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The Annual Report on Postnatal Diagnostic Testing in Victoria, 2021

Reproductive Epidemiology group

Genetics theme

Murdoch Children's Research institute

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This report is produced by the **Reproductive Epidemiology group** in the Genetics theme at the MCRI. For more information about us, go to our page at *https://www.mcri.edu.au/reproductiveepidemiology*

How to cite this report: Pynaker C, Hui L, Halliday J. *Report on Postnatal Diagnostic Testing in Victoria, 2021*, The Victorian Postnatal Diagnosis Database, Murdoch Children's Research Institute 2022. doi: 10.25374/MCRI.20479512

Ethics approval for this data collection was provided by the Royal Children's Hospital (RCH) Human Research Ethics Committee (HREC) on 17 December 2020 (Ref. No. 31135) and Monash Health local governance authorisation on 17 December 2020 (Ref. No. SSA/42279/RCHM-2020).

Funding: The following institutions have contributed support to the work of the Victorian Prenatal Diagnosis Data Collection: National Health and Medical Research Council (NHMRC), Medical Research Future Fund (MRFF), Murdoch Children's Research Institute (MCRI) and the VIC Department of Health.

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Background

The most common cause of spontaneous miscarriage is aneuploidy. When women experience a pregnancy loss, postnatal chromosome analysis may be offered, particularly in the setting of recurrent miscarriage. Molecular karyotyping with chromosomal microarrays is preferred over G-banded karyotype for postnatal samples as there is no requirement for cell culture, and hence failure rates are low. This report complements the Victorian Prenatal Diagnosis Report, providing results of postnatal chromosome testing in 2021 for women resident in Victoria, Australia. This report includes samples from placenta, umbilical cord, and "products of conception" (POC) but no paediatric samples.

We acknowledge our collaborators – the Victorian Clinical Genetics Service and Monash Pathology – who contributed the data contained in this report.

Definitions

Major chromosome conditions: autosomal trisomies, autosomal monosomies, polyploidy, sex chromosome aneuploidies, pathogenic copy number variants (CNVs), unbalanced rearrangements, gestational trophoblastic disease, and high-level mosaicism.

Minor chromosome conditions: genomic CNVs of uncertain or unknown significance, long continuous stretches of homozygosity (LCSH), uniparental disomy (UPD), confined placental mosaicism (CPM), and balanced rearrangements.

Diagnostic yield: the percentage of women with a major fetal chromosome condition confirmed on diagnostic testing as a proportion of total tests.

Positive non-invasive prenatal testing (NIPT) result: 'increased chance', 'high risk', 'aneuploidy detected' or other result indicating an increased probability of a chromosome condition in the pregnancy.

Classification of genomic copy number variants (CNVs): CNVs were classified as *pathogenic, likely pathogenic, uncertain, or unknown significance, likely benign, or benign* according to the clinical laboratory interpretation, which is guided by the American College of Medical Genetics standards and guidelines for interpretation and reporting of copy number variants.[1, 2]

Variant of uncertain or unknown significance (VUS): CNV with uncertain, or unknown clinical significance as classified by the reporting laboratory

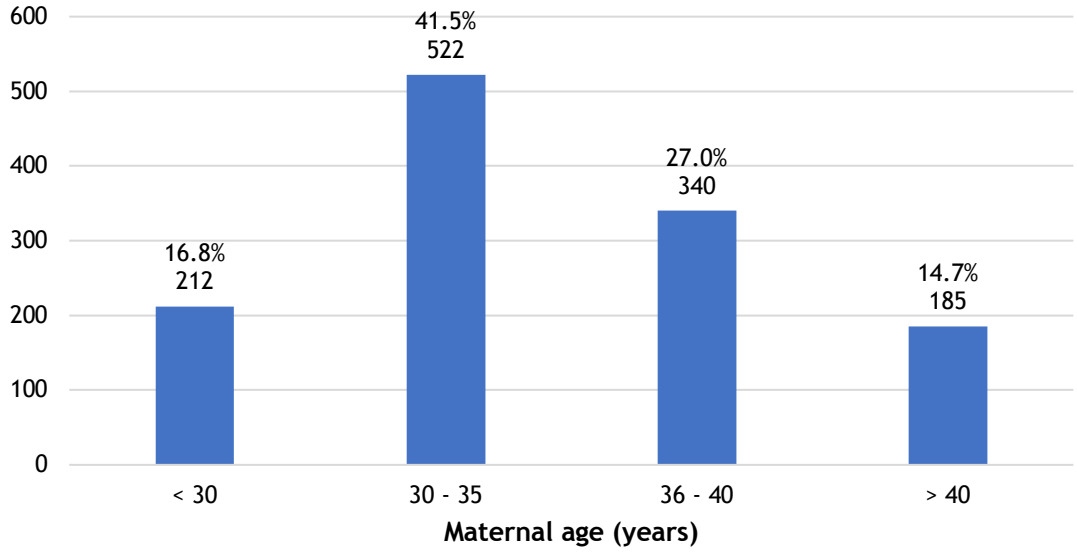
Summary statistics

In 2021, 1259 postnatal samples were referred for diagnostic testing. Of these, 3.8% (48/1259) were found through record linkage to also have had a prenatal diagnostic test in the same pregnancy. Most samples (95.9%) were evaluated by chromosomal microarray.

Maternal age

Maternal age at the time of diagnostic testing was calculated. The most common maternal age group was 30-35 years (**Figure 1**).

Figure 1. Maternal age at diagnostic test date



Specimen types

Postnatal specimens included 1010 "POC" samples (not otherwise specified), 165 fetal tissue samples, and 48 umbilical cord samples (**Table 1**). Pregnancy outcome was inconsistently recorded in the clinical referrals for testing: a livebirth was presumed in 23 (1.8%) of postnatal samples based on the clinical indication for testing, e.g., where testing was performed to investigate fetoplacental mosaicism, such as when a positive NIPT result is followed by a 'normal' karyotype result on amniocentesis (n=13).

Table 1. Specimen types

Specimen types	n (%)
'POC' (unspecified)	1010 (80.2)
Fetal (fetal tissue, rib/cartilage, skin, spleen)	165 (13.1)
Umbilical cord or cord blood	48 (3.8)
Placenta (biopsy, cyst, villus)	32 (2.5)
Multiple samples	4 (0.3)
Total	**1259 (100.0)**

Gestational age

Gestational age (GA) was available for 631 (50.1%) of specimens. Approximately one in five tests were performed between 14- and 23-weeks' gestation. (**Table 2**).

Table 2. Gestational age

Gestational age (weeks)	n (%)
<14	281 (22.3)
14 - 23	270 (21.4)
≥ 24	80 (6.4)
Missing data	628 (49.9)
Total	**1259 (100.0)**

Clinical indications for testing

Testing indications were recorded according to the written clinical referral. Independent verification of the indications for testing was not performed. More than one indication could be recorded for each sample. Consequently, there were 1429 indications recorded for 1259 postnatal samples.

The most common reason for diagnostic testing was fetal loss at an unspecified gestation (20.5%), followed by pregnancy loss at < 20wks gestation (18.8%), and fetal abnormality on ultrasound (17.8%)(**Table 3**).

Table 3. Indications for diagnostic testing

Indication	n (%)
Fetal loss, gestation unspecified	293 (20.5)
Pregnancy loss at < 20 weeks' gestation[1]	268 (18.8)
Fetal abnormality on antenatal ultrasound[2]	254 (17.8)
Previous or 'recurrent' miscarriage[3]	222 (15.5)
Termination of pregnancy	105 (7.3)
Positive NIPT result	87 (6.1)
Stillbirth, fetal death in utero, or preterm prelabour rupture of membranes ≥ 20 weeks	78 (5.5)
High chance first or second trimester screening	17 (1.2)
Other[4]	105 (7.3)
Total	**1429 (100.0)**

NIPT, non-invasive prenatal testing

[1]Indications for miscarriages < 20 weeks included: 'miscarriage', 'missed abortion', 'preterm premature rupture of membranes', and 'fetal demise'.

[2]Fetal abnormality on antenatal ultrasound included a structural abnormality, isolated increased nuchal translucency , and isolated absent nasal bone.

[3]'Recurrent' miscarriages included all miscarriages described as 'recurrent' by the clinical referrer.

[4]Other included unexpected congenital anomaly at birth, failed NIPT, negative ('low chance') NIPT, neonatal death, no clinical notes, repeat testing (not specified), single gene condition, and history of chromosomal condition.

Chromosome results

Of the 1259 total postnatal tests, 572 detected a major chromosome condition, resulting in a diagnostic yield of 45.4%.

The most common autosomal trisomies were Trisomy 16 (5.2%), Trisomy 21 (4.4%), Trisomy 22 (3.4%), Trisomy 15 (2.5%), Trisomy 18 (2.3%), and Trisomy 13 (2.1%).

Turner's syndrome (45, X) was the most frequent sex chromosomal aneuploidy (4.4%).

Rare autosomal aneuploidies (autosomal aneuploidies other than Trisomy 21, 13 or 18) were the most common group of chromosome conditions detected (17.3%) (**Table 4**).

Table 4. Diagnostic results

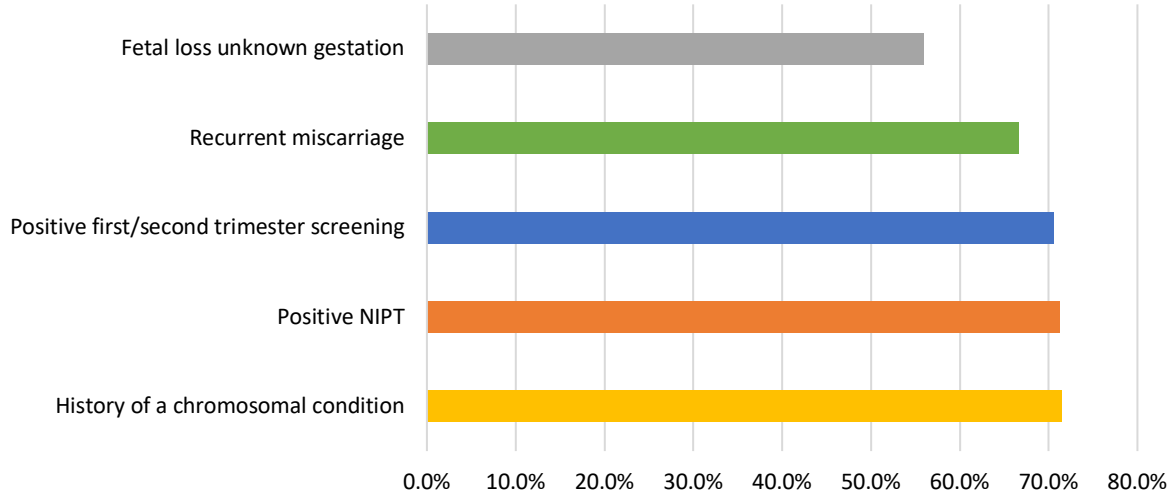
Result	n (%)
Normal/benign CNV	658 (52.3)
Rare autosomal aneuploidies	**218 (17.3)**
Trisomy 16	65 (5.2)
Trisomy 22	43 (3.4)
Trisomy 15	31 (2.5)
Other rare autosomal aneuploidy	79 (6.3)
Common autosomal aneuploidies	**111 (8.8)**
Trisomy 21	55 (4.4)
Trisomy 13	27 (2.1)
Trisomy 18	29 (2.3)
Sex chromosomal aneuploidies	**59 (4.7)**
Turner syndrome (45,X)	56 (4.4)
Klinefelter syndrome (47,XXY)	1 (0.1)
Jacob syndrome (47,XYY)	1 (0.1)
Triple XXX (47,XXX)	1 (0.1)
Triploidy	**56 (4.4)**
Multiple autosomal or sex chromosomal aneuploidies	51 (4.1)
Pathogenic CNV	21 (1.7)
CNV of uncertain or unknown clinical significance	17 (1.4)
Gestational trophoblastic disease	19 (1.5)
Confined placental mosaicism	5 (0.4)
Other major chromosome condition	37 (2.9)
Other minor chromosome condition	7 (0.6)
Total	**1259 (100.0)**

CNV; copy number variant

Diagnostic yield

Diagnostic yield was highest for women undergoing testing with a history of a chromosomal condition (71.4%), a positive ('high chance') NIPT result (71.3%), a positive first or second trimester screening result (70.6%), a previous or 'recurrent' miscarriage (66.7%), and fetal loss at an unknown gestation (56.0%) (**Figure 2, Table 5**).

Figure 2. Diagnostic yield by indication for testing



'Recurrent' miscarriage included all miscarriages described as 'recurrent' by the clinical referrer.

Chromosome results by indication for testing

Chromosome results differed by indication for testing. The chromosome results for the five indications with the highest diagnostic yield are shown in **Table 6**.

Trisomy 21 was the most common chromosome result following testing for a positive NIPT result (27.6%) or following positive first trimester or second trimester screening result (24.1%).

The most common indications for testing among the rare autosomal trisomies were a history of a chromosomal condition (38.5%), a previous or recurrent miscarriage (35.4%), or a fetal loss at an unknown gestation (30.0%).

Table 5. Chromosome results by indication for testing

Indication	Total Indications‡	Normal/ benign	Minor chromosome abnormality	Total major chromosome abnormality	Major chromosome abnormalities									
					T21	T18	T13	RAT	SCA	pCNV	Other*	Multiple AA/SCA	Polyploidy	GTD
History chromosomal condition n (%)	14 (100.0)	4 (28.6)	0 (0.0)	10 (71.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (42.9)	1 (7.1)	1 (7.1)	1 (7.1)	1 (7.1)	0 (0.0)	0 (0.0)
Positive NIPT n (%)	87 (100.0)	16 (18.4)	9 (10.3)	62 (71.3)	24 (27.6)	8 (9.2)	5 (5.7)	3 (3.4)	13 (14.9)	3 (3.4)	3 (3.4)	2 (2.3)	1 (1.1)	0 (0.0)
Positive first or second screening n (%)	17 (100.0)	5 (29.4)	0 (0.0)	12 (70.6)	3 (17.6)	3 (17.6)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	1 (5.9)	2 (5.9)	0 (0.0)
Previous or 'recurrent' miscarriage n (%)	222 (100.0)	71 (32.0)	3 (1.4)	148 (66.7)	9 (4.1)	1 (0.5)	6 (2.7)	81 (36.5)	11 (5.0)	3 (1.4)	7 (3.2)	15 (6.8)	15 (6.8)	0 (0.0)
Fetal loss gestation unknown n (%)	293 (100.0)	128 (43.7)	1 (0.3)	164 (56.0)	5 (1.7)	6 (2.0)	4 (1.4)	85 (29.0)	15 (5.1)	7 (2.4)	16 (5.5)	10 (3.4)	15 (5.1)	1 (0.3)

‡More than one indication could be recorded for each pregnancy. Hence, totals may vary.

*Other results included mosaic autosomal or sex chromosomal aneuploidies, and unbalanced translocations.

AA, autosomal aneuploidy; GTD, gestational trophoblastic disease; pCNV, pathogenic copy number variant; NIPT, non-invasive prenatal testing, RAT, rare autosomal trisomies; SCA, sex chromosomal aneuploidy; T21, Trisomy 21; T18, Trisomy 18; T13, Trisomy 13.

References

1. South ST, Lee C, Lamb AN, Higgins AW, Kearney HM. ACMG Standards and Guidelines for constitutional cytogenomic microarray analysis, including postnatal and prenatal applications: revision 2013. Genet Med. 2013;15(11):901-9.

2. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24.