The Annual Report on Prenatal Diagnostic Testing in Victoria, 2022

Reproductive Epidemiology group

Genomic Medicine theme

Murdoch Children's Research institute

CONTENTS

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About this report

This annual report from the **Victorian Prenatal Diagnosis Database** (VPDD) summarises the results of fetal chromosome testing in Victoria during 2022. Victoria has approximately 74,000 confinements annually, and a median maternal age of 32.5 years (Australian Bureau of Statistics; https://www.abs.gov.au/).

The VPDD has been collecting state-wide data on prenatal diagnostic procedures since 1976. We acknowledge our long-standing collaborators - the Victorian Clinical Genetics Service (VCGS) and Monash Pathology (current contributors), Melbourne Pathology and Australian Clinical Labs (former contributors).

All amniocentesis and chorionic villus sampling (CVS) results performed prior to 25 weeks' gestation on women living in Victoria are included in the annual report. This gestational age limit was chosen to capture diagnostic testing performed after routine screening for chromosome and fetal structural conditions in the first and second trimester.

The data fields collected for each woman include: maternal age and gestation at the time of testing, type of diagnostic test, indication for testing, chromosome results, and pregnancy plurality. A single record is created for twin pregnancies or women who required repeat testing in the same pregnancy.

Definitions

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

Minor chromosome conditions: genomic CNVs of uncertain or unknown significance, long continuous stretches of homozygosity (LCSH), 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.

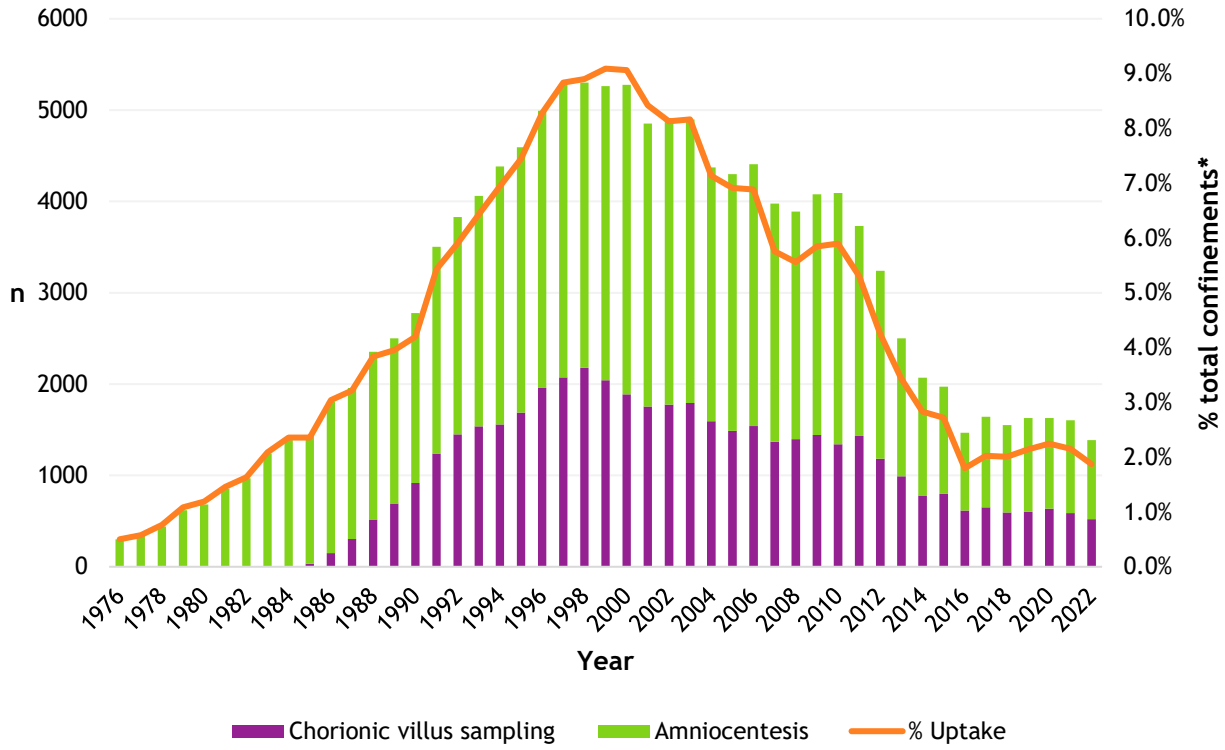
Classification of genomic copy number variants (CNVs): CNVs classified as *pathogenic, likely pathogenic, uncertain, or unknown significance, likely benign, or benign* according to the clinical laboratory interpretation, which is guided by the American College of Medical Genetics standards and guidelines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

Trends in the uptake of prenatal diagnostic procedures

The annual uptake of prenatal diagnostic procedures is calculated from the number of women who had prenatal diagnostic testing as a percentage of total confinements (number of pregnancies resulting in at least one birth ≥ 20 weeks) in Victoria (Australian Bureau of Statistics; https://www.abs.gov.au).

In 2022, 1388 women underwent a prenatal diagnostic procedure < 25 weeks' gestation, including 521 CVS and 867 amniocenteses (**Figure 1**). This represents 1.9% of the 74,118 confinements in Victoria in 2022.

Figure 1. Prenatal diagnostic tests and uptake as % total confinements

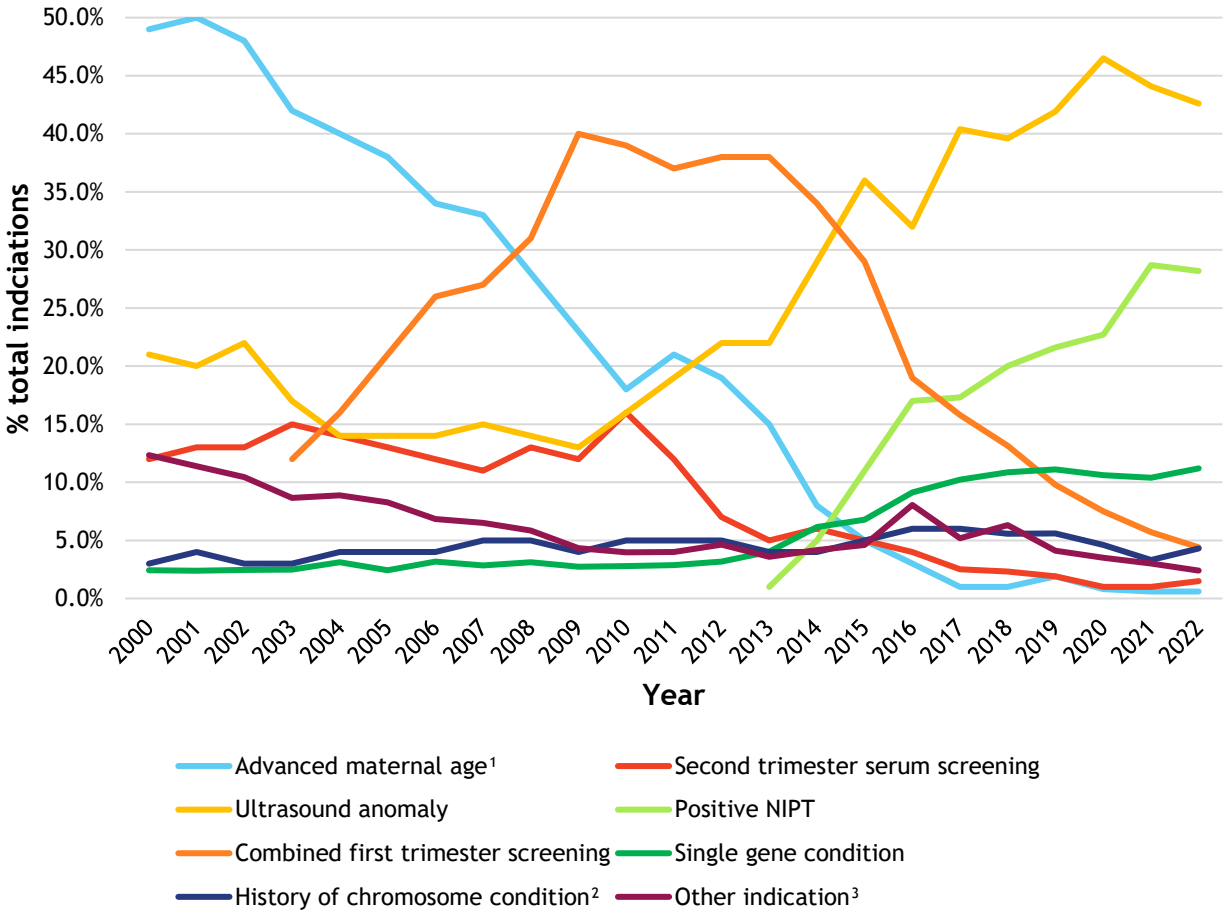


*Number of pregnancies in Victoria resulting in at least one birth ≥ 20 weeks (Australian Bureau of Statistics; https://www.abs.gov.au)

Indications for prenatal diagnostic procedures

Indications for prenatal diagnosis are obtained from the clinical referral information. More than one indication may be recorded. In 2022, 1570 indications were recorded for 1388 diagnostic procedures. The three most common indications for prenatal diagnosis were ultrasound abnormality (n=669/1570, 42.6%), positive ('high chance') NIPT result (n=443/1570, 28.2%) and testing for a single gene condition (n=176/1570, 11.2 %) (**Figure 2**).

Figure 2. Relative proportions of indications for prenatal diagnosis



[1]Maternal age >36 years at estimated due date of delivery.

[2]History of a chromosomal condition included a parental chromosome condition or previous pregnancy with a chromosomal condition.

[3]Other indication included: suspected fetal infection, follow up diagnostic testing after preimplantation genetic testing, maternal anxiety, twin-twin-transfusion syndrome, amnioreduction, previous child with a structural abnormality (not genetic), and family history (unspecified).

Single gene conditions

In 2022, 176 prenatal diagnostic procedures were performed to test for 91 different single gene conditions. Prenatal diagnostic testing for a single gene condition was the third most common indication for a procedure. The five most common conditions for which testing was performed were fragile X, thalassaemia, cystic fibrosis, spinal muscular atrophy, and Duchenne muscular dystrophy (**Table 1**). Data on samples sent for genomic sequencing (exome sequencing, whole genome sequencing, gene panels) are not included here.

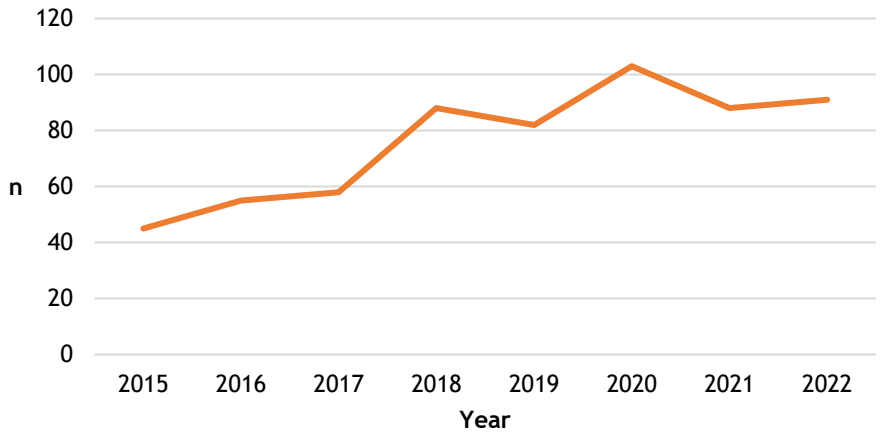
Table 1. Prenatal diagnosis for single gene testing

Single gene	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**
Total tests for a single gene condition	134	134	168	169	181	174	193	176
Total tests for the 5 most common single gene conditions	75	68	85	81	76	90	92	71
Fragile X	20	21	22	29	33	33	33	25
Thalassaemia	31	23	28	31	18	28	36	24
Cystic fibrosis	13	14	23	14	12	21	13	11
Spinal Muscular atrophy	6	6	5	5	8	3	6	7
Duchenne Muscular dystrophy	5	4	7	2	5	5	4	4

The results of the single gene testing are not available from our data collection.

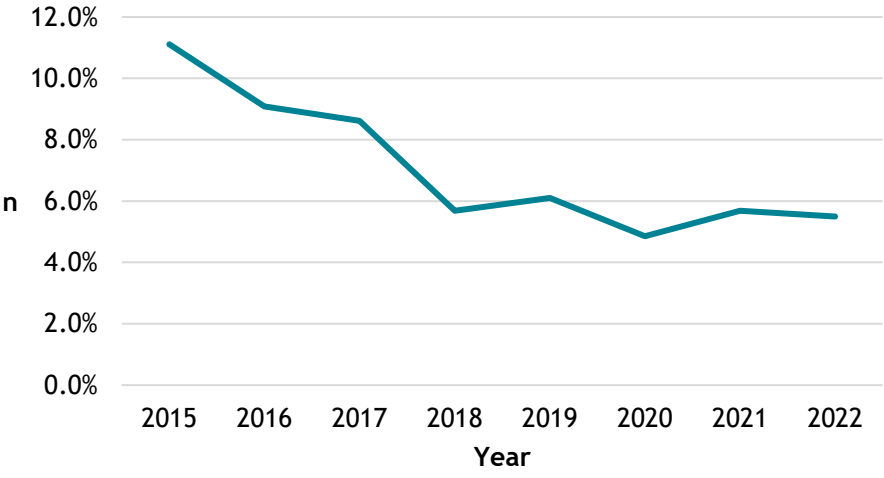
The number of different single gene conditions tested for has increased from 45 in 2015 to 91 in 2022 (**Figure 3**).

Figure 3. Number of different single gene conditions



As a proportion of different single gene conditions, the group of five most common single gene conditions has declined from 11.1% (n=5/45) in 2015 to 5.5% (n=5/91) in 2022 (p=0.005) (Figure 4).

Figure 4. Five most common single gene conditions as a % of total different single gene conditions



Results of prenatal diagnosis

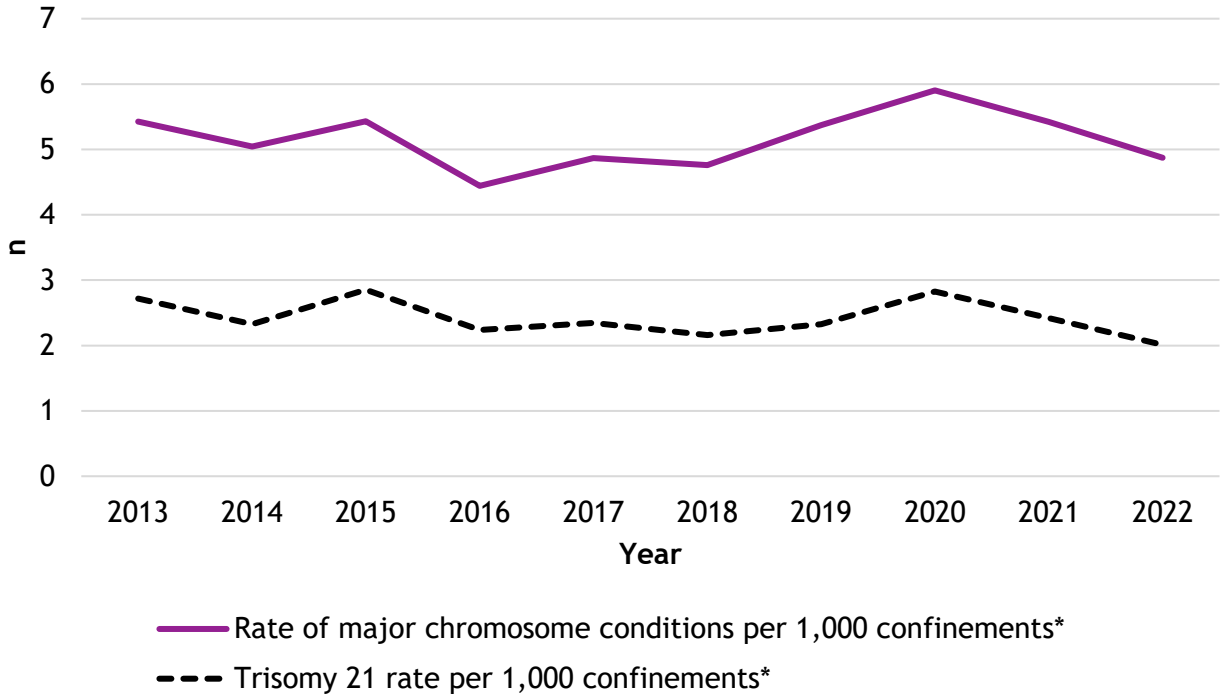
The annual number of major chromosome conditions detected by prenatal diagnosis declined in 2022, reaching a 10 year low of 361 diagnoses. However, the rate of a major chromosome condition per 1,000 confinements (number of pregnancies resulting in at least one birth) in Victoria has remained relatively stable (**Figure 5**). **Table 2** shows the details of these chromosome results for the last ten years.

Table 2. Prenatal diagnosis results

Result	**2013** n, (%)	**2014** n, (%)	**2015** n, (%)	**2016** n, (%)	**2017** n, (%)	**2018** n, (%)	**2019** n, (%)	**2020** n, (%)	**2021** n, (%)	**2022** n, (%)
Normal/benign variant	2014 (81)	1548 (76)	1427 (73)	1037 (71)	1152 (70)	1104 (71)	1130 (70)	1138 (70)	1129 (70)	1000 (72)
Total major chromosome conditions	395 (16)	369 (18)	394 (20)	363 (25)	394 (24)	368 (24)	409 (25)	428 (26)	403 (25)	361 (26)
Trisomy 21	198 (8)	176 (9)	204 (10)	183 (12)	190 (12)	167 (11)	177 (11)	205 (13)	180 (11)	149 (11)
Trisomy 18	61 (2)	49 (2)	42 (2)	44 (3)	55 (3)	60 (4)	61 (4)	54 (3)	41 (3)	45 (3)
Trisomy 13	30 (1)	21 (1)	14 (1)	25 (2)	18 (1)	19 (1)	17 (1)	20 (1)	11 (1)	14 (1)
Other autosomal aneuploidy, polyploidy	18 (1)	22 (1)	22 (1)	9 (1)	14 (1)	5 (0)	10 (1)	16 (1)	12 (1)	11 (1)
Sex chromosome aneuploidy	31 (1)	33 (2)	28 (1)	39 (3)	52 (3)	41 (3)	52 (3)	61 (4)	76 (5)	55 (4)
Pathogenic copy number variation	25 (1)	39 (2)	45 (2)	29 (2)	44 (3)	59 (4)	54 (3)	38 (2)	52 (3)	61 (4)
Other conditions[1]	32 (1)	29 (1)	43 (2)	34 (2)	21 (1)	15 (1)	38 (2)	29 (2)	31 (2)	31 (2)
Variations of unknown/uncertain significance	97 (4)	108 (5)	126 (6)	68 (5)	93 (6)	81 (5)	75 (5)	60 (4)	43 (3)	18 (1)
Total diagnostic tests	**2500**	**2046**	**1957**	**1468**	**1643**	**1553**	**1614**	**1628**	**1603**	**1388**
Total confinements in Victoria	**72,817**	**73,134**	**72,552**	**81,713**	**80,934**	**77,352**	**76,111**	**72,501**	**74,354**	**74,118**
% uptake	**3.4**	**2.8**	**2.7**	**1.8**	**2.0**	**2.0**	**2.1**	**2.2**	**2.2**	**1.9**

[1]Including unbalanced rearrangements and high level mosaics

Figure 5. Major chromosome conditions per 1,000 confinements



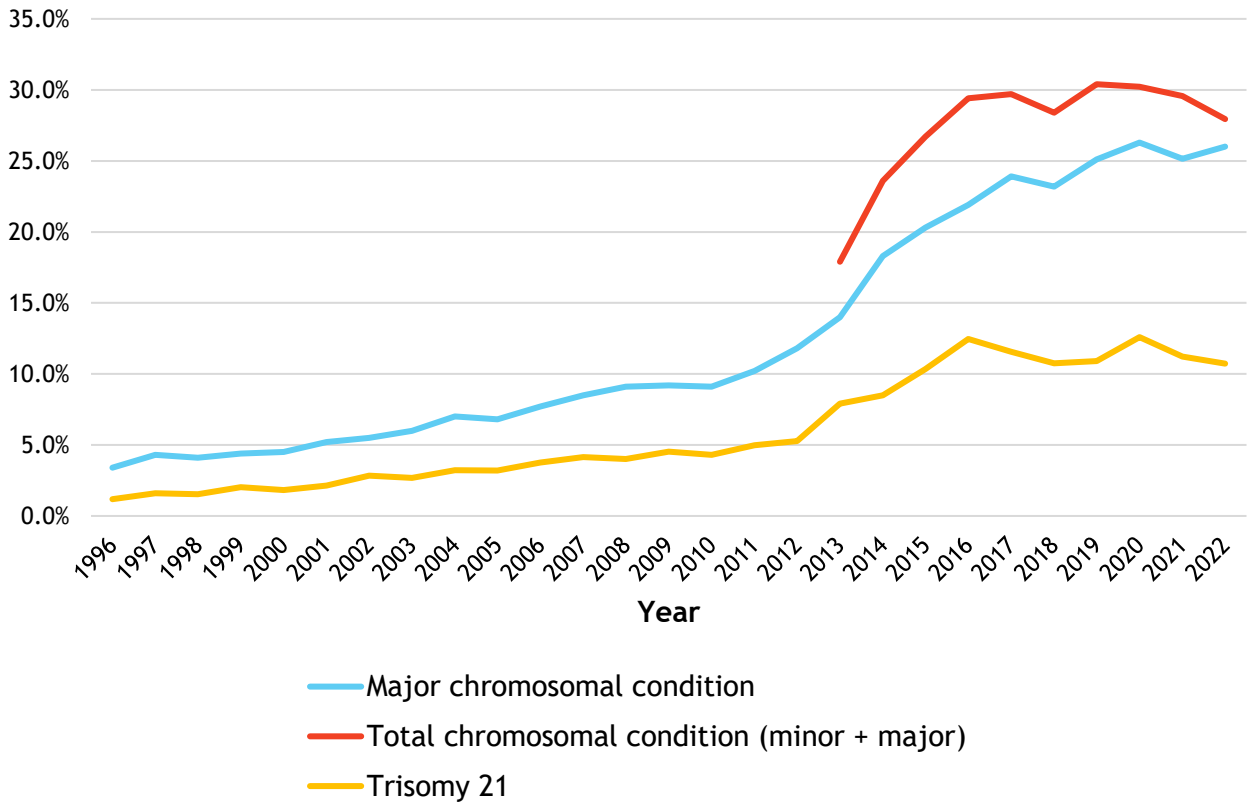
*Number of pregnancies resulting in at least one birth in Victoria (Australian Bureau of Statistics; https://www.abs.gov.au).

Overall diagnostic yield

Most samples were analysed with chromosomal microarray (91.3%), regardless of the indication for testing. The total diagnostic yield is calculated from the number of chromosomal conditions confirmed on diagnostic testing as a proportion of total tests. In 2022, Major chromosome conditions were detected in 26.0% (261/1388) of prenatal diagnostic tests. With minor chromosome conditions included, the total diagnostic yield was 28.0% (**Figure 6**).

Trisomy 21 remained the most common major chromosome condition detected on prenatal diagnosis in 2022 (n=149). There were 61 pathogenic CNVs, the most common of which was the 22q11.2 deletion syndrome (n=8). The number of copy number variants of unknown or uncertain significance detected by chromosomal microarray was 18 (1.3%) in 2022 compared to 43 (2.7%) in 2021.

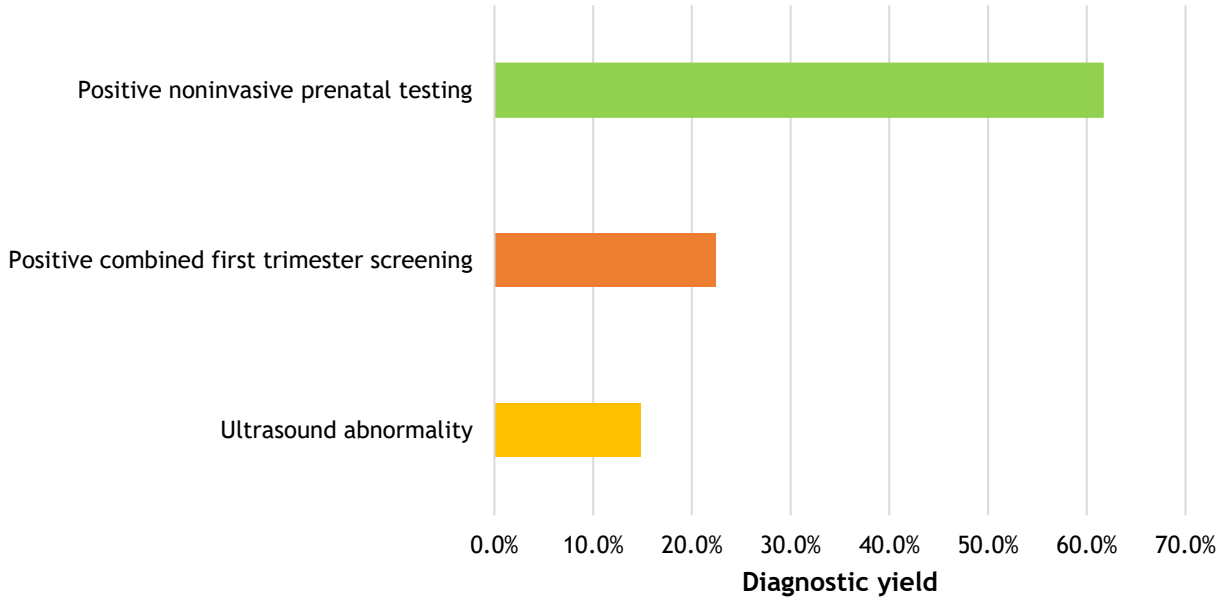
Figure 6. Diagnostic yield of prenatal diagnostic tests by year



Prenatal diagnostic yield by indication

Diagnostic yield for a major chromosome condition varied according to clinical indication for testing. In 2022, the yield was highest for women undergoing testing for a positive ('high chance') NIPT result (61.6%, n=273/443), followed by combined first trimester screening (22.4%, n=15/67), and an ultrasound abnormality (14.9%, n=85/572) (**Figure 7**).

Figure 7. Diagnostic yield by indication for testing



Publications from the Victorian Prenatal Diagnosis Data Collection

1. Pynaker C, Norris F, Hui L, Halliday J. Perinatal outcomes and genomic characteristics of fetal copy number variants: An individual record linkage study of 713 pregnancies. Prenat Diagn. 2023 Apr;43(4):516-526. doi: 10.1002/pd.6305. Epub 2023 Jan 16. PMID: 36631928.
2. Loughry L, Pynaker C, White M, Halliday J, Hui L. State-wide increase in prenatal diagnosis of klinefelter syndrome on amniocentesis and chorionic villus sampling: Impact of non-invasive prenatal testing for sex chromosome conditions. Prenat Diagn. 2023 Feb;43(2):156-161. doi: 10.1002/pd.6103. Epub 2022 Jan 27. PMID: 35048400.
3. Hui L, Pynaker C, Kennedy J, Lewis S, Amor DJ, Walker SP, Halliday J; PALM cohort study group. Study protocol: childhood outcomes of fetal genomic variants: the PrenatAL Microarray (PALM) cohort study. BMC Pediatr. 2021 Oct 11;21(1):447. doi: 10.1186/s12887-021-02809-7. PMID: 34629048; PMCID: PMC8502634.
4. Hui L, Pynaker C, Bonacquisto L, Lindquist A, Poulton A, Kluckow E, Hutchinson B, Norris F, Pertile MD, Gugasyan L, Kulkarni A, Harraway J, Howden A, McCoy R, DA Silva Costa F, Menezes M, Palma-Dias R, Nisbet D, Martin N, Bethune M, Poulakis Z, Halliday J. Re-examining the optimal nuchal translucency cutoff for diagnostic testing in the cell-free DNA and microarray era: results from the Victorian Perinatal Record Linkage study. Am J Obstet Gynecol. 2021 May 3:S0002-9378(21)00537-8. doi: 10.1016/j.ajog.2021.03.050. Epub 2021 May 3. PMID: 33957116.
5. Kelley J, McGillivray G, Meagher S, Hui L. Increased nuchal translucency after low risk noninvasive prenatal testing: What should we tell the prospective parents? Prenat Diagn. 2021 Jul 23. doi: 10.1002/pd.6024. Epub 2021 Aug 6. PMID: 34297420.
6. Lindquist A, Hui L, Poulton A, Kluckow E, Hutchinson B, Pertile MD, Bonacquisto L, Gugasyan L, Kulkarni A, Harraway J, Howden A, McCoy R, Da Silva Costa F, Menezes M, Palma-Dias R, Nisbet D, Martin N, Bethune M, Poulakis Z, Halliday J. State-wide utilization and performance of traditional and cell-free DNA-based prenatal testing pathways: the Victorian Perinatal Record Linkage (PeRL) study. Ultrasound Obstet Gynecol. 2020 Aug;56(2):215-224. doi: 10.1002/uog.21899.
7. Hui L, Poulton A, Kluckow E, Lindquist A, Hutchinson B, Pertile MD, Bonacquisto L, Gugasyan L, Kulkarni A, Harraway J, Howden A, McCoy R, Costa FDS, Menezes M, Palma-Dias R, Nisbet D, Martin N, Bethune M, Poulakis Z, Halliday J. A minimum estimate of the prevalence of 22q11 deletion syndrome and other chromosome abnormalities in a combined prenatal and postnatal cohort. Hum Reprod. 2020 Mar 27;35(3):694-704. doi: 10.1093/humrep/dez286.
8. Kluckow E, Halliday J, Poulton A, Lindquist A, Hutchinson B, Bethune M, Bonacquisto L, Da Silva Costa F, Gugasyan L, Harraway J, Howden A, Kulkarni A, Martin N, McCoy R, Menezes M, Nisbet D, Palma-Dias R, Pertile MD, Poulakis Z, Hui L. Association between timing of diagnosis of trisomy 21, 18, and 13 and maternal socio-economic status in Victoria, Australia: A population-based cohort study from 2015 to 2016. Prenat Diagn. 2019 Dec;39(13):1254-1261. doi: 10.1002/pd.5577.
9. Lostchuck E, Hui L. Should second-trimester hypoplastic nasal bone be sole indication for diagnostic testing with chromosomal microarray analysis? Ultrasound Obstet Gynecol. 2019 Jun;53(6):848-850. doi: 10.1002/uog.20141.
10. Lostchuck E, Poulton A, Halliday J, Hui L. Population-based trends in invasive prenatal diagnosis for ultrasound-based indications: two decades of change from 1994 to 2016. Ultrasound Obstet Gynecol. 2019 Apr;53(4):503-511. doi: 10.1002/uog.19107.

11. Howard-Bath A, Poulton A, Halliday J, Hui L. Population-based trends in the prenatal diagnosis of sex chromosome aneuploidy before and after non-invasive prenatal testing. Prenat Diagn. 2018 Dec;38(13):1062-1068. doi: 10.1002/pd.5363.
12. Poulton A, Lewis S, Hui L, Halliday JL. Prenatal and preimplantation genetic diagnosis for single gene disorders: A population-based study from 1977 to 2016. Prenat Diagn. 2018 Nov;38(12):904-910. doi: 10.1002/pd.5352.
13. Hui L, Norton M. What is the real "price" of more prenatal screening and fewer diagnostic procedures? Costs and trade-offs in the genomic era. Prenat Diagn. 2018 Mar;38(4):246-249. doi: 10.1002/pd.5228. Epub 2018 Feb 21.
14. Hui L, Barclay J, Poulton A, Hutchinson B, Halliday JL. Prenatal diagnosis and socioeconomic status in the non-invasive prenatal testing era: A population-based study. Aust N Z J Obstet Gynaecol. 2018 Aug;58(4):404-410. doi: 10.1111/ajo.12778.
15. Lindquist A, Poulton A, Halliday J, Hui L. Prenatal diagnostic testing and atypical chromosome abnormalities following combined first-trimester screening: implications for contingent models of non-invasive prenatal testing. Ultrasound Obstet Gynecol. 2018 Apr;51(4):487-492. doi: 10.1002/uog.18979.
16. Hui L, Hutchinson B, Poulton A, Halliday J. Population-based impact of noninvasive prenatal screening on screening and diagnostic testing for fetal aneuploidy. Genet Med. 2017 Dec;19(12):1338-1345. doi: 10.1038/gim.2017.55.
17. Hui L, Muggli EE, Halliday JL. Population-based trends in prenatal screening and diagnosis for aneuploidy: a retrospective analysis of 38 years of state-wide data. BJOG. 2016 Jan;123(1):90-7. doi: 10.1111/1471-0528.13488.
18. Susman MR, Amor DJ, Muggli E, Jaques AM, Halliday J. Using population-based data to predict the impact of introducing noninvasive prenatal diagnosis for Down syndrome. Genet Med. 2010 May;12(5):298-303. doi: 10.1097/GIM.0b013e3181d5d022.
19. Jaques AM, Collins VR, Muggli EE, Amor DJ, Francis I, Sheffield LJ, Halliday JL. Uptake of prenatal diagnostic testing and the effectiveness of prenatal screening for Down syndrome. Prenat Diagn. 2010 Jun;30(6):522-30. doi: 10.1002/pd.2509.
20. Muggli EE, Collins VR, Halliday JL. Mapping uptake of prenatal diagnosis for Down syndrome and other chromosome abnormalities across Victoria, Australia. Aust N Z J Obstet Gynaecol. 2006 Dec;46(6):492-500. doi: 10.1111/j.1479-828X.2006.00648.x.
21. Muggli EE, McCloskey D, Halliday JL. Health behaviour modelling for prenatal diagnosis in Australia: a geodemographic framework for health service utilisation and policy development. BMC Health Serv Res. 2006 Sep 1;6:109. doi: 10.1186/1472-6963-6-109.
22. Muggli EE, Halliday JL. Prenatal diagnostic testing and Down Syndrome in Victoria 1992--2002. Aust N Z J Public Health. 2004 Oct;28(5):465-70. doi: 10.1111/j.1467-842x.2004.tb00029.x.
23. Collins VR, Webley C, Sheffield LJ, Halliday JL. Fetal outcome and maternal morbidity after early amniocentesis. Prenat Diagn. 1998 Aug;18(8):767-72.
24. Halliday J, Lumley J, Watson L. Comparison of women who do and do not have amniocentesis or chorionic villus sampling. Lancet. 1995 Mar 18;345(8951):704-9. doi: 10.1016/s0140-6736(95)90872-2.
25. Halliday JL, Watson LF, Lumley J, Danks DM, Sheffield LJ. New estimates of Down syndrome risks at chorionic villus sampling, amniocentesis, and livebirth in women of advanced maternal age from a uniquely defined population. Prenat Diagn. 1995 May;15(5):455-65. doi: 10.1002/pd.1970150509.
26. Halliday JL, Lumley J, Sheffield LJ, Robinson HP, Renou P, Carlin JB. Importance of complete follow-up of spontaneous fetal loss after amniocentesis and chorion villus sampling [published correction appears in Lancet 1992 Nov 14;340(8829):1236]. Lancet. 1992;340(8824):886-890.

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.