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Diagnostic and service impact of genomic testing technologies in a neonatal intensive care unit

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**ABSTRACT**

**Aim**: To investigate the diagnostic and service impact of chromosomal microarray (CMA) and whole exome sequencing (WES) in a neonatal intensive care unit (NICU).

**Methods**: Retrospective medical record review of NICU patients referred for genetics consultation at three time-points over a 9-year period at a single centre to determine referral indications, genetic consultation outcomes, and time to diagnosis.

**Results**: The number of NICU patients referred for genetics consultation increased from 44 in 2007 to 95 in 2015. The proportion of NICU patients suspected of having a genetic condition following clinical geneticist assessment remained stable, averaging 5.3% of all admissions. The proportion of patients receiving a confirmed diagnosis rose from 21% in 2007 to 53% in 2015, with a shift from primarily chromosomal abnormalities to a broad range of monogenic disorders, increasingly diagnosed by WES as a first-tier test. The average age at diagnosis in 2015 was 19 days (range 12-38 days) for chromosomal abnormalities, and 138 days (range 10-309 days) for monogenic conditions.

**Conclusion**: The adoption of new genetic technologies at our centre has increased the proportion of patients receiving a confirmed genetic diagnosis. This study provides important benchmark data to measure further improvements as turn-around-times for genomic testing decrease.

**Word count**: 200

**Key words**: NICU, diagnostic yield, microarray, exome sequencing

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**What Is Already Known On This Topic**

Genetic conditions are the leading cause of infant morbidity and mortality in the developed world. Genomic testing in neonatal intensive care unit (NICU) patients has high diagnostic and clinical utility, and NICUs are priority areas for implementation of genomic medicine.

**What This Paper Adds**

Approximately 5% of NICU patients are assessed as having a genetic condition after clinical genetics consultation at our centre. The early adoption of chromosomal microarray and whole exome sequencing has doubled the proportion of patients receiving a confirmed genetic diagnosis.



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## INTRODUCTION

Genetic conditions are a leading cause of infant morbidity and mortality in the developed world.[1] Accurate and timely genetic diagnosis in this patient group can avoid unnecessary investigations, optimise management, institute timely surveillance for complications, and provide families and clinicians with prognostic information.[2-5] Over the last ten years, the ability to make a specific diagnosis in patients with an underlying genetic disorder has advanced significantly through the implementation of new genetic testing technologies, such as chromosomal microarray (CMA) and next generation sequencing (NGS). In patients with multiple congenital anomalies and neurodevelopmental delay, CMA has improved diagnostic yield, when compared with G-banded karyotype analysis, from 3% to 15-20%,[6] and is now the accepted first-tier genetic test. In infants with a suspected genetic diagnosis NGS has improved diagnostic rates further with diagnostic yields ranging from 30-73% using whole exome or whole genome sequencing (WES/WGS).[2-5, 7-9] There is also evidence that in this patient population clinical utility is improved by decreasing turn-around testing times.[2, 4, 5]

The implementation of these new genetic testing technologies is expected to impact significantly on diagnostic pathways for sick neonates with suspected genetic diagnoses. Yet there is a paucity of longitudinal outcome data to assess the impact of new genetic testing technologies on overall diagnostic yield in NICU patients, rather than just in those selected for WES/WGS testing. Benchmarking of patient outcome data is an important driver for improvements in health care quality and efficacy, and is essential for effective service planning.[10-13] We sought to evaluate the impact of different genetic testing technologies – G-banded karyotype, CMA and WES – on diagnostic yield and age at diagnosis for patients admitted to a single NICU at three separate time points over a period of nine years.

## MATERIALS AND METHODS

### Study population



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A retrospective review was conducted of medical records of infants referred by The Royal Children's Hospital (RCH) NICU for genetics inpatient consultations. Records were analyzed for consultations that took place in three separate calendar years: 2007 (pre-CMA introduction), 2011 (post-CMA introduction) and 2015 (post-WES introduction). RCH has 250 inpatient beds, and a 38-bed neonatal intensive care unit that cares for newborns with complex medical and surgical needs from the states of Victoria, southern New South Wales and Tasmania. All neonates are transferred in as the hospital does not perform deliveries. Newborns with severe congenital heart disease and/or requiring extra-corporeal membrane oxygenation (ECMO) are generally admitted to the hospital's paediatric intensive care unit (PICU) and were not included in this study.

The following data were collected: demographics, referral indications, time from admission to genetics referral, outcomes of genetic consultation, genetic tests undertaken, and the rate of clinical and cytogenetic or molecular genetic diagnoses achieved in the first year of life. Data were extracted from the medical record using a standardised case report form. Mean and standard deviation were determined for age at referral and diagnosis, in order to have a measure of central tendency that best reflects the spread of the data. Other data are presented categorically. Differences in age at referral were investigated using 2 sided t-test. Chi-squared tests were used to explore difference for categorical variables. Power calculations were performed to compute power for the given sample size and values of the control-group and experimental-group proportions. The following comparisons were performed: proportion of all NICU patients referred for genetics consultation, gender of referred patients, referral indications, genetic tests performed, outcome of genetic consultation – proportion of patients with a suspected genetic condition receiving a molecular/cytogenetic diagnosis. The two time points compared in the statistical analysis are 2007 and 2015. P values are reported for results where $p<0.05$. Statistical analyses were performed using Stata 11 (Stata Corporation, College Station, TX, USA).

Genetic testing was performed using accredited laboratories. Singleton WES was performed as previously described.[3] Eleven of the 13 patients who underwent WES in 2015 were part of



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the Melbourne Genomics Health Alliance study under Human Research Ethics approval (13/MH/326), and of these, eight have been previously published.[3] The remaining two patients underwent clinical WES initiated using the same patient selection criteria.

**Ethical Considerations**

Research ethics approval for the audit was granted by the RCH Human Research and Ethics Committee (36079A).

## RESULTS

**Referral Population**

The number of NICU patients referred for genetics consultation each year increased from 44 in 2007 to 95 in 2015 (Table 1). Within the same time period the number of admissions to the RCH NICU increased by 23%, with the proportion of inpatients referred for genetics consultation increasing from 6% to 11% (p=0.001).

**Referral Indications**

The number of referrals for multiple congenital anomalies (MCA) with or without dysmorphism has remained steady over the study period, as has the number of patients referred for more than one indication. Referrals for neurometabolic conditions had the greatest increase over time, with no patients referred for genetics consultation in 2007, three patients referred in 2011 and 10 patients referred in 2015 (Table 1). There was also a significant increase in the number of referrals for isolated congenital abnormalities (e.g. congenital diaphragmatic hernia).

**Outcome of Genetic Consultations**

The proportion of referrals considered following genetics assessment to have a likely underlying '*genetic'* (chromosomal, monogenic or epigenetic) aetiology has decreased over



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time, making up 75% of referrals in 2007 compared with 58% in 2011 and 2015 (insufficient power to determine significance). Examples of diagnoses considered to be '*likely not genetic'* included VACTERL (vertebral, anorectal, cardiac, tracheo-oesophageal fistula, renal and limb defects) association, OAV (oculo-auriculo-vertebral) association, field defects, and teratogen exposures.

In 2007, 33 of 44 referred patients (75%) were thought to have an underlying genetic condition with a diagnosis confirmed in 7 of these (21%) through genetic testing, primarily G-banded karyotype (Table 1). In 2011, 30 of 52 referrals (58%) were thought to have an underlying genetic condition, with 11 out of 30 (37%) receiving a molecularly confirmed diagnosis, primarily through CMA. In 2015, 56 of 95 referrals (59%) were thought to have an underlying genetic condition, with 29 of 56 (53%) receiving a confirmed cytogenetic or molecular diagnosis to date – over half (16, 28%) being monogenic disorders. Of these, seven were achieved through singleton WES as a first-tier sequencing test (Table 2).

**Age at Diagnosis**

The average age at confirmed diagnosis for those with chromosomal conditions has remained relatively stable: 10 days (standard deviation, SD = 3) in 2007, 21 days (SD = 11) in 2011 and 19 days (SD = 9) in 2015. The average age at confirmed diagnosis for those with monogenic conditions is longer and far more variable: 66 days in 2007 (single case of achondroplasia), 137 days in 2011 (33, 73, 304 days with SD = 146), and 138 days (SD = 99, range 10-309) in 2015.

**Prenatal Testing**

Of those patients referred for genetics assessment following admission to the NICU, 3 had prenatal testing in 2007 (G-banded karyotype with or without FISH), 5 had prenatal testing in 2011 (G-banded karyotype or CMA, with or without FISH), and 9 had prenatal testing in 2015 (CMA with or without FISH).



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## DISCUSSION

The adoption of new genetic testing technologies, such as CMA and genomic sequencing has resulted in significant increases in diagnostic yield and changes in referral patterns at our centre over a period of nine years. The proportion of NICU patients suspected of having a genetic condition following clinical geneticist assessment has remained stable, averaging 5.3% of all NICU admissions, which is consistent with previous reports from the 1990s.[14] However the proportion of those receiving a confirmed molecular diagnosis has more than doubled from 21% to 53%, with a shift in diagnosis types from chromosomal abnormalities to a broad range of monogenic disorders, increasingly diagnosed by singleton WES as a first-tier sequencing test.

The increase in referrals from the NICU to our genetics service reflects changes in the referral practice of neonatologists. Increased referral rates are likely driven by improvements in diagnostic yield over time, and the perceived benefits of accurate diagnosis such as directed management and the provision of prognostic information and reproductive choices for families. While infants with multiple congenital abnormalities and dysmorphic features represent a steady proportion of genetic referrals, there has been increased recognition that conditions such as epileptic encephalopathies and some isolated congenital abnormalities such as diaphragmatic hernia may have an underlying genetic basis,[15, 16] as well as increased recognition of the utility of NGS testing in the diagnosis of metabolic disorders.[17]

A recent retrospective chart review of 132 patients admitted to the NICU of a single Canadian centre between 2013 to 2015 showed that 26% received a cytogenetic or molecular diagnosis following medical genetics evaluation.[18] The range of tests employed included karyotype, microarray, rapid aneuploidy detection, single gene or panel-based sequencing, multiplex ligation-dependent probe amplification, and methylation studies. Only two patients had WES, with a diagnosis made in one child. Of those without a common aneuploidy or pathogenic copy number variant on CMA, the diagnostic rate was 14/132 (10%). In contrast, the diagnostic rate achieved in our centre in 2015 for patients without a chromosomal



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abnormality was 21/95 (22%), largely due to the use of WES as a first-tier molecular diagnostic test. The persistence of diagnoses reached through CMA and other genetic testing modalities (e.g. methylation studies) across the study period emphasizes the ongoing utility of these tests, and the need for careful consideration in selecting patients in whom WES should be performed as a first-tier sequencing test.[19] Fifty-five NICU patients were assessed as likely having a genetic condition in 2015, and a diagnosis was made in 20 using testing modalities other than WES. Of the remaining 35 undiagnosed patients, WES was only performed in 13 within the first year of life, indicating significant unmet need at our centre as genomic testing transitions from a test of last resort to a first-line sequencing test in this patient population.[3] Assuming a similar diagnostic yield, a further 11 patients could have received a diagnosis through WES. As access to genomic testing improves, it will be important to continue monitoring the proportion of patients tested and diagnostic yield in this patient population.

Multiple studies have now demonstrated that genomic sequencing in selected NICU patients with suspected genetic conditions has high diagnostic and clinical utility,[2-5, 7-9, 20, 21] and the present study demonstrates significant impact on overall diagnostic outcomes following genetics consultation in the NICU. Previous studies at our centre have examined the health economic impact of the early introduction of genomic testing in the diagnostic pathway for infants presenting with features suggestive of an underlying monogenic disorder, providing evidence in support for reimbursement as a first-tier clinical test.[12,21] Whilst a detailed health economic analysis is outside the scope of this study, the early use of genomic testing in this patient population would obviate the need for some non-genetic tests (in particular complex and invasive investigations), and also has the potential to reduce healthcare costs by reducing length of stay in NICU, particularly when a result is available in a timely manner. There is increasing evidence that providing rapid turnaround results for genomic tests in this clinical setting increases clinical utility.[2, 4, 5, 20, 21] However, rapid turnaround test times need to be coupled with rapid patient ascertainment to fully realise the clinical benefits of timely genetic diagnosis. The mean age at which patients are referred for genetics consultation has decreased significantly over time at our centre, but in 2015 was still 15 days. As more centres implement rapid genomic diagnosis programs, timely ascertainment of patients by



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neonatologists will become crucial. Developing testing protocols and guidelines, up-skilling in consent processes and the interpretation of results will be important in facilitating the provision of genomic testing in the acute clinical setting. Equally, there needs to be appropriate resourcing to meet the increasing demand for inpatient clinical genetics consultations.

This study has been conducted at a single centre and therefore may not be representative of the impact of new genetic technologies in other neonatal units, or other common inpatient referral sources such as paediatric intensive care units or neurology units. It only assesses the outcomes following an inpatient genetic consultation, and we have not captured the outcomes of patients who received genetic testing initiated by other subspecialists without clinical genetics involvement, or diagnostic outcomes in patients who were only referred following discharge, or patients who died prior to a full evaluation. This study also did not look specifically at patients for whom a genetic diagnosis was made prenatally. As part of our study, we observed an increasing number of patients referred for inpatient genetics consultation who have had chromosomal testing prenatally. It will be important as part of future studies to assess the impact of other technologies, such as non-invasive prenatal screening (NIPS) and prenatal genomic testing, on parental decisions and on the number of infants with genetic conditions admitted to NICUs.

The clinical implementation of genome-wide tests such as chromosomal microarray and whole exome sequencing has already made a significant impact on diagnostic outcomes in the NICU setting. Our study provides important benchmarking data to enable effective service planning and to measure further improvements in diagnostic outcomes and service delivery, particularly as test turnaround times continue to improve, and other testing modalities such as whole genome sequencing (WGS) become implemented in clinical practice.



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***Table 1***. *Clinical characteristics of study cohort, referral indication, genetic testing undertaken and outcomes of genetic consultations. *Chi-squared test; **2-sided t test; ns not significant; BWS Beckwith-Wiedemann syndrome; PWS Prader-Willi syndrome*

| | **2007** | **2011** | **2015** | **p value** (2007 v 2015) |
|---|---|---|---|---|
| **Total number of patients admitted to NICU** | 692 | 672 | 851 | |
| **Total number of NICU patients referred for genetics consultation (% of all admissions)** | 44 (6%) | 52 (8%) | 95 (11%) | p = 0.001* |
| | | | | |
| **Demographics, n (% of all NICU referrals to genetics)** | | | | |
| Male | 24 (55%) | 28 (54%) | 45 (47%) | |
| Female | 20 (45%) | 24 (46%) | 50 (53%) | |
| | | | | ns* |
| Mean age (SD) at time of referral | 29 (±41) | 18 (±25) | 15 (±21) | p = 0.008** |

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| | | | | |
|---|---|---|---|---|
| **Referral indication, n (% of all NICU referrals to genetics)** | | | | |
| Multiple congenital abnormalities +/- dysmorphic features | 20 (45%) | 24 (46%) | 24 (25%) | p = 0.001* |
| Neurometabolic condition | 0 (0%) | 3 (6%) | 10 (11%) | |
| Isolated congenital abnormality or single system condition | 7 (16%) | 14 (27%) | 39 (41%) | |
| More than one indication | 17 (39%) | 11 (21%) | 22 (23%) | |
| **Genetic tests performed, n (number of diagnostic results; % diagnostic yield)** | | | | |
| FISH | 13 (0; 0%) | 6 (1; 16%) | 12 (0; 0%) | |
| Standard karyotype | 21 (5; 23%) | 12 (1; 8%) | 4 (0) | |
| Subtelomere MLPA | 4 (0;0%) | 0 | 0 | |
| SNP microarray | 0 | 26 (6; 23%) | 78 (8; 10%) | |
| Single gene sequencing | 1 (1; 100%) | 1 (1; 100%) | 5 (5; 100%) | |

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| | | | |
|---|---|---|---|
| Multi-gene panel sequencing | 1 (0) | 2 (2; 100%) | 4 (2; 50%) |
| Whole exome sequencing | 0 | 0 | 13 (7; 54%) |
| *SMN1* deletion testing | 1 (0;0%) | 1 (0;0%) | 6 (2;33%) |
| Myotonic dystrophy/Fragile X triplet expansion | 1 (0;0%) | 4 (0;0%) | 6 (0;0%) |
| Methylation tests (BWS/PWS) | 2 (1;50%) | 3 (1;33%) | 6 (3; 50%) |
| | | | |
| **Outcome of genetics consultation (% of all NICU referrals to genetics)** | | | |
| Genetic condition, cytogenetically/molecularly confirmed diagnosis | 7 (16%) | 11 (21%) | 29 (31%) |
| Likely genetic condition, clinical diagnosis | 12 (27%) | 6 (12%) | 5 (5%) |
| Likely genetic condition, no specific diagnosis made | 14 (32%) | 13 (25%) | 21 (22%) |
| Genetic condition unlikely | 11 (25%) | 22 (42%) | 40 (42%) |

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|---|---|---|---|---|
| **NICU patients suspected of having a genetic condition following genetics consultation, n (% of all admissions)** | 33/692 (4.8%) | 30/672 (4.5%) | 55/851 (6.4%) | ns* |
| **NICU patients receiving a cytogenetically/molecularly confirmed diagnosis, n (% of those assessed as having a genetic condition)** | 7/33 (21%) | 11/30 (37%) | 29/55 (53%) | p = 0.004* |

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***Table 2***. *Monogenic disorder diagnoses at RCH NICU in 2007, 2011 and 2015 (gene names in italics).* [†]*Diagnoses reached via WES; #OMIM phenotype*

*Legend for Table 2*

| | |
|---|---|
| | Clinical diagnosis |
| | Chromosomal abnormality (G-banded karyotype) |
| | Chromosomal abnormality (microarray) |
| | Imprinting disorder (methylation studies) |
| | Molecularly confirmed single gene disorders |

| 2007 | 2011 | 2015 |
|---|---|---|
| Apert syndrome (#101200) | Autosomal recessive polycystic kidney disease (#263200) | Anemia, congenital dyserythropoietic, Type Ib (#615631) |
| Autosomal recessive polycystic kidney disease (#263200) | CHARGE syndrome (#214800) | Burn-McKeown syndrome (#608572) |
| Beckwith-Wiedemann syndrome (#130650) | Ectodermal dysplasia (#305100) | Congenital ichthyosis (#242300) |
| Epidermolysis bullosa simplex (#131900) | Visceral heterotaxy (#306955) | Feingold syndrome (#164280) |
| Feingold syndrome (#164280) | Ohtahara syndrome (#308350) | Joubert syndrome (#213300) |



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| | | |
|---|---|---|
| Feingold syndrome (#164280) | Prothrombin deficiency (#613679) | Cat-eye syndrome |
| Muscle-eye-brain disease (#236670) | Trisomy 21 | arr[hg19] 7p22.3 (2,119,657-2,662,818)x1 |
| Opitz G/BBB syndrome (#300000) | Trisomy 21<br>47,XY,+21 | arr[hg19] 15q11.1q13.1 (20,161,372-30,328,060)x4dn, 15q13.2q13.3(30,333,884-32,443,813)x3dn |
| Osteogenesis imperfecta type III (#259420) | arr[hg18] 13q32.3q34 (99,334,817-114,125,098)x1 | arr[hg19] 4q32.1q35.2 (160,751,151-190,880,409)x1dn |
| Schinzel-Giedion syndrome (#269150) | arr[hg18] 3q29 (197,222,803-197,852,333)x1 mat | arr[hg19] 22q11.21 (20,733,667-21,462,353)x1mat |
| Simpson-Golabi-Behmel syndrome (#312870) | arr[hg18] (21)x3, (XY)x1 | arr[hg19] 9p24.3p22.3 (46,587-15,188,106)x1dn |
| Townes-Brocks syndrome (#107480) | arr[hg18] 16p11.2q24.3 (312,908,850-88,685,456) x3 | arr[hg19] Xp22.31p22.2 (6,572,336-14,981,889)x1mat |
| 2p deletion<br>46,XY,del(2)(p24.1p24.3)dn | arr[hg18] 22q11.21 (17,224,632-19,792,353) x1 | arr[hg19] 19q12q13.11 (29,685,293-34,450,946)x1, 19q13.41q13.43(52,941,540- |



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| | | |
|---|---|---|
| | | 57,105,726)x3 |
| Turner syndrome<br><br>45,X (100%) | arr[hg18] (1-22)x2, (X)x2, (Yx1) | Beckwith-Wiedemann syndrome (#130650) |
| Unbalanced translocation<br><br>46,XY,der(6)t(6;17)(p25;p13) | EB simplex *KRT14* (#131900) | Beckwith-Wiedemann syndrome (#130650) |
| Variant Turner syndrome<br><br>45,X (85%), 46,X,r(X) (15%) | Familial hyperinsulinemic hypoglycaemia *ABCC8* (#256450) | Beckwith-Wiedemann syndrome (#130650) |
| Balanced paracentric inversion<br><br>46,XY,inv(10)(q22.3q24.3) | Long QT syndrome 3 *SCN5A* (#603830) | Prader-Willi syndrome (#176270) |
| Beckwith-Wiedemann syndrome (#130650) | | Prader-Willi syndrome (#176270) |
| Achondroplasia *FGFR3* (#100800) | | Congenital adrenal hyperplasia *CYP21A2* (#201910) |
| | | D-bifunctional function deficiency *HSD17B4* (#261515) |
| | | [†]Epidermolysis bullosa *ITGB4* (#226730) |



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| |
|---|
| Glucose-galactose malabsorption, *SLC5A1* (#606824) |
| Junctional epidermolysis bullosa, *LAMB3* (#226700) |
| MELAS, m.13513G>A (#540000) |
| †Megacystis microcolon intestinal hypoperistalsis syndrome *ACTG2* (#155310) |
| †Multiple intestinal atresia syndrome, *TTC7A* (#243150) |
| †Myotubular myopathy *MTM1* (#310400) |
| †Ohdo syndrome *KAT6B* (#606170) |
| Osteogenesis imperfecta type VIIII *P3H1* (#610915) |
| †Pyridoxamine 5'-phosphate oxidase deficiency *PNPO* (#610090) |
| Reticular dysgenesis *AK2* |



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| |
|---|
| (#267500) |
| Spinal muscular atrophy<br>*SMN1* (#253300) |
| Spinal muscular atrophy<br>*SMN1* (#253300) |
| †Sotos syndrome *NSD1*<br>(#117550) |

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# Diagnostic and service impact of genomic testing technologies in a neonatal intensive care unit

**Original Article**

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