**Please nominate 1 category that best fits your submitted abstract:**

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| Paediatric and/or congenital diseases  Maternal and/or prenatal health  Cardiometabolic diseases  Chronic diseases  Healthy aging  Cancer  Neurodegenerative diseases  Public health  Other |

**Please nominate 2-5 subject areas relevant to your submitted abstract:**

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| Aged care  Allied health  Animal models  Biochemistry  Bioinformatics  Biomarker research  Biotechnology  Cardiovascular research  Cancer  Cell biology  Clinical research  Commercialisation  Computational biology and/or statistics  Consumer advocacy  Dentistry  Developmental biology  Drug discovery  Drug target identification and validation  Education and training  Endocrinology  Environment  Epidemiology  Genetic counselling  Genetics, epigenetic or small RNAs  Healthcare | Health economics  Health policy  Health promotion  Imaging and computing  Immunology  Indigenous health  Industry  Invisible illnesses  Medicinal chemistry  Microbiology  Molecular biology  Neuroscience  Nutrition  Pain management  Pathology  Personalised Medicine  Rare diseases  Physiology  Psychology  Public health  Reproductive biology  Technology  Tele-health  Virology  Other (please specify): |

**Screening for X chromosome abnormalities in Victorian newborns**

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**Background and Aims:** Newborn screening using DNA methylation analysis for specific rare diseases, may generate health benefits through early diagnosis and treatment. This study describes development and application for 2nd and 3rd-tier testing utilizing droplet digital PCR (ddPCR) and Low-Coverage Whole Genome Sequencing (LC-WGS) using a single 3mm newborn blood spot (NBS) punch for each infant tested. This workflow was developed to determine if individuals with abnormal DNA methylation, reflective of skewed X-inactivation, have structural X chromosome abnormalities.

**Methods:** A novel ddPCR method was developed for 2nd-tier testing that targeted specific sex chromosome markers. Male and female reference ranges were established using newborn blood spots (NBS) of 15 male and 20 female infant controls from the general population. For 3rd-tier testing, the bioinformatic pipeline for LC-WGS was developed using data from NBS of 14 male and 14 female infant controls. The 2nd-tier ddPCR test was applied to 314 individuals shortlisted from 9,149 female NBS (consented for de-identified research) by 1st-tier methylation testing to have abnormal *FMR1* methylation signatures suggesting severe skewing in X-inactivation.

**Results:** Of the 314 shortlisted female NBS, 2nd-tier ddPCR testing identified 36 individuals with abnormal X chromosome copy number. Individuals’ sex was confirmed as female with negative results for an *SRY* marker located on the Y chromosome. An initial batch of four NBS with the greatest outlier X-Chromosome marker results were reflexed for LC-WGS, which confirmed two samples with presence of trisomy X. The LC-WGS for the second batch of 32 NBS samples are currently pending.

**Conclusion and Significance/Impact:** It was feasible to perform confirmatory testing for X chromosome structural abnormalities using ddPCR and LC-WGS on a single 3mm NBS punch per infant from 314 females with skewed X-inactivation. These material requirements for this workflow are in line with those of the current standard-of-care newborn screening programs.

**Lay Title: Screening for X chromosome abnormalities in Victorian newborns**

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**Lay Summary:** Affecting one in every300 - 400 births, sex chromosome abnormalities are one of the most common forms of chromosomal anomaly within the general population. Current standard-of-care newborn screening programs do not include these disorders in their testing and many affected newborns often do not receive a correct diagnosis within their first year of life. This study describes a new testing approach which could be used to identify these conditions in infants.