Genetics and Komodo Health. Summary data and code lists are available from the Myriad research team upon request. If any researcher requires access to the analytic files that were derived from the Komodo Health database, a third-party use agreement must be executed by all involved parties.

Ethics Approval and Informed Consent

This study utilized de-identified data obtained in compliance with HIPAA regulations. Consequently, the study did not meet the US Department of Health and Human Services' definition of research involving human subjects (45 CFR 46.102). Therefore, it was not submitted for Institutional Review Board approval, nor did it require consent to participate. Additionally, the study adhered to the ethical principles outlined in the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

DCM, DC, SP, and KJT are current employees of Myriad Genetics, Inc., from which they receive salary and stock. The authors report no other conflicts of interest in this work.

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