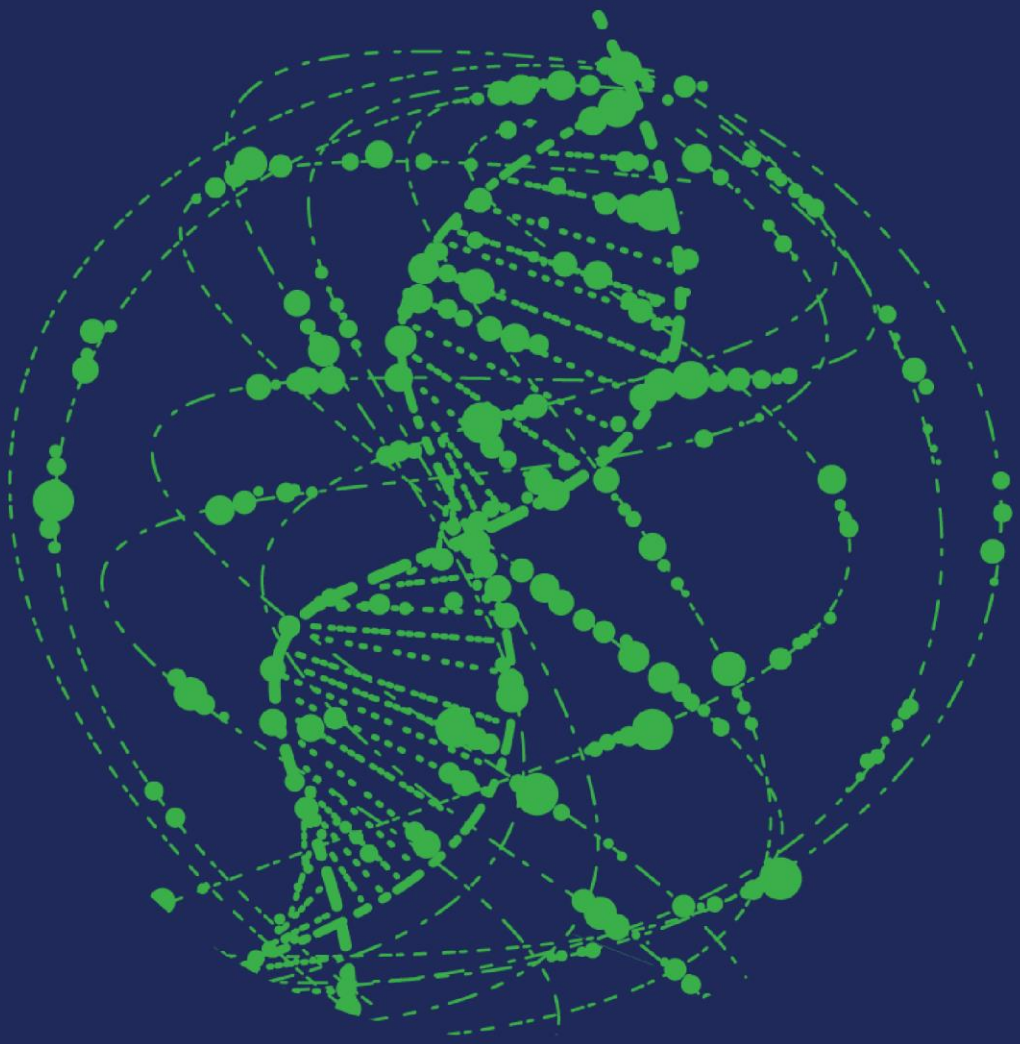
NEXT BIOSCIENCES

POCScreen Products of Conception Testing Statistics

Cumulative Statistics 2024



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Introduction

Dear Colleague,

Recurrent miscarriage continues to be a challenging reproductive problem for patients and clinicians. It is a traumatic event which has psychological implications.

Although many chromosomal abnormalities that cause miscarriages are sporadic, some abnormalities (such as translocations) are inherited and expected to significantly increase the risk of recurrence, therefore, possibly necessitating parental cytogenetic karyotyping. By identifying the approximate 50% of women whose pregnancy loss was due to chromosomal abnormalities, comprehensive chromosome screening will prevent a large proportion of patients from undertaking unnecessary and costly evaluations. If a fetal chromosomal abnormality is excluded, there may be a possible treatable cause for a given miscarriage, and investigations can be focused on identifying this. Genetic testing outcomes can therefore be used to guide counselling for future pregnancies. Furthermore, the psychological benefit of identifying the aetiology of a fetal loss, cannot be overstated.

The POCScreen test offered by Next Biosciences employs next generation sequencing (NGS) technology to rapidly and accurately screen products of conception (POC) for abnormal chromosome numbers (aneuploidies), and large deletions and/or duplications of chromosomal material. We have compiled statistics on tests done at our laboratory in Midrand, for the five-year period from 2019 to 2023. We hope that you will find these informative with regard to the trends seen in POC screening in the private sector in South Africa.

Warm Regards,

Dr Yvonne Holt
Chief Medical Officer

Overall results

Aneuploidy is defined as an atypical number of chromosomes, meaning more or less than the expected 46 chromosomes, or segments of a chromosome deleted or duplicated. We detected aneuploidy in 45.8% of the POC samples tested, with 54% of samples having a normal chromosome complement (Figure 1). Our aneuploidy rate is consistent with current literature which reports that approximately 50% of pregnancy losses, especially in the first trimester, are caused by chromosomal abnormalities[1].

Mitotic errors post-fertilisation can give rise to two distinct cell populations in the developing embryo, this phenomenon is called mosaicism. The association between mosaicism and pregnancy loss is not well documented, however, the rate of mosaicism seen in prenatal diagnosis ranges from 1 to 2%[2]. We found that 3.3% of the POC samples tested in our laboratory revealed mosaicism. The clinical consequences are dependent on the chromosome(s) involved and the level of mosaicism. It is, however, important to note that maternal cell contamination can mask a full aneuploidy, resulting in a mosaic result.

The failure rate of conventional karyotyping is recorded to be between 10% to 40%[3]. POCScreen uses next generation sequencing (NGS) technology to obtain a molecular profile on DNA extracted from fetal or placental tissue, which mitigates the need for cell culture. This allows us to report a test failure rate of as low as 0.2%, highlighting the advantage of using NGS technology for POC testing.

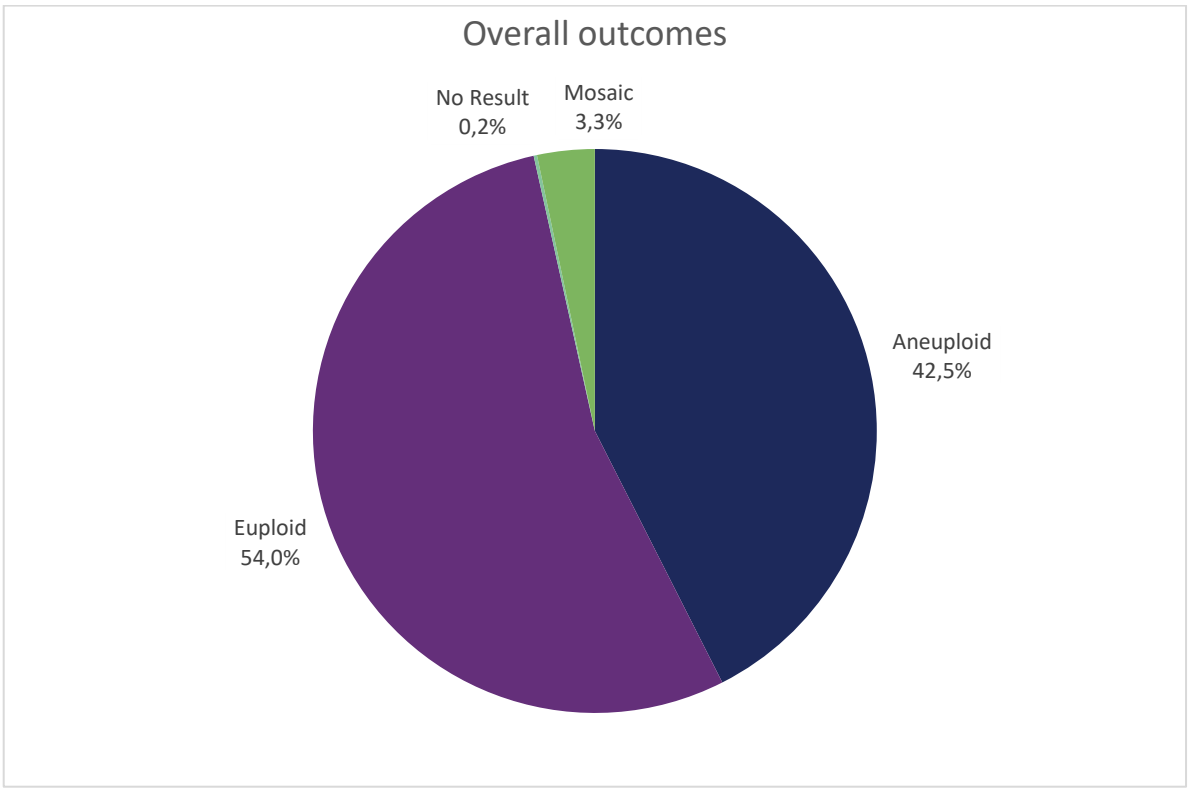

Figure 1. Overall outcome data on POCScreen for the period 2019 to 2023.

Results per maternal age group

As expected, aneuploidy rates increase with maternal age. The overall aneuploidy rate observed in younger patients was 38.1%, compared to 55% in patients older than 35 (Figures 2 and 3). The incidence of chromosome segregation errors is higher in ageing oocytes; consequently, the number of good quality oocytes in older mothers is fewer than in younger mothers, which increases the frequency of miscarriage[4]. The paternal age effect on aneuploidy is still unclear.

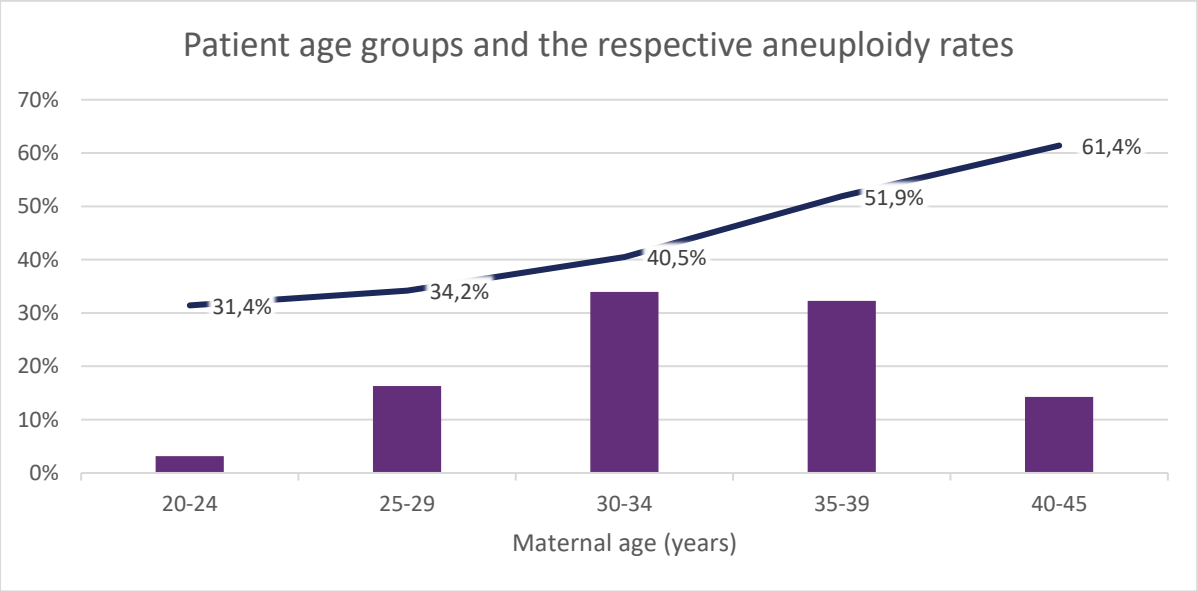

Figure 2. The vertical bars represent the distribution of patients referred across the different maternal age groups. Aneuploidy rates for the various maternal age groups are shown by the solid line.

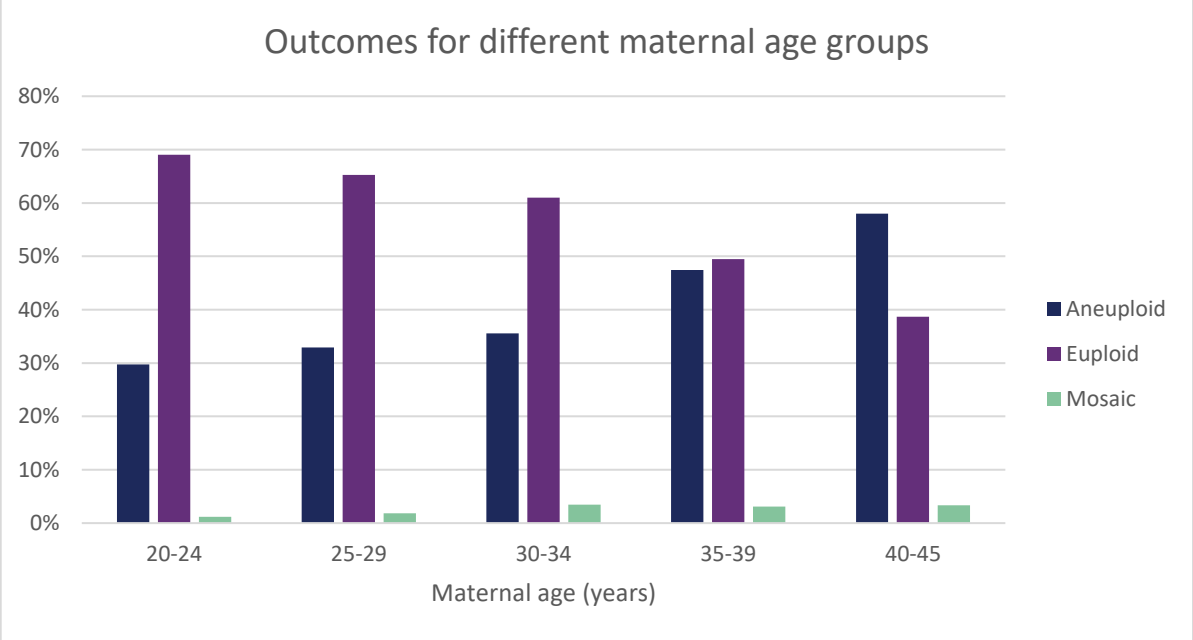

Figure 3. The distribution of aneuploid and euploid results for the different maternal age groups.

Reason for referral

POCScreen is requested after an unexplained pregnancy loss, with recurrent miscarriage as the most common referral reason. The contribution of aneuploidy reported for recurrent miscarriage patients varies[5]. Our data showed that a chromosomal anomaly is identified in 47.5% of POCs referred after unexplained recurrent miscarriages (Figure 4), illustrating the value it could add for these presumably chance events. This information may aid clinicians in focusing their investigations.

Complete hydatidiform moles (CHM) have no identifiable fetal tissue and abnormal growth of the placenta. CHM result from receiving two paternal genomes with no maternal contribution and will, therefore, present as euploid since there is no change in chromosome number. Partial moles are triploid, with two paternal and one maternal genomes. As with non-molar triploidy, certain types cannot be detected with POCScreen.

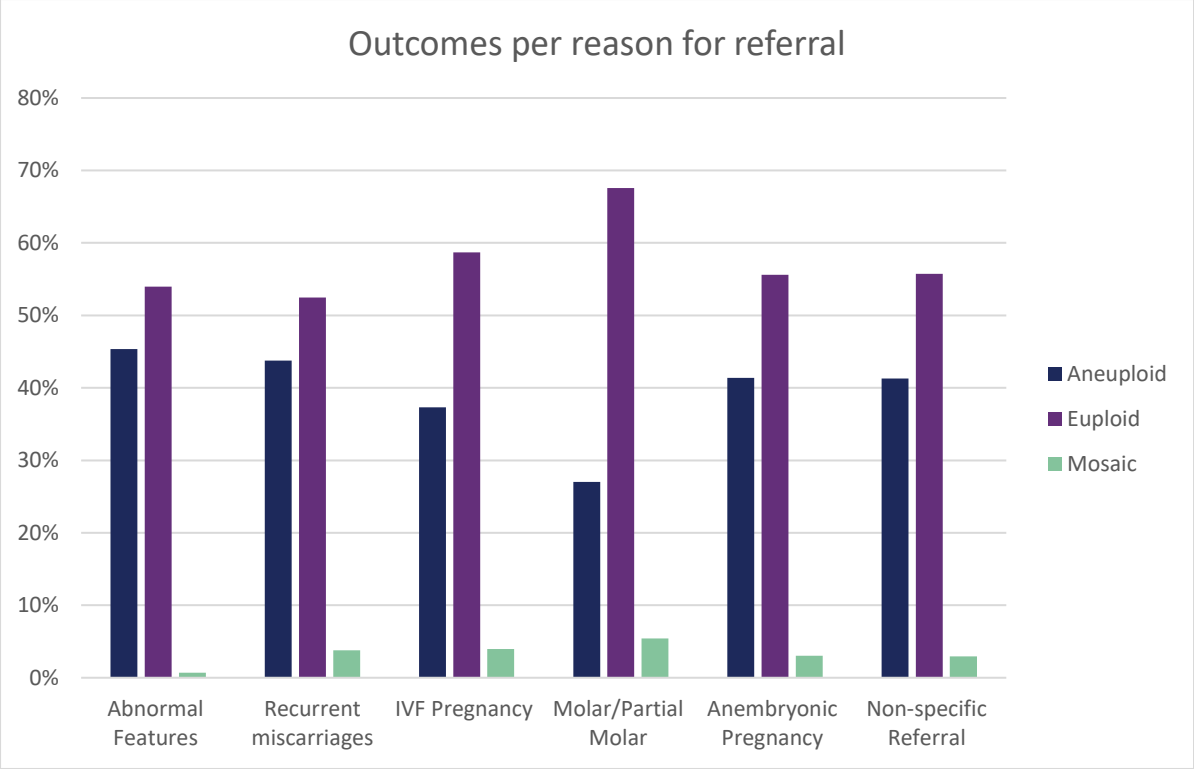

Figure 4. Distribution of tests performed across the different indications.

Results per gestational age group

It is accepted that about 50% of early pregnancy loss is caused by chromosomal abnormalities. This was also observed in the current dataset where 46.6% of POCScreen results for first-trimester losses showed an aneuploidy (Figure 5). As gestational age increases, the frequency of aneuploidy decreases. Most trisomies and monosomies are not compatible with life, therefore, chromosomal abnormalities are less likely to be the cause of miscarriage further along in the pregnancy. Alternative or higher-resolution testing is recommended in late-trimester pregnancy losses if no aneuploidies are identified, especially if abnormal features indicative of a genetic abnormality are reported.

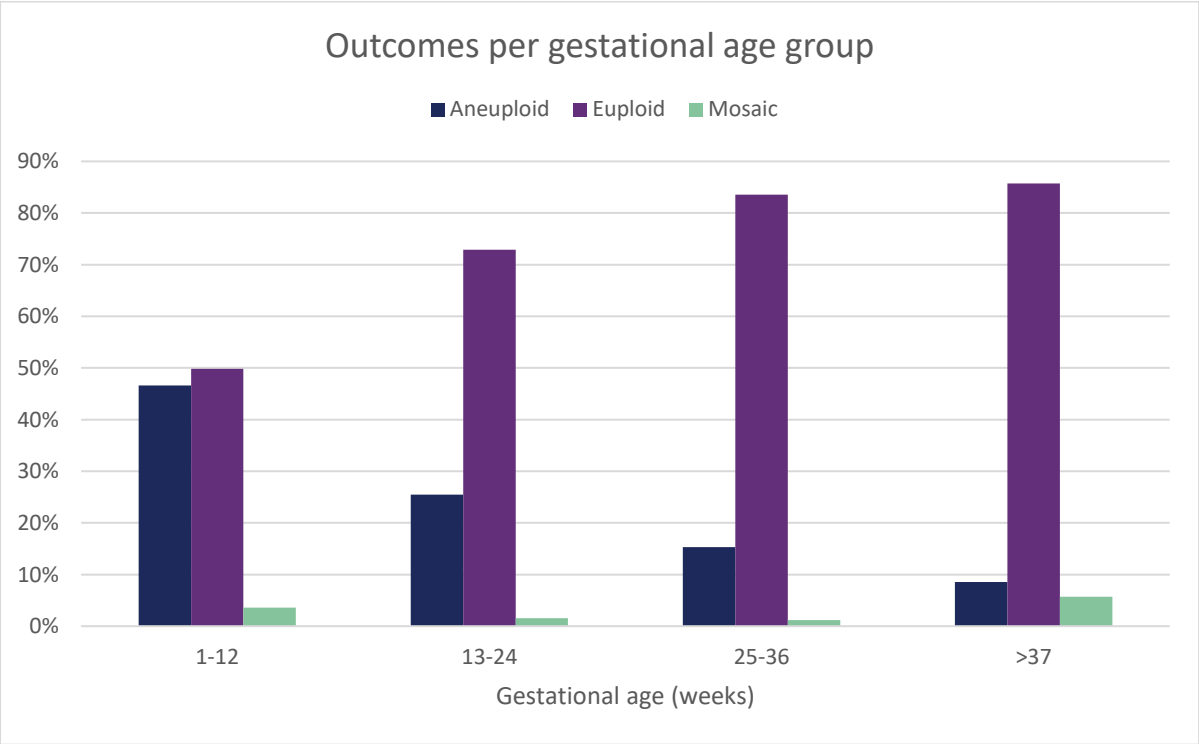

Figure 5. Outcome data for the different gestational ages.

Types of anomalies

The spectrum of chromosomal abnormalities in our dataset was represented by numeric events, ploidy changes, and segmental/partial chromosomal events. Ploidy changes refer to the gain of an additional full set of chromosomes and comprise 7.9% of anomalies detected (Figure 6). It is important to note that the technology does not allow for the detection of certain types of polyploids, e.g., 69, XXX.

Segmental chromosomal gains or losses are reported when smaller, sub-chromosomal regions are duplicated or deleted. NGS allows for the identification of gains or losses larger than 10 mega base pairs (Mbp), but smaller gains/losses may still be detected based on the quality of the sample. The molecular profile observed for 4.4% of POC samples showed a gain and/or loss of genetic material from one or more chromosomes, which can be indicative of an unbalanced structural chromosomal rearrangement. In these cases, parental karyotyping is recommended to determine if this is an inherited or *de novo* chromosomal abnormality. It is reported that in approximately 4% of couples with multiple miscarriages, one or both parents have an unknown inherited balanced translocation[6]. NGS does not allow for the distinction between a balanced translocation and a euploid profile.

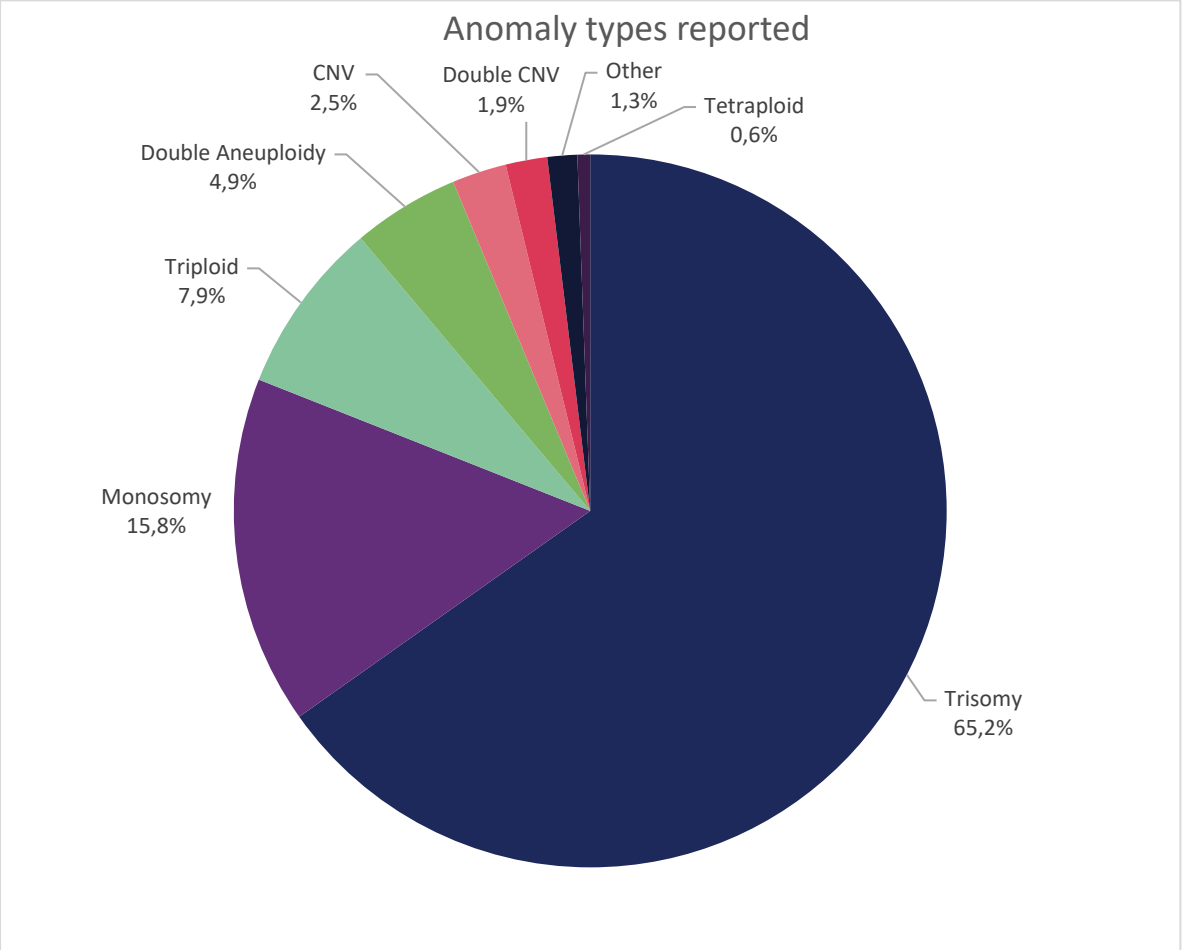

Figure 6. Distribution of anomaly types reported. CNV – copy number variants, represented by segmental gains and losses larger than 10 mega base pairs. Other refers to results with more than one type of aneuploidy.

Abnormalities per chromosome

Chromosome 16 was the most frequently observed autosomal trisomy, which is consistent with published studies[1] (Figure 7). Other common aneuploidies in POCs included trisomies of chromosomes 13, 15, 18, 21, and 22. Most of these are described as the most frequent both in preimplantation embryos at blastocyst stage, and POCs[8,9]. Monosomy X was the only type of whole chromosome loss observed, apart from a few cases of monosomy 21, and is consistent with the clinical diagnosis of Turner syndrome in live-born individuals. Monosomy X is one of the most common cytogenetic abnormalities in spontaneous abortions, only 1% of conceptuses survive to term[10]. There is no increased risk of recurrence of this abnormality. However, if recurrent pregnancy loss is observed, maternal karyotyping would be recommended to rule out mosaic monosomy X as it is associated with a higher risk of adverse obstetric outcomes.

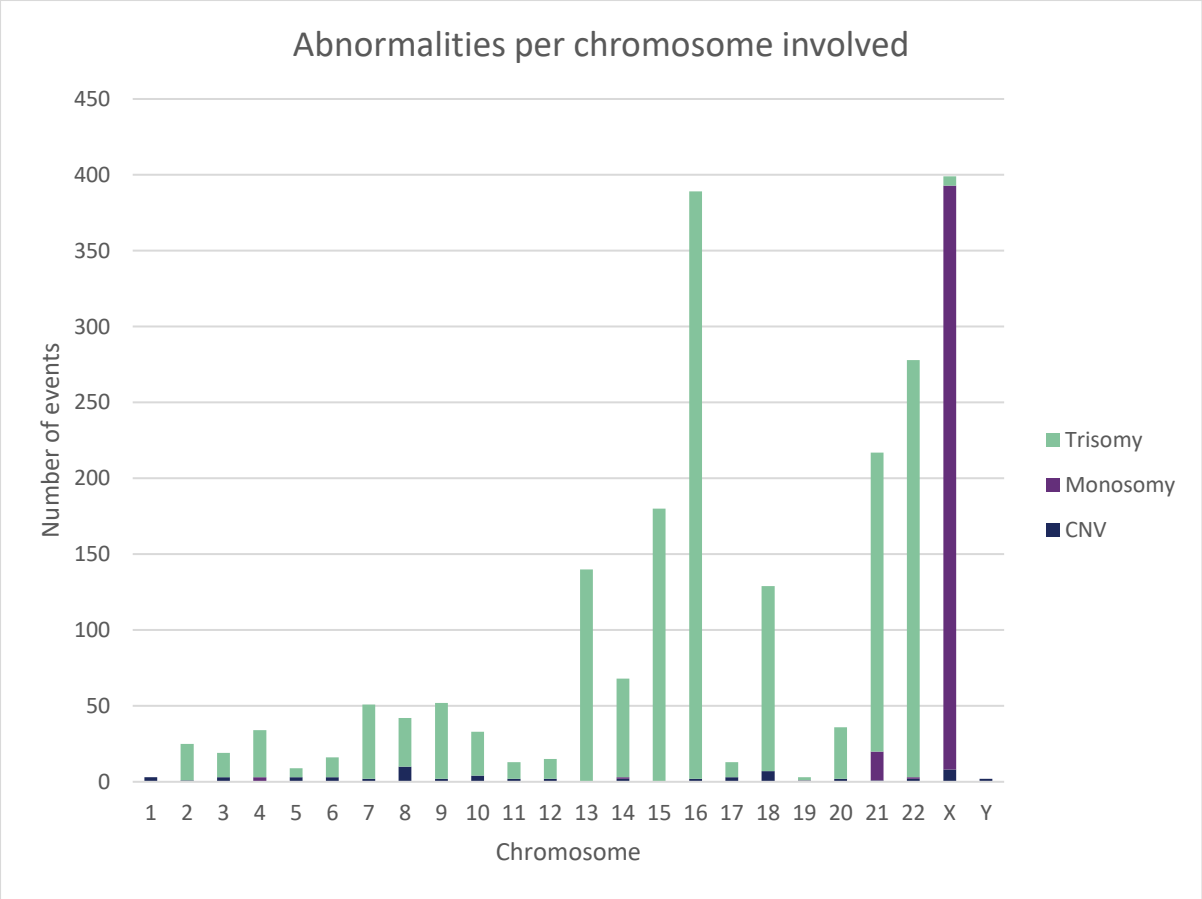

Figure 7. Chromosomes involved in reports of trisomy, monosomy, and segmental gains and losses (CNVs).

The aneuploidies reported for losses in the third trimester (after 24 weeks), are trisomy 13, 18, 21, Monosomy X, and CNVs (Figures 8 and 9). As these aneuploidies may result in live births, these pregnancies may progress further before a miscarriage occurs.

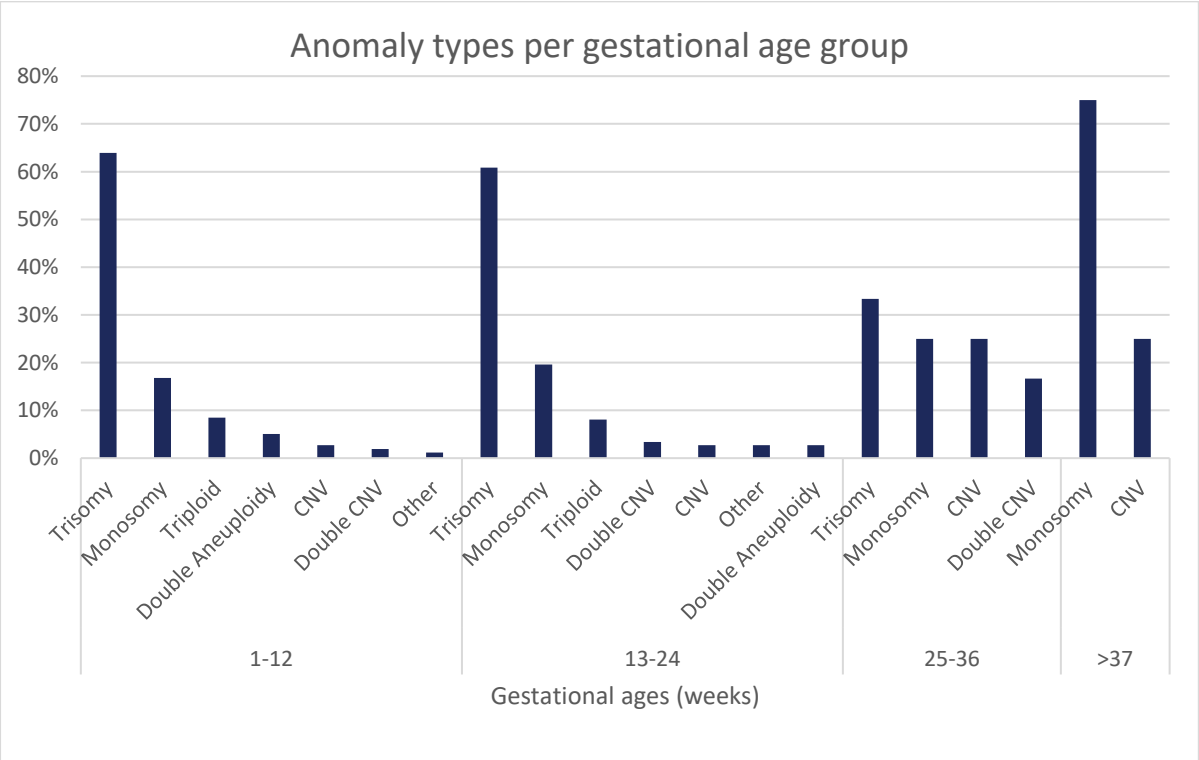

Figure 8. Types of aneuploidies identified for progressing gestational ages. 'Double Aneuploidy' and 'Double CNV' refer to cases with more than one anomaly of the same type, whereas 'Othr' refers to cases with more than one type of anomaly. 'CNV' – copy number variation.

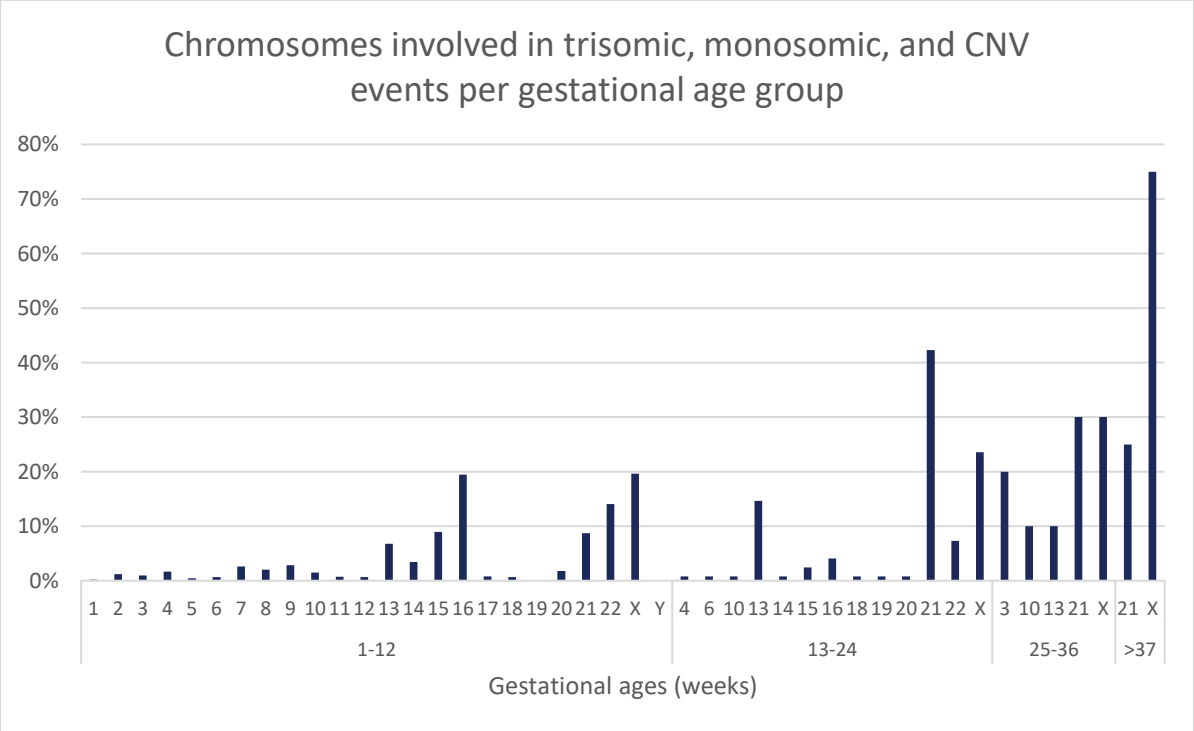

Figure 9. The chromosomes involved in anomalies reported for progressing gestational ages are shown on the x-axis. Trisomies, monosomies, and copy number variations are included in these numbers.

Sample types received and tested

Samples received for POCScreen testing are examined and dissected to exclude maternal cell contamination (MCC) as far as possible. Ideally, products clearly identified to be of fetal or placental origin (fetal skin or muscle biopsy, chorionic villi, chorionic or amniotic membrane, and umbilical cord) are isolated for testing. Chorionic villi are by far the most frequent tissue type submitted and isolated for testing, seconded only by-products of unknown origin (unidentifiable tissue) (Figure 10).

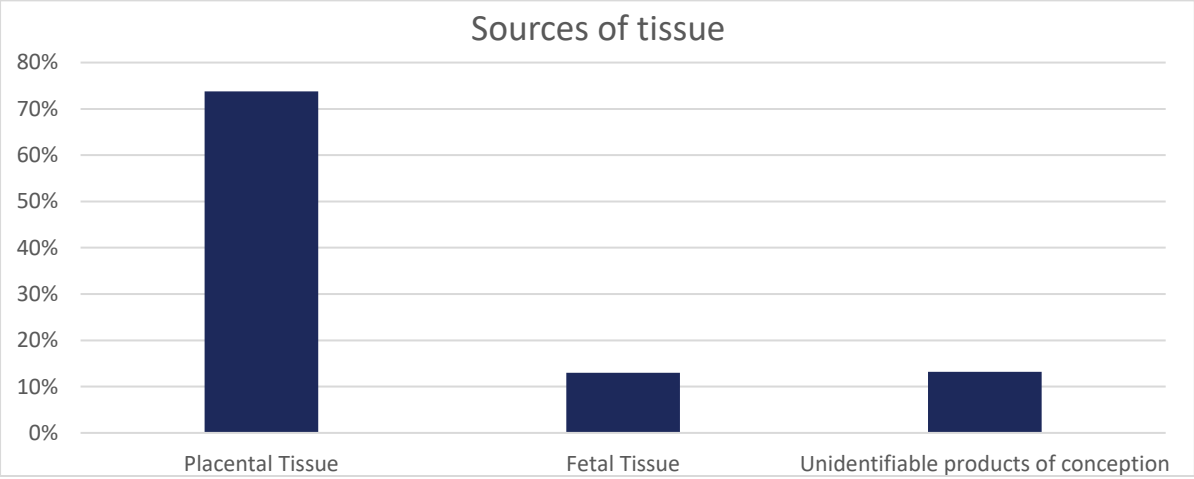

Figure 10. Distribution of tissue types isolated for POCScreen.

Testing unidentifiable tissue significantly increases the risk of MCC. MCC is probably the most frequent laboratory factor leading to a decrease in the rate of detecting chromosomal abnormalities in POCs due to an over-reporting of a normal female profile. Figure 11 shows that euploid female results were obtained for 94.9% of unidentifiable POC samples, which likely represent maternal cells. Submitting fetal or placental tissue therefore greatly improves the diagnostic yield for POC samples, and the value of sampling these tissue types after a miscarriage cannot be overstated.

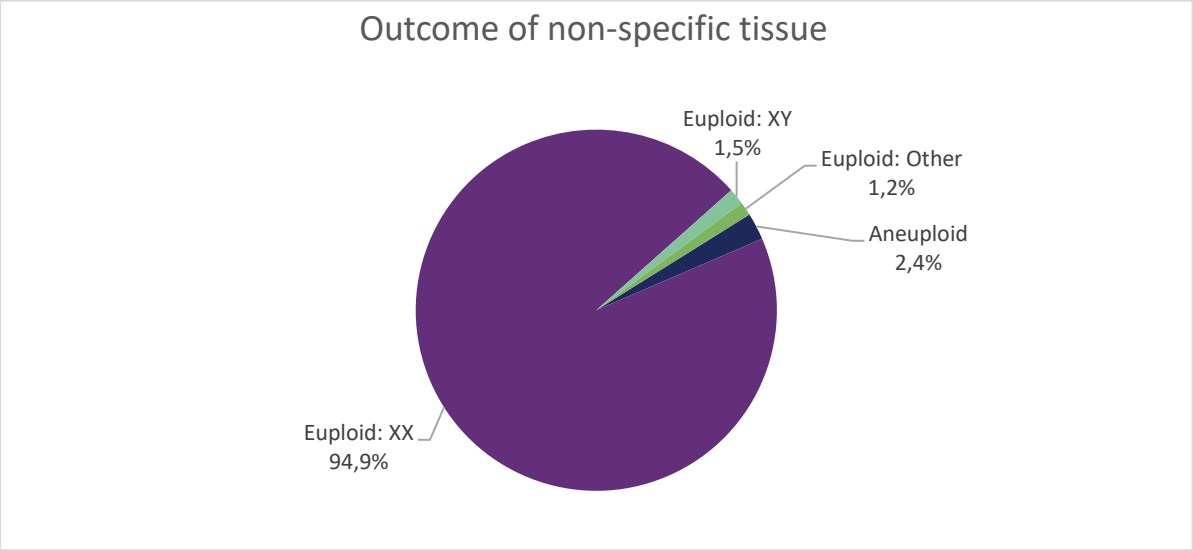

Figure 11. Outcomes reported for unidentifiable products of conception tissue. 'Euploid: Other' refers to XX/XY profiles which is attributable to the presence of maternal cell contamination in an XY profile.

Test cancellations

POCScreen is generally reimbursed by medical funders if the miscarriage is managed with an in-hospital/clinic procedure. A significant number of tests are cancelled by the patients after the sample has been received by the laboratory. Figure 12 shows that the majority of these cancelled tests are not funded by the patients' medical aid, indicating that financial constraints could be an important indication.

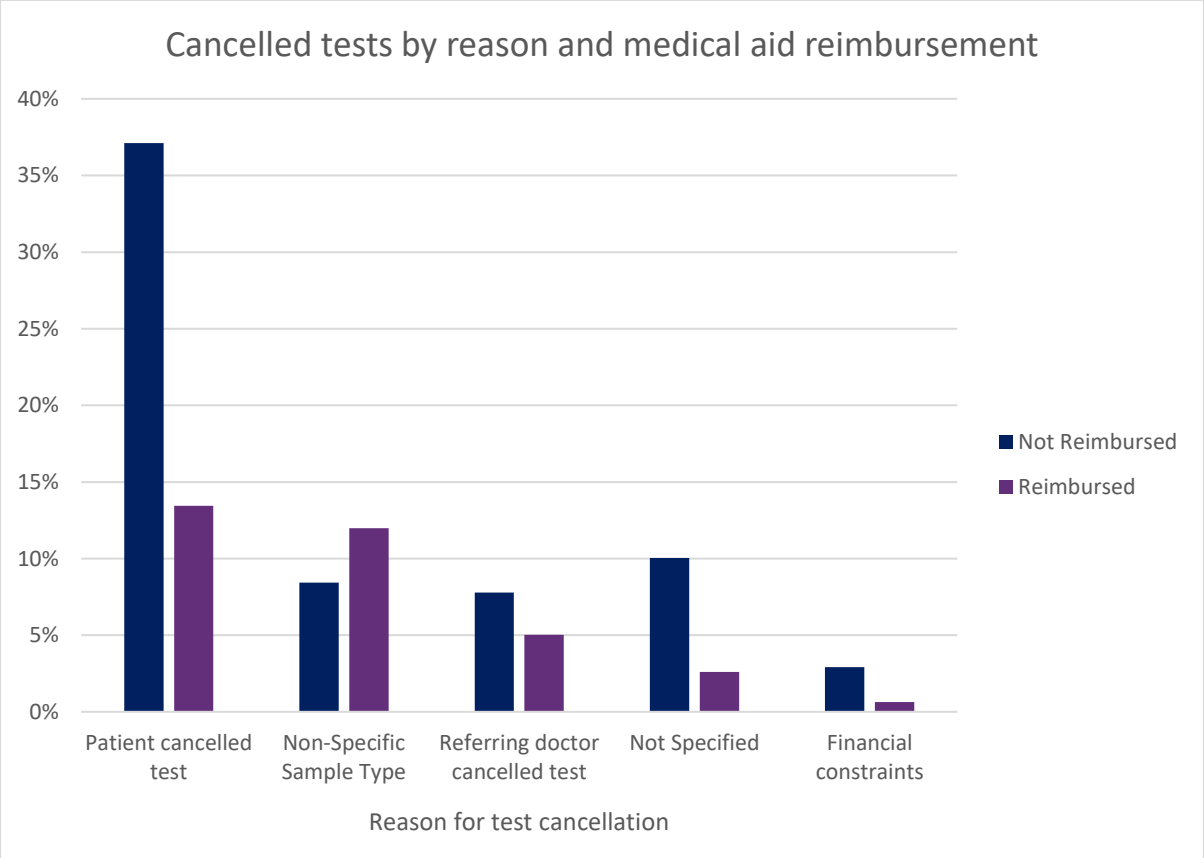

Figure 12. Cancelled tests categorised based on the reason provide for the cancellation. The ratio of funder reimbursed vs. not reimbursed are shown for each category.

Document compiled and/or reviewed by Renee Briers (Head of Laboratory), Kelly Loggenberg (Genetic Counsellor), and Gloudi Agenbag (Laboratory Research & Technical Specialist).

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