Author/s:
Poulton, A;Lewis, S;Hui, L;Halliday, JL

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Poulton Alice (Orcid ID: 0000-0003-3506-9035)
Hui Lisa (Orcid ID: 0000-0002-9720-3562)

Title Prenatal and preimplantation genetic diagnosis for single gene disorders: a population-based study from 1977 to 2016.

Running title: Prenatal and preimplantation genetic diagnosis of single gene disorders

Authors and affiliations

Alice Poulton BA BSc(Hons)[1]

Sharon Lewis PhD[1,3]

Lisa Hui MBBS PhD[1,2,4]

Jane L. Halliday PhD[1,3]

[1]Public Health Genetics, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Rd, Parkville, Victoria 3052, Australia

[2]Department of Perinatal Medicine, the Mercy Hospital for Women, 163 Studley Rd Heidelberg, Victoria 3084, Australia

[3]Department of Paediatrics, University of Melbourne, Parkville, Victoria 3052, Australia

[4]Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, Victoria 3052, Australia

Corresponding Author

Alice Poulton

Public Health Genetics, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Rd, Parkville, Victoria 3052, Australia

E-mail: alice.poulton@mcri.edu.au

Phone: 61 405 068 333

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necessary for this study and aiding with the interpretation of the data. We also thank Dr Avihu Boneh and Dr Lilian Downie for their invaluable insights regarding the categorisation of disorders.

What we already know

- Single gene disorders collectively constitute a major health burden.
- Parental carrier testing based on family or obstetric history followed by prenatal diagnosis (PNDx) has been the mainstay of reproductive testing for single gene conditions for decades.
- Recent advances such as preimplantation genetic diagnosis (PGT-M), carrier screening, noninvasive prenatal diagnosis, and novel postnatal therapies are changing the field rapidly.

What this study adds

- The first population-based data on PNDx and PGT-M for single gene disorders spanning the entire 40 year history of PNDx in the Australian state of Victoria.
- PGT-M for monogenic conditions is increasing each year and now exceeds the annual numbers of PNDx for these conditions.
- Adult onset disorders make up a significantly larger proportion of PGT-M testing compared with PNDx, suggesting differences in our community perceptions of testing for late onset conditions.

Abstract:

Objective: To examine the state-wide utilization of prenatal diagnosis (PNDx) and preimplantation genetic diagnosis (PGT-M) for single gene disorders.

Methods: Population-based study of all women utilizing PNDx in the Australian state of Victoria from 1977-2016. Single gene disorders were categorised using a systematic approach that aimed to reflect aspects of the PNDx decision-making process. Data on PGT-M for single gene disorders from 2005 to 2016 were similarly examined for comparison. Statistical significance testing was performed with χ^2test.

Results: Following an initial uptake period, annual PNDx rates for single gene disorders stabilized between 1.3 to 2.2 per 1,000 births after the year 2000. The majority of PNDx (72%) was performed for disorders that primarily impair physical ability, while PNDx for adult onset conditions was rare (3%). PGT-M for single gene disorders has seen rapid growth since its introduction, and annual numbers now equal that of PNDx. In contrast to PNDx, one quarter of PGT-M tests were performed for adult onset conditions.

Conclusions: Our population-wide analysis has demonstrated a steady demand for PNDx for single gene disorders over the past decade, in contrast to the rapidly increasing utilization of PGT-M. PGT-M appears to be the preferred testing modality for adult onset disorders.

Key words: Prenatal diagnosis, single gene disorders, preimplantation genetic diagnosis, pregnancy

Introduction

Variations in single genes are responsible for over 5,000 human disorders and although individually rare, collectively they are as significant as chromosomal conditions.[1] When the molecular basis of a disorder is known, it is possible to offer prenatal diagnostic testing to identify the genetic status of a fetus at risk[2-4]. In a recent special issue of this journal, the promises and challenges of the advances in this field were explored in depth.[5]

Prenatal diagnosis may facilitate reproductive decision making, allowing couples and their healthcare providers to prepare for the birth of a child with a single gene disorder, to consider the option of terminating an affected pregnancy, to reassure the couple of specific risks to the fetus, or, in some circumstances, to allow *in utero* treatment.[5]

Advances in preimplantation genetic diagnosis (PGT-M) now provide couples with a means to avoid having a pregnancy affected by a heritable disorder altogether.[6-8] For many couples, undergoing *in vitro* fertilization (IVF), PGT-M and selective transfer of an unaffected embryo is ethically more acceptable than conceiving by chance, undergoing prenatal diagnosis, and considering termination of an affected pregnancy.[9-11]

Historically, pregnancies at increased risk of single gene disorder were usually identified from a positive family or obstetric history, and confirmation of parental carrier status. Carrier testing for common monogenic disorders is now expanding to 'at population risk' couples planning a family, regardless of family history.[12, 13]

The emergence of PGT-M and expansion of reproductive carrier screening to 'at population risk' couples are expected to have a significant impact on prenatal diagnosis of single gene disorders. The emergence of new technologies for noninvasive prenatal diagnosis using maternal plasma cell-free DNA is also anticipated to influence rates of prenatal diagnostic testing.[14]

These global developments have led us to examine population-wide trends, examining the scope of prenatal diagnosis for single gene disorders over a 39-year period. The aim of our study was to analyse (i) annual numbers of PNDx and PGT-M performed for single gene disorders, (ii) the range of individual disorders for which PNDx and PGT-M diagnosis was performed, and (iii) single gene conditions according to broad phenotypic categorizations.

Materials and Methods

This was a retrospective population-based cohort study of PNDx and PGT-M performed for the indication of single gene testing in the Australian state of Victoria from 1977 to 2016.

During the study period, there were a total of 2,578,168 births. Annual confinements rose from 58,720 in 1977 to 81,713 in 2016, while the corresponding total fertility rate declined from 2.0 to 1.8.[15] The most recent census data from 2011 reported that 35.5% of Victorians were born outside Australia; the six most common countries of birth outside Australia in descending order were the United Kingdom (5.1% of total population), New Zealand (2.0%), India (2.8%), China (2.5%), Italy (1.9%) and Vietnam (1.7%).[16] Approximately 4.6% of live births in Victoria were the result of assisted reproduction in 2015[17].

During this period, all PNDx procedure-related costs and diagnostic tests were government-funded if performed in a public hospital with confirmed carrier status.

PGT-M was initially offered under research protocols in 1999 before becoming available during clinical care from 2002. PGT-M is not government-funded, and the costs are directly charged to the couple by the private fertility clinics. The typical out-of-pocket cost of one cycle of IVF is approximately AUD4600, with PGT-M costing an additional AUD600 per test and AUD700 per thawed embryo transfer.[18]

Data sources

(i) The Victorian Prenatal Diagnosis Database contains amniocentesis and CVS results from the four cytogenetic laboratories in Victoria. This dataset has been described in detail elsewhere[19]. Results from 1977 to 2016 were obtained, and data regarding PNDx <25 weeks gestation for the identification of single gene disorders were extracted. Pregnancies ≥25 weeks were excluded as women accessing PNDx at this gestational age are part of a different antenatal pathway, with the majority undergoing testing due to an ultrasound abnormality.[20]

(ii) Population demographics were obtained from the Australian Bureau of Statistics, including live births and ethnic composition. Total births from the ABS do not include terminations of pregnancy or stillbirths, underestimating total confinements by less than 1%.[21]

(iii) De-identified datasets containing numbers of PGT-M for single gene disorders were obtained from the two Victorian fertility clinics providing this service to our population (see acknowledgements). PGT-M data were only available from 2005 onwards.

(iv) Victorian IVF birth rates were obtained from the Victorian Assisted Reproductive Treatment Authority.[17]

We calculated annual numbers and rates per 1,000 births of PNDx and PGT-M for single gene indications, the number and type of different disorders tested, and their frequencies. For PNDx, each pregnancy for which amniocentesis or CVS was performed for a single gene indication was counted as an individual case. For PGT-M, each IVF cycle leading to PGT-M was counted as an individual case, regardless of the number of embryos tested or whether pregnancy was achieved from that cycle.

We developed a systematic approach allocate each single gene disorder included in the study period to one of four categories. This categorisation process grouped conditions according to the perceived severity of the disorder, the age of its onset, and the type of potential disability resulting from the disorder (i.e. does the disorder primarily impair neurodevelopmental ability, or physical ability). This was done to reflect aspects of each disorder that may play an important role in parental decision-making prior to accessing prenatal diagnosis.

If a disorder was lethal at birth, or in the first year of life it was assigned the category 'lethal in infancy'. Any condition with onset expected over the age of 18 was classified as 'adult onset'. Disorders that were not lethal in infancy or adult onset were assigned to one of two categories that distinguished between the type of potential disability – neurodevelopmental or physical impairment. If both neurodevelopmental and physical impairment were associated with a condition, a hierarchical process was used to reach a final category, with neurodevelopmental impairment taking precedence over physical.

Information obtained from scientific literature and internet genetic resources (Supplementary Table 1) was used to inform the categorisation process. Expert clinicians were also consulted throughout the process.

Statistical analysis was performed using the χ^2 test for trend, or proportions as appropriate, with a *p* value of > 0.05 considered statistically significant.

Ethics approval for this study was provided by the Human Research Ethics Committees of the Royal Children's Hospital (ref. no. 3115A) and Monash Health (ref. no. 12073B).

Results

Trends in annual uptake of PNDx (1977-2016)

Over the study period (1977-2016), a total of 3496prenatal diagnostic tests for single gene indications were undertaken for women <25 weeks gestation (Figure 1). Overall, there was a significant increase in the annual frequency of single gene tests (χ^2=19.18, p<0.001). Annual test numbers increased rapidly in an initial uptake phase following the introduction of prenatal diagnosis in 1976, and then stabilized between 1.3 and 2.2 per 1,000 Victorian births from the year 2000.

Trends in annual uptake of PGT-M (2005-2016)

There has been a rapid uptake of PGT-M for single gene disorders since 2005. By 2016, the number of PGT-M tests performed for a single gene disorder (n=138) exceeded that of PNDx (n=134) (Figure 2).

Characterization of disorders in the PNDx dataset (1993-2016)

Data collection prior to 1993 did not include information on the specific test ordered (only recording the indication as a 'single gene disorder'); hence detailed analyses of the categories were confined to the period 1993-2016 (n=2478). Some data within this timeframe were also unclassifiable, due to inadequate information regarding the reason for referral (e.g. referral recorded as 'x-linked disorder'). These data were excluded from categorical analysis. In total, PNDx was performed for 180 individual conditions (Supplementary table 2). Since 1993, the number of different disorders for which testing was performed annually has more than doubled, rising from 22 disorders in 1993 to 55 in 2016. The majority of PNDx single gene tests were performed for disorders that primarily impaired physical ability (71.5%), while disorders impairing neurodevelopmental function comprised 22.9% of PNDx (Table 1). Disorders with adult onset had comparatively low testing numbers (3.3%) and those categorised as lethal in infancy comprised the smallest proportion of all PNDx (2.3%) The most common single gene PNDx indications from 1993 were thalassemia (n=681), cystic fibrosis (n=408) and fragile X syndrome (n=282) (Table 2).

Characterization of disorders in the PGT-M dataset (2005-2016)

In total, n=843 PGT-M tests were performed for 138 individual conditions. The most common conditions were cystic fibrosis, fragile X, and Huntington disease. The majority of PGT-M tests were undertaken to identify disorders that primarily impair physical ability (59.9%) followed by adult onset disorders (24.3%) and disorders that primarily impair neurodevelopmental ability (14.7%) (Table 2). The greatest growth over the past five years was in the impairment of physical ability and adult onset categories. The proportion of tests for adult onset disorders was significantly higher in the PGT-M population compared with the PNDx population (24.3% vs 3.3% respectively, $p < 0.001$).

Discussion

This large retrospective cohort study is the first to assess trends in the prenatal and preimplantation genetic diagnosis of single gene disorders on a population-wide basis in Australia. Furthermore, we are unaware of any comparable studies internationally. We have ascertained a baseline single gene PNDx rate of approximately 1 in 500 births, and a rapidly increasing PGT-M rate that now exceeds that of PNDx. The number and scope of individual disorders subject to testing also increased rapidly, reflecting advances in genetic knowledge and rapid clinical translation.

Our data reveal an emerging demand for reproductive testing during the preimplantation, rather than post-implantation stage. This is despite the considerably higher patient costs associated with PGT-M compared with PNDx. Our results support the widely-held assumption that PGT-M is the preferred diagnostic option for couples who are known carriers, as preimplantation embryos are commonly conferred a different moral status to a fetus developing in the womb[22, 23]. While the option of PGT-M is limited by patient affordability and medical suitability for IVF treatment, its rising utilization shows an increased awareness of its availability, and is likely to have attenuated demand for prenatal diagnosis in recent years.

The range of disorders in the PGT-M and PNDx dataset was notable for several reasons. First, there was a significantly higher proportion of adult onset disorders in the PGT-M cohort compared with the PNDx cohort (24.3% vs 3.3%). Prenatal diagnosis for adult onset disorders (e.g. Huntington disease), or mutations that predispose to illness later in life (e.g. BRCA1/2 mutations and other cancer risk) is an ethically complex area as an individual is expected to have many years of good quality life prior to disease onset.[24] This complexity may be further compounded by the knowledge that one parent is at risk of developing the condition. After birth, other ethical issues arise, such as the timing of disclosure to the child, depriving the child of the right "not to know" their genetic status, and the unknown long-term health implications of embyro biopsy.[25] The preferential use of PGT-M for adult onset conditions suggests that couples believe that testing at this stage creates fewer dilemmas than PNDx, and that discarding affected embryos is a morally acceptable trade-off for avoiding late onset morbidity in their future child. The widening scope of PGT-M testing observed in our study has relevance for the debate within bioethics regarding "neo-eugenics" and the future of embyro screening using PGT-M.[26] Our local practice appears consistent with the American Society for Reproductive Medicine statement that: "Preimplantation genetic diagnosis (PGT-M) for adult-onset conditions is ethically justifiable when the conditions are serious and when there are no known interventions for the conditions or the available interventions are either inadequately effective or significantly burdensome. For conditions that are less serious or of lower penetrance, PGT-M for adult onset conditions is ethically acceptable as a matter of reproductive liberty."[27]

Another significant observation in our study was the steady expansion in the total number of conditions analysed by PGT-M and PNDx, reflecting advances in our understanding of the genetic basis of many diseases and the rapid translation of this knowledge into clinical diagnostics (e.g. the identification of the *CFTR* gene responsible for cystic fibrosis in 1989). Not surprisingly, given the ethnic composition of our population, the two most common single gene tests were for thalassemia (PNDx) and cystic fibrosis (PGT-M). The majority of the single gene disorders were categorized as primarily affecting physical ability across both PNDx and PGT-M cohorts, reflecting their higher prevalence in the general population compared with conditions that primarily affect cognition. Testing for lethal conditions was very rare, probably reflecting the very low prevalence of these conditions in the general population, as well as the reduced clinical utility of prenatal testing for such conditions.[28, 29]

Despite the increase in the numbers of conditions for which testing is available, there has only been a small growth in total PNDx for single gene disorders since 2013. As well as the influence of PGT-M, developments in postnatal management of some disorders may have also contributed to this observed plateau. These advances promise better long-term

outcomes for some single gene disorders, such as spinal muscular atrophy and beta thalassemia.[30-32] Such improvements may reduce a couple's perception of the health burden of some single gene disorders and continue to exert downward pressure on PNDx numbers and increasing pressure on PGT-M into the future.[33, 34]

The major strength of our study was the population-based approach, which allowed annual testing rates to be estimated from the very commencement of PNDx in our state, and avoided the selection bias introduced by tertiary referral or laboratory based populations.[35] Our systematic categorization of disease phenotypes enabled us to discover the trend in PGT-M for adult onset disorders, which has not previously been reported in our population.

However, there were some limitations in our data sources. We did not have access to the results of the diagnostic testing or pregnancy outcomes, and therefore could not make any conclusions on how testing may have informed clinical management. Furthermore, we were not able to perform individual patient linkage between single gene PNDx, PNDx for other indications, prenatal aneuploidy screening, parental carrier testing and PGT-M. Consequently, our overview of PNDx and PGT-M for single gene disorders does not capture all elements of the screening and diagnostic pathways available. For example, our study period spanned the introduction of self-funded multi-disorder reproductive carrier screening in Victoria in late 2012.[6] More than 12,000 carrier screening panels incorporating cystic fibrosis, spinal muscular atrophy and fragile X have been performed in Victoria since 2012.[6] We were not able to ascertain from our dataset whether the introduction of this screening has had any direct impact on PNDx or PGT-M as linkage to carrier screening tests was not possible.

The introduction of NIPD in the foreseeable future will undoubtedly lead to further changes in diagnostic pathways for this indication group. It is expected these changes will cause downstream influences on the uptake of prenatal diagnosis for single gene disorders. Ongoing surveillance of PNDx and PGT-M for single gene disorders will be central to monitoring the impact of new technologies in reproductive testing.

Conclusion

Our study provides the first population-wide analysis of PNDx and PGT-M for single gene disorders in Australia. While demand for PNDx has remained steady at approximately 1 in 500 births over the past decade, PGT-M has grown rapidly and is expected to continue exceeding PNDx in the future, despite the high patient costs. PGT-M appears to be the

preferred testing modality for adult onset disorders, presumably because it avoids many of the ethical issues associated with testing for such conditions during pregnancy.

Conflict of interest

The authors declare no conflict of interest.

Contribution to authorship

JH contributed to the intellectual planning and conception of the study, data collection, analysis and interpretation, and critically reviewed the manuscript for intellectual content. SL and LH contributed to study design, data analysis and interpretation, and critically reviewed the manuscript for intellectual content. AP contributed to study design, data collection, analysis and interpretation, and wrote the manuscript.

Details of ethics approval

Human Research Ethics Committee (HREC) approval for the prenatal diagnosis data collection and related research was received from the Royal Children's Hospital HREC on 17 Jan 2012 (Ref. No. 31135A) and Monash Health HREC on 18 April 2012 (Ref. No. 12063B).

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Tables

Table 1. Total categorisation numbers for prenatal diagnosis (PNDx) (1993-2016) and preimplantation genetic diagnosis (PGT-M) (2005-2016).

Disease category	PNDx (1993-2016) N = 2597 n (%)	PGT-M (2005-2016) N = 843 n (%)	P value†
Physical	1858 (71.5%)	505 (59.9%)	p<0.001
Neurodevelopmental	594 (22.9%)	124 (14.7%)	p<0.001
Adult onset	85 (3.3%)	205 (24.3%)	p<0.001
Lethal in infancy	609 (2.3%)	9 (1.1%)	p=0.0031

†Chi-squared test for proportions

Table 2. Ten most common conditions in prenatal diagnosis (PNDx) (1993-2016) and preimplantation genetic diagnosis (PGT-M) datasets (2005-2016)

Prenatal Diagnosis (1993-2016)		
Disorder	**Frequency**	**% total PNDx (n=2597)**
Thalassaemia	681	26.2%
Cystic fibrosis	408	15.7%
Fragile X syndrome	282	10.9%
Duchenne muscular dystrophy	143	5.5%
Spinal muscular atrophy	122	4.7%
Haemophilia	68	2.6%
Huntington disease	55	2.1%
Myotonic dystrophy	51	2.0%
X-linked hydrocephalus	33	1.3%
Congenital adrenal hypoplasia	31	1.2%
Preimplantation Genetic Diagnosis (2005-2016)		
Disorder	**Frequency**	**% total PGD (n=843)**
Cystic fibrosis	125	14.8%
Huntington disease	95	11.3%
Fragile X	71	8.4%
Thalassaemia	56	6.6%
BRCA	33	3.9%
Myotonic dystrophy	30	3.6%
Spinal muscular atrophy	25	3.0%
Neurofibromatosis	25	3.0%
Marfan syndrome	18	2.1%

Familial adenomatous polyposis	17	2.0%

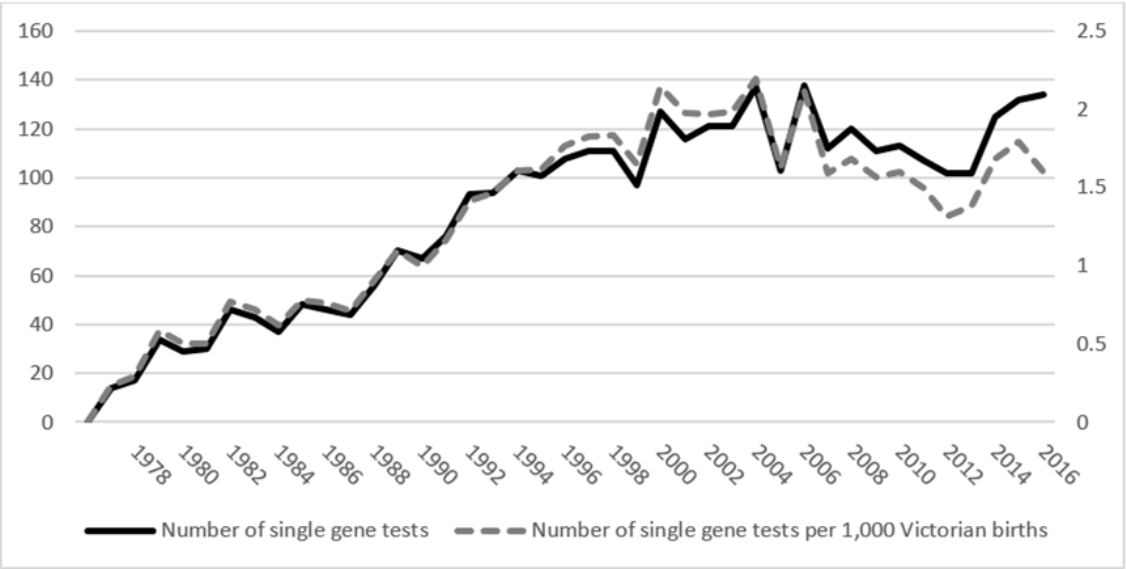


Figure 1: Annual number and rate per 1000 births of prenatal diagnostic procedures performed for a single gene indication at <25 weeks gestation in Victoria from 1977-2016.

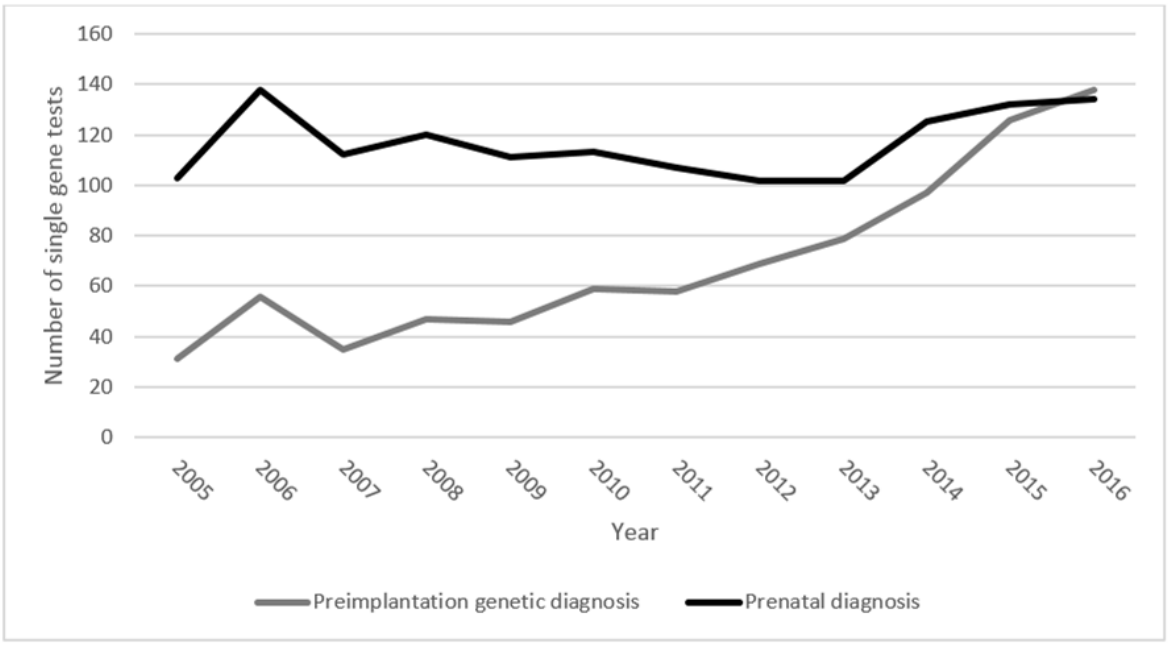
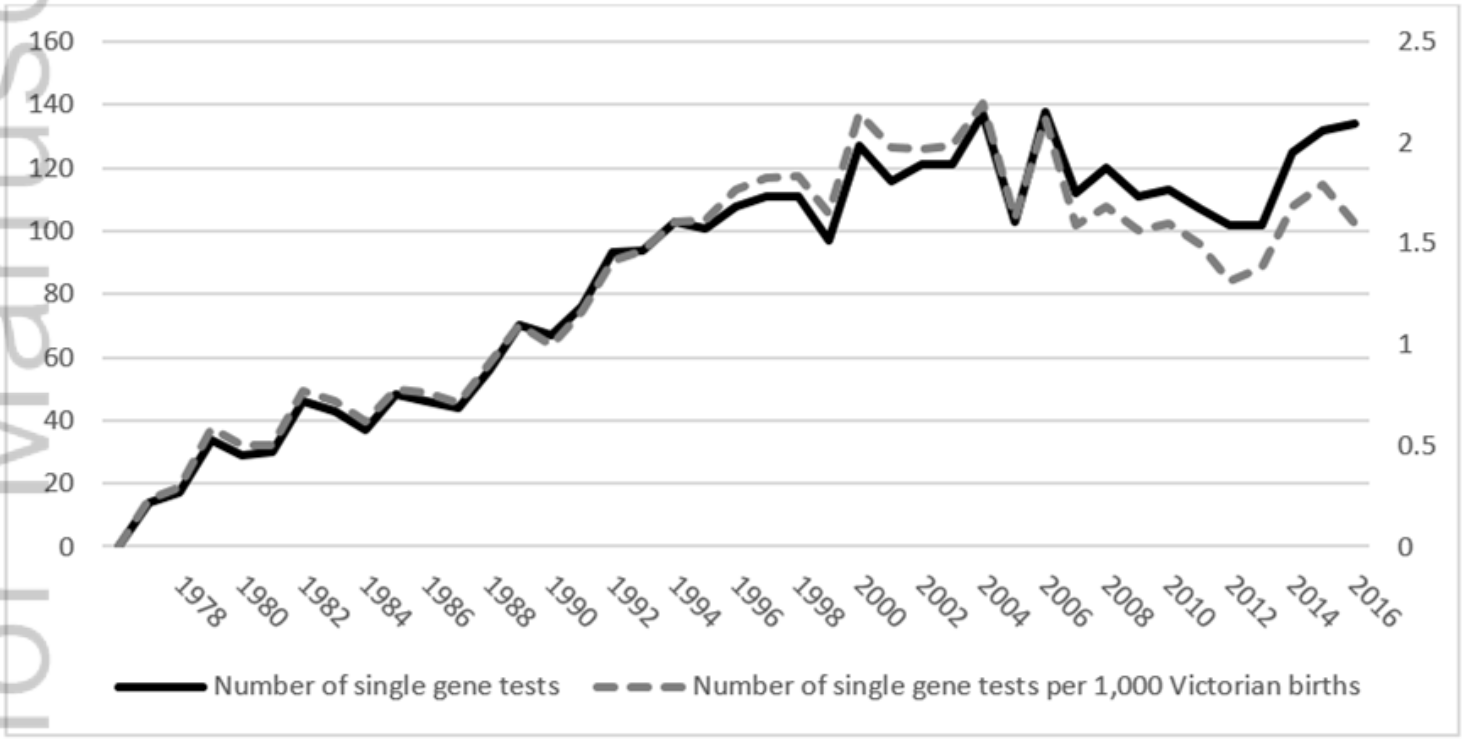


Figure 2. Annual number of single gene preimplantation genetic diagnosis, and prenatal diagnostic procedures performed for a single gene indication at <25 weeks gestation, in Victoria from 2005 to 2016.



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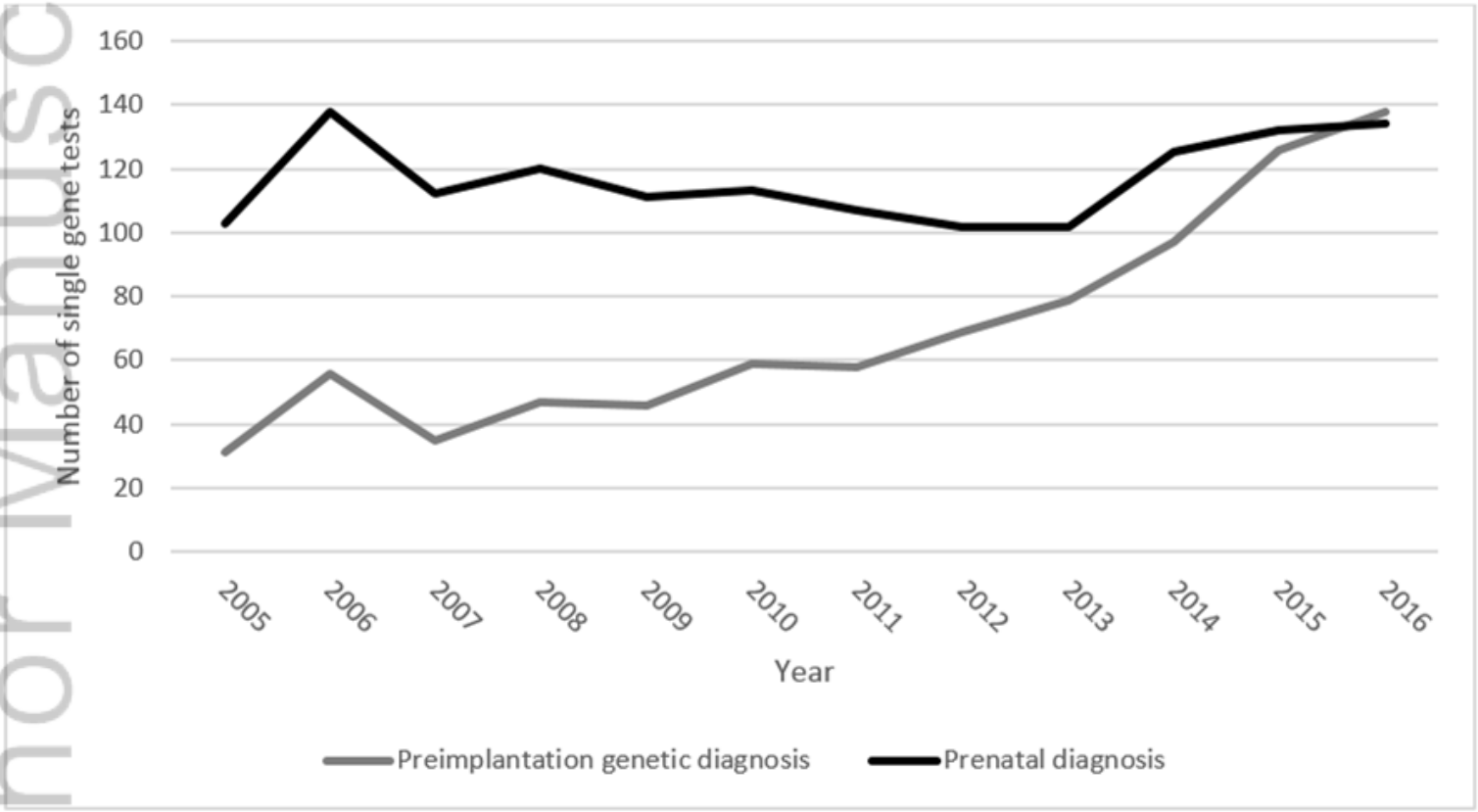

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