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The Annual Report on Prenatal Diagnostic Testing in Victoria, 2021

Reproductive Epidemiology group

Genetics theme

Murdoch Children's Research institute

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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 2021. Victoria has approximately 76,000 confinements annually, and a median maternal age of 31.6 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, 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.

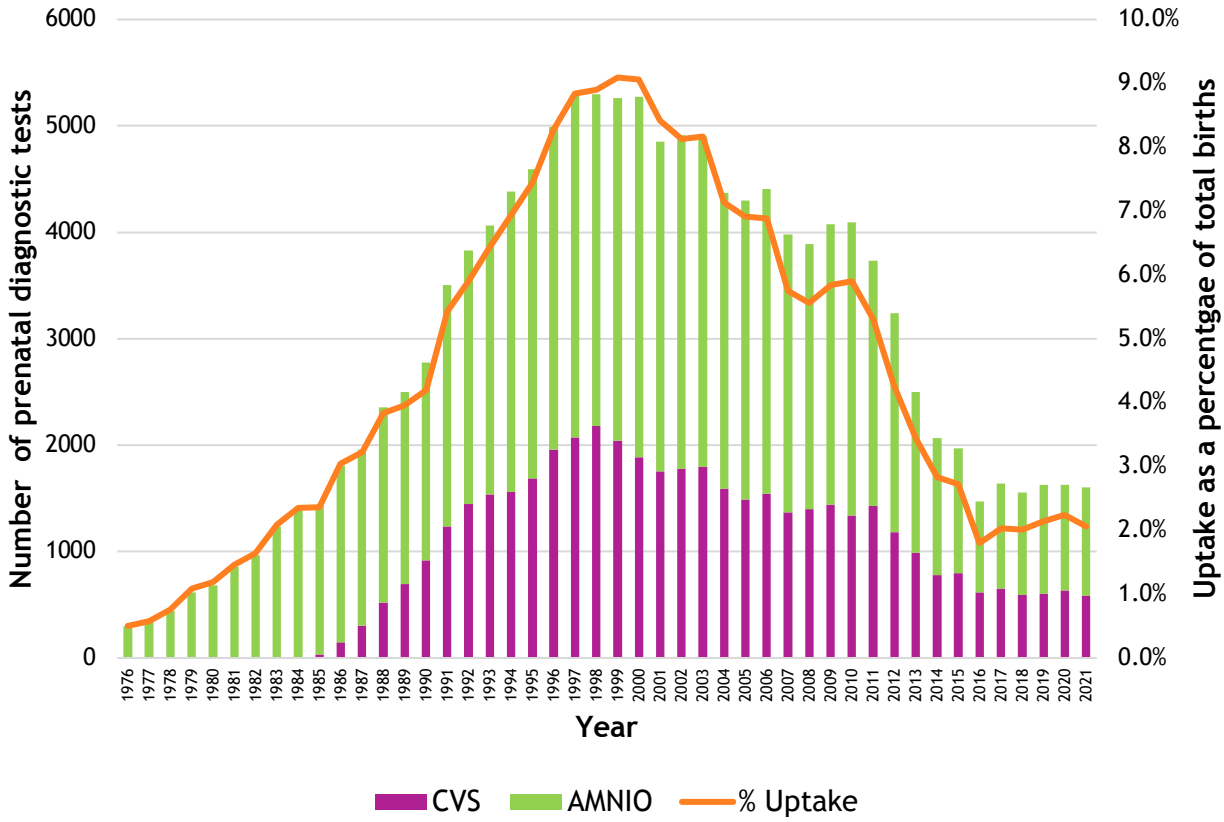
Classification of genomic copy number variants (CNVs): CNVs classified as *pathogenic, likely pathogenic, uncertain, or unknown significance, likely benign, or benign* according to the clinical laboratory interpretation, which is guided by the American College of Medical Genetics standards and guidelines 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 registered births in Victoria (Australian Bureau of Statistics; https://www.abs.gov.au/).

In 2021, 1603 women underwent a prenatal diagnostic procedure before 25 weeks' gestation, representing 2.06% of total births in Victoria. The steep decline in prenatal diagnostic procedures since the peak in 1998 (n=5300) appears to have plateaued since 2016 (**Figure 1**).

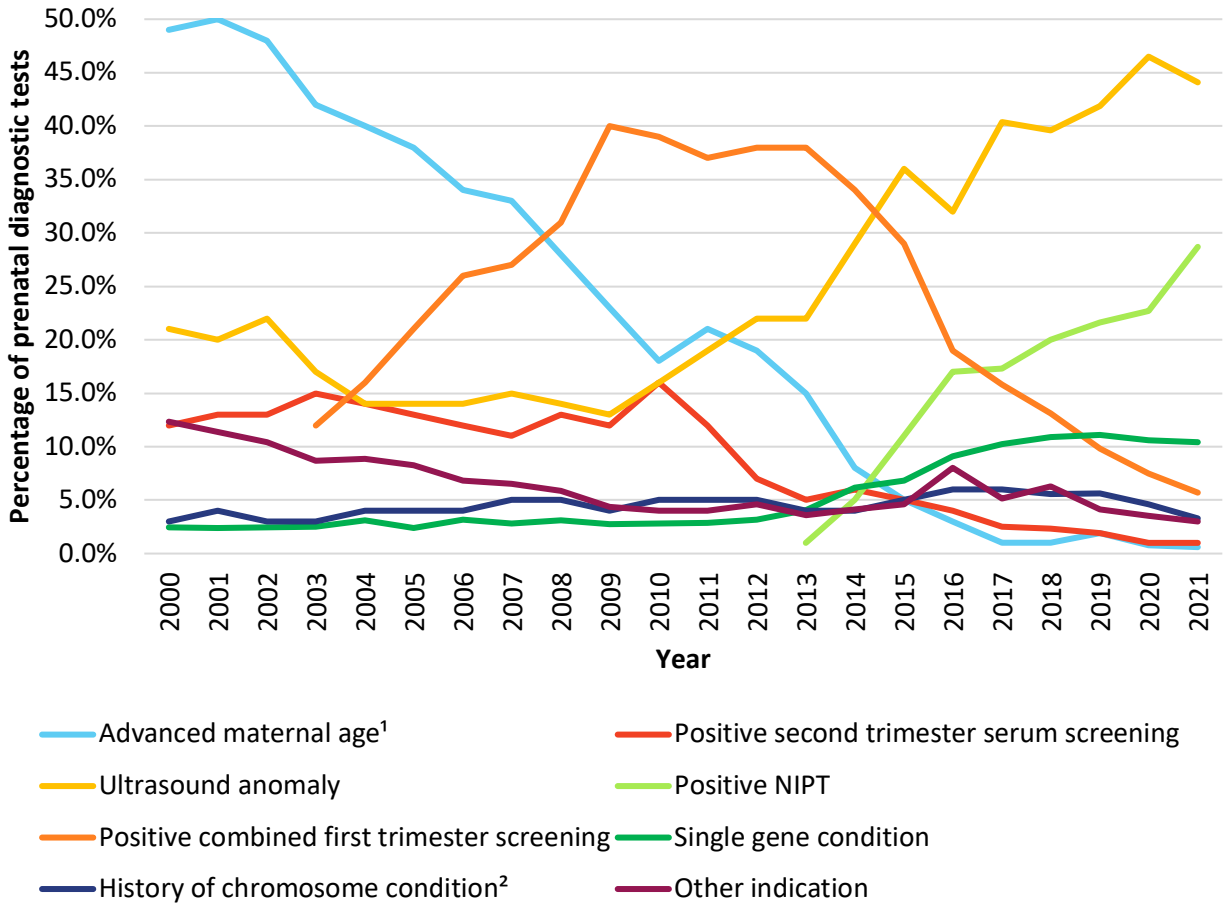
Figure 1. Annual number of prenatal diagnostic tests and uptake as a percentage of total births (1976-2021)



Indications for prenatal diagnostic procedures

Indications for prenatal diagnosis are obtained from the clinical referral information. More than one indication may be recorded. In 2021, 1858 indications were recorded for 1603 diagnostic procedures. The three most common indications for prenatal diagnosis were ultrasound abnormality (44.1%), positive NIPT result (28.7%) and testing for single gene conditions (10.4%) (**Figure 2**).

Figure 2. Indications for prenatal diagnosis as a percentage of total indications, 2000-2021



[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.

Single gene conditions

Prenatal diagnostic testing for a single gene condition has now replaced first trimester combined screening as the third most common indication for a prenatal diagnostic procedure.

In 2021, the five most common conditions for which testing was done were fragile X, thalassaemia, cystic fibrosis, spinal muscular atrophy, and Duchenne muscular dystrophy. Testing for one of these five common single gene conditions has increased from 75 in 2015 to 92 in 2021 (**Table 1**).

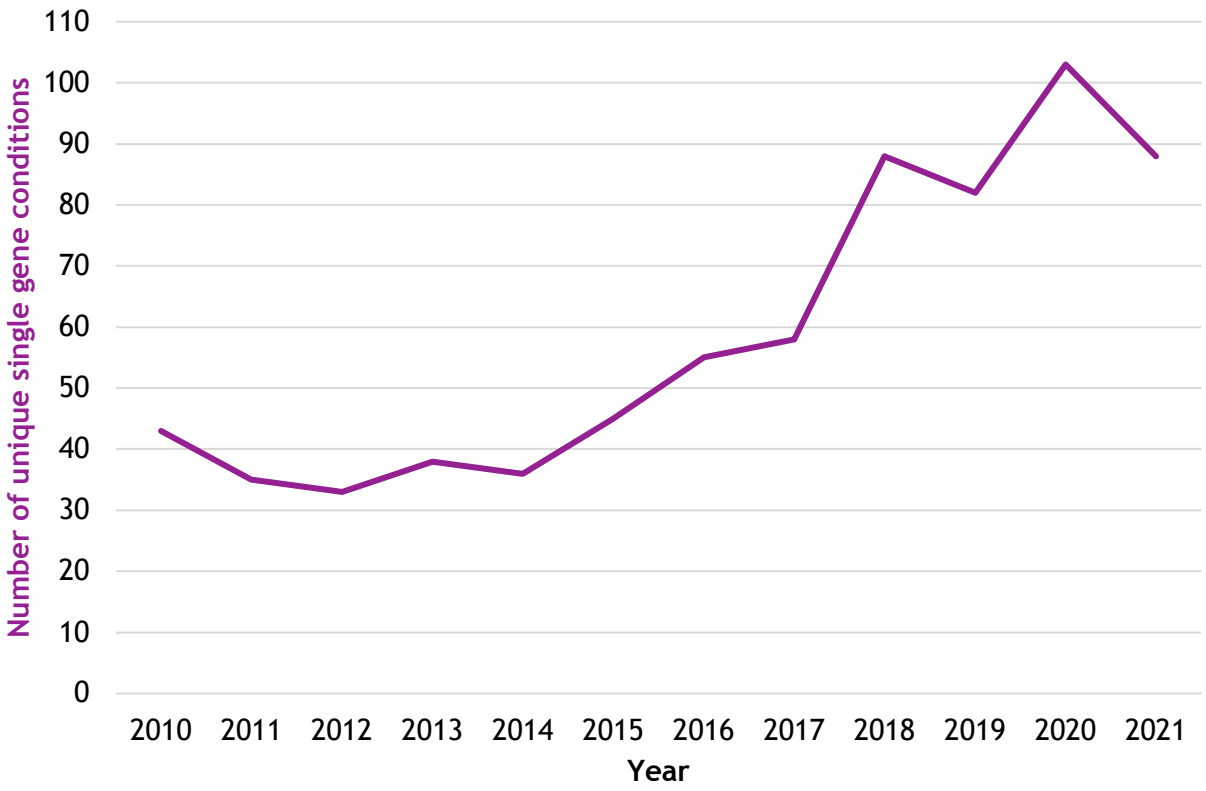
Table 1. Annual frequencies of the top 5 prenatal single gene tests

Single gene conditions	2015	2016	2017	2018	2019	2020	2021
Fragile X	20	21	22	29	33	33	33
Thalassaemia	31	23	28	31	18	28	36
Cystic fibrosis	13	14	23	14	12	21	13
Spinal Muscular atrophy	6	6	5	5	8	3	6
Duchenne Muscular dystrophy	5	4	7	2	5	5	4
Number of unique single gene conditions	45	55	58	88	82	103	88
Total tests for the 5 most common single gene conditions	75	68	85	81	76	90	92
Total number of single gene tests	135	130	165	178	196	207	193

Results from single gene testing are not available from our data collection.

In 2021, 193 prenatal diagnostic procedures were performed to test for 88 different single gene conditions. As a proportion of unique single gene conditions, the group of five most common single gene conditions has declined from 11.6% (5/43) in 2010 to 5.7% (5/88) in 2021 (p=0.005) (**Figure 3**).

Figure 3. Annual number of unique single gene conditions for which prenatal diagnosis



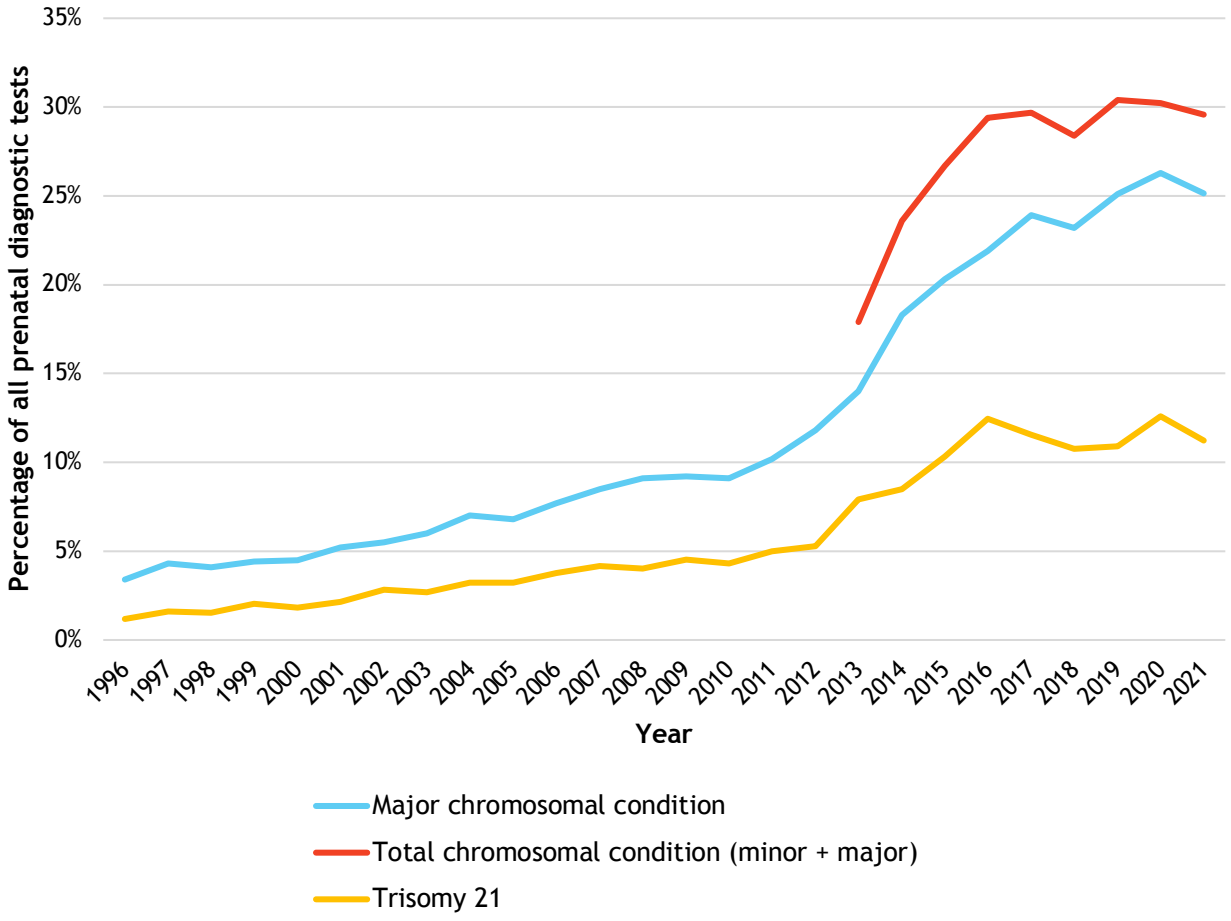
Overall diagnostic yield

Most samples were analysed with chromosomal microarray (93.1%), regardless of the indication for testing.

The diagnostic yield is calculated from the number of major chromosomal conditions confirmed on diagnostic testing as a proportion of total tests. In 2021, 403 (25.1%) prenatal tests detected a major chromosome condition. The total diagnostic yield including major and minor chromosome conditions was 29.6% (**Figure 4**).

Trisomy 21 remained the most common major chromosome condition detected on prenatal diagnosis in 2021 (n=180). There were 52 pathogenic CNVs, the most common of which was the 22q11.2 deletion syndrome (n=4). The number of genomic variants of unknown or uncertain significance detected by CMA was 43 (2.7%).

Figure 4. Diagnostic yield of prenatal diagnostic tests by year

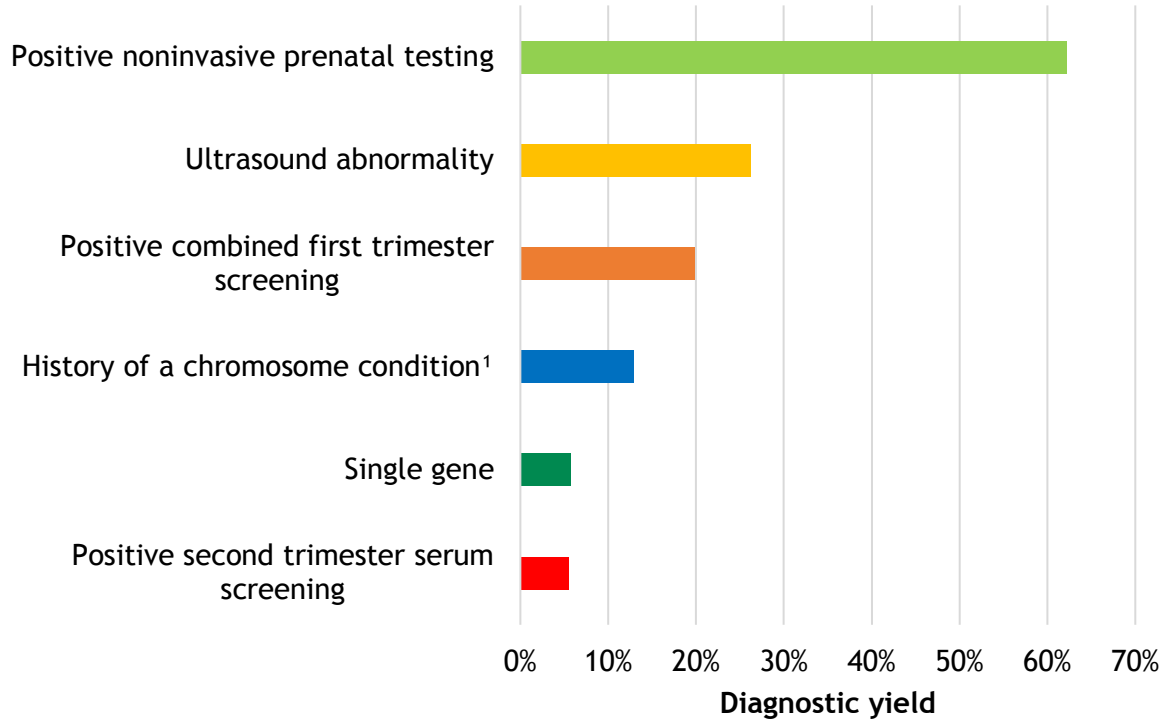


The most common indication for testing among pregnancies with Trisomy 21 in 2021 was a positive NIPT result (65.5%).

Prenatal diagnostic yield by indication

Diagnostic yield for a major or minor chromosome condition varied according to clinical indication for testing. In 2021, the yield was highest for women undergoing testing for a positive NIPT result (62.2%), followed by an ultrasound abnormality (26.2%), combined first trimester screening (19.8%), history of a chromosome condition (12.9%), a single gene condition (5.9%), and second trimester serum screening (5.6%) (Figure 5).

Figure 5. Diagnostic yield by indication for testing



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

Trends in prenatal diagnosis of chromosome conditions

The annual number of major chromosome conditions has not changed markedly for many years, despite the decline in overall prenatal diagnostic testing numbers. **Table 2** shows the details of all chromosome result for the last nine years.

Table 2. Prenatal diagnosis results 2013-2021

Result	2013	2014	2015	2016	2017	2018	2019	2020	2021
Normal/benign variant	2014	1548	1427	1037	1152	1104	1130	1138	1129
Total major chromosome conditions	395	369	394	363	394	368	409	428	403
Trisomy 21	198	176	204	183	190	167	177	205	180
Trisomy 18	61	49	42	44	55	60	61	54	41
Trisomy 13	30	21	14	25	18	19	17	20	11
Other autosomal aneuploidy, polyploidy	18	22	22	9	14	5	10	16	12
Sex chromosome aneuploidy	31	33	28	39	52	41	52	61	76
Pathogenic copy number variation	25	39	45	29	44	59	54	38	52
Other conditions[1]	32	29	43	34	21	15	38	29	31
Variations of unknown/uncertain significance	97	108	126	68	93	81	75	60	43
Total diagnostic tests	**2500**	**2046**	**1957**	**1468**	**1643**	**1553**	**1614**	**1628**	**1603**

[1]Including unbalanced rearrangements and high level mosaics

Publications from the Victorian Prenatal Diagnosis Data Collection

1. 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. 2022 Jan 19. doi: 10.1002/pd.6103. Epub ahead of print. PMID: 35048400.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.

11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. Collins VR, Webley C, Sheffield LJ, Halliday JL. Fetal outcome and maternal morbidity after early amniocentesis. Prenat Diagn. 1998 Aug;18(8):767-72.
23. 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.
24. 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.
25. 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.