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ORIGINAL ARTICLE

RAPIDOMICS: rapid genome-wide sequencing in a neonatal intensive care unit—successes and challenges

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Abstract

Genetic disorders are one of the leading causes of infant mortality and are frequent in neonatal intensive care units (NICUs). Rapid genome-wide sequencing (GWS; whole genome or exome sequencing (ES)), due to its diagnostic capabilities and immediate impacts on medical management, is becoming an appealing testing option in the NICU setting. RAPIDOMICS was a trio-based rapid ES pilot study of 25 babies with suspected genetic disorders in the BC Women's Hospital NICU. ES and bioinformatic analysis were performed after careful patient ascertainment. Trio analysis was performed using an in-house pipeline reporting variants in known disease-causing genes. Variants interpreted by the research team as definitely or possibly causal of the infant's phenotype were Sanger validated in a clinical laboratory. The average time to preliminary diagnosis was 7.2 days. Sanger validation was pursued in 15 patients for 13 autosomal dominant and 2 autosomal recessive disorders, with an overall diagnostic rate (partial or complete) of 60%.

Conclusion: In total, 72% of patients enrolled had a genomic diagnosis achieved through ES, multi-gene panel testing or chromosomal microarray analysis. Among these, there was an 83% rate of significant and immediate impact on medical decision-making directly related to new knowledge of the diagnosis**.** Health service implementation challenges and successes are discussed.

What is Known:

- *Rapid genome-wide sequencing in the neonatal intensive care setting has a greater diagnostic hit rate and impact on medical management than conventional genetic testing. However, the impact of consultation with genetics and patient ascertainment requires further investigation.*

What is New:

- *This study demonstrates the importance of genetic consultation and careful patient selection prior to pursuing exome sequencing (ES).*
- *In total, 15/25 (60%) patients achieved a diagnosis through ES and 18/25 (72%) through ES, multi-gene panel testing or chromosomal microarray analysis with 83% of those having immediate effects on medical management.*

Keywords Genome-wide sequencing (GWS) · Exome sequencing (ES) · Multi-gene panel · Chromosomal microarray analysis · Health implementation · Medical management · Genetic counselling

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Abbreviations

NICU	Neonatal intensive care unit
GWS	Genome-wide sequencing
ES	Exome sequencing
WGS	Whole genome sequencing
OMIM	Online Mendelian Inheritance in Man
CMA	Chromosomal microarray analysis
CMV	Cytomegalovirus
TPN	Total parenteral nutrition
VUS	Variant of uncertain significance

Introduction

Genetic disorders and malformations are the leading causes of infant mortality in the neonatal intensive care unit (NICU) [1]. Identification of genetic disorders in the NICU is challenging: the full clinical phenotype may not have evolved or be recognizable in the neonate, clinical signs may be compounded by prematurity, the presentation may be atypical, and genetic heterogeneity is frequent. Even when a genetic basis is suspected, the underlying intrinsic genetic heterogeneity does not lend well to a candidate gene approach where testing for disease-causing variants of individual disease-causing variants with genes or multiple gene panel testing is considered. These approaches can be costly, time-consuming, and may not be available. Consequently, many patients with genetic disorders are discharged or die prior to the diagnosis being established. The NICU at BC Women's Hospital, a referral center for the province of British Columba, treats approximately 1400 premature or ill infants annually.

Rapid GWS (genome-wide sequencing; whole genome or exome sequencing (ES)) has demonstrated significant diagnostic capability in the NICU setting, immediately influencing clinical management by alleviating parental guilt and enabling precision treatments (therapeutic or palliative), anticipatory guidance, and accurate genetic counselling [2–9]. Clinical GWS is currently not routinely available in British Columbia and can only be obtained through special requests by physicians in restricted situations. When funded, rapid trio (proband and both parents) ES is outsourced to a commercial laboratory, at a cost of > $11,500 CAD per patient with reporting and bioinformatic analysis of variants performed completely separate from the clinical care group. RAPIDOMICS was a trio-based rapid ES pilot study of 25 neonates with suspected genetic disorders at the BC Women's Hospital NICU. The goals of the study included the following: (i) establishment and validation of a rapid ES pilot platform for critically ill babies with suspected genetic disorders in the NICU, (ii) demonstration of the clinical and economic feasibility and the clinical utility of ES as a first-tier clinical test for these patients, and (iii) identification of health services implementation issues related to this testing. The last of these is the focus of this paper.

Methods

Inclusion criteria and genetic counselling

The selection criteria were similar to those published [2, 6, 7, 9] and included NICU neonates with one or more of the following presentations: unexplained seizures, metabolic disturbances, neurological abnormalities or depressed level of consciousness, multiple congenital anomalies, or significant physiological disturbance in keeping with a genetic disorder (e.g., fetal growth retardation) for which diagnosis would likely change clinical management or genetic counselling [2, 6, 7, 9]. Patients not eligible for enrolment included patients for whom both parents were not available for testing. Infants considered likely to have disorders caused by cytogenetic abnormalities were not enrolled unless chromosomal microarray analysis (CMA) failed to provide a diagnosis.

Each patient was evaluated for enrolment on a case-by-case basis after consultation between a clinical geneticist and a neonatologist and approval by the RAPIDOMICS research team. Once a patient was identified as appropriate for the study, the neonatologist and/or clinical geneticist informed the family of the study, and a board-certified genetic counsellor from the RAPIDOMICS research team who was not involved with the care of the patient met with the family to explain the study. At the meeting, pre-test genetic counselling was provided and informed consent was obtained for families interested in participating.

Clinical information

Demographic information, including patient age and sex and key phenotypic findings, were obtained for all patients enrolled from the medical genetics consultation and the NICU hospital health record. Patients were classified based on the primary system(s) involved at enrollment. Categories included the following: multiple congenital anomalies, neurologic disorder, fetal growth retardation, and suspected metabolic disorder. Clinical data were recorded using a secure Research Electronic Data Capture (REDCap) information system hosted at BC Children's Hospital Research Institute [10].

Exome sequencing and bioinformatics

ES and bioinformatic analysis were performed in the research laboratory of Professor Matthew Farrer. Genomic DNA was extracted from whole blood using the ReliaPrep Blood gDNA Miniprep System (Promega, Madison, WI) following the manufacturers' protocol. Exonic regions were captured using the Ion AmpliSeq Exome Kit (57.7 Mb), and ES was performed on an Ion Proton System (Thermo Fisher Scientific, Waltham, MA) according to manufacturers' instructions. All samples were required to meet minimum quality standards, with an ES average coverage > 80×.

Raw sequencing data were processed with Torrent Suite Software 5.0 (Thermo Fisher Scientific). Reads were aligned against the human reference genome NCBI Build 37 hg19 using Torrent Mapping Alignment Program (Thermo Fisher Scientific). Variant calling was performed with Torrent Variant Caller plugin version 5.0 using in-house optimized parameters. Variant annotation was performed with ANNOVAR [11], integrating data from PHAST PhyloP [12], SIFT [13],

Polyphen2 [14], LRT [15] and MutationTaster [16] algorithms, Combined Annotation Dependent Depletion (CADD) scores [17], dbSNP (www.ncbi.nlm.nih.gov/SNP/), the Exome Aggregation Consortium (ExAC; exac.broadinstitute.org), and ClinVar [18] (www.ncbi.nlm.nih.gov/clinvar). Additionally, variants were compared to an in-house database (https://www.neuroseq.ca/) containing almost 3000 exomes to exclude platform artifacts and common variants not present in public databases.

Trio analysis was performed using an in-house developed semi-automated pipeline using custom perl scripts. Analysis was restricted to exonic nonsynonymous and splicing (± 5 bp) substitutions within OMIM (Online Mendelian Inheritance in Man)—known disease genes. Initially, only de novo, autosomal dominant, X-linked, and autosomal recessive variants were reported. The RAPIDOMICS team reviewed the list of variants generated by the ES analysis pipeline, taking clinical presentation, medical history, and investigations into consideration. High-quality, predicted damaging variants in OMIM that were associated with phenotypic findings consistent with those seen in the patient were classified as definitely or possibly causal by the research team and treating clinician and represented the preliminary diagnoses. Prior to the launch of the study, teaching sessions were provided to members of the neonatal healthcare team to describe the study aims including pipeline (with the focus being known disease-causing (OMIM) genes; not a gene discovery exercise), genetic counselling, and Sanger confirmation of ES results.

Sanger validation

All patients with suspected definitely, possibly, or partially causal variants generated by ES as determined by the research team underwent Sanger validation and interpretation in a certified clinical laboratory that generated a report for the health record.

Impact on medical management

Impacts on management that derived from the genomic diagnosis, within a 1-week period following diagnosis, were assessed by a combination of chart review and physician report.

Results

Of 30 families of newborn infants with a suspected genetic disease approached, 25 (83%) agreed to participate. Patients ranged in age from 1 to 104 days (median 13 days; interquartile range = 2 to 31 days). The infant tested at 104 days of age was born at 25 weeks gestation. Thirteen females and 12 males were enrolled. The most frequent indications were multiple congenital anomalies (14/25, 56%) neurologic disorders (7/25, 28%), fetal growth retardation (3/25, 12%), and suspected metabolic disorder (1/25, 4%). Eight patients enrolled died by the study conclusion (Patients R01, 06, 07, 15, 18, 21, 23, 24). The average time to preliminary diagnosis was 7.2 days. The time to obtain the clinical Sanger report varied and for some cases was more than 8 weeks.

Sanger validation in a clinical laboratory was performed in 15 patients on variants considered by the RAPIDOMICS research team to be definitely or possibly causal of the infant's phenotype. These variants included 13 associated with autosomal dominant disorders (involving the genes *RAF1*, *KCNT1*, *CHD7*, *SMARCB1*, *EFTUD2*, *KCNQ2*, *SAMD9*, *COL4A1*, *PHOX2B*, *HRAS*, *ZMYND11*, *SLC12A5*, and *KMT2D*) and two autosomal recessive conditions (involving the genes *AGK* and *BBS4*). All autosomal dominant disease-associated variants were de novo with the exception of *PHOX2B*, where a parent was found to be mosaic. Demographic, phenotypic data, and genomic findings for this cohort are shown in Table 1.

The *SLC12A5* variant (interpreted as a variant of unknown significance (VUS)) on Sanger confirmation by the clinical laboratory) represented a possible partial phenotype association for patient R23, who was later diagnosed with Zellweger syndrome after a clinical multi-gene panel revealed two likely pathogenic variants of *PEX1*. Only one of these *PEX1* variants was detected by our ES research pipeline. The *SMARCB1* variant (R11) classified as a VUS for Coffin–Siris syndrome 3 by the clinical laboratory has been previously reported in a patient with Kleefstra syndrome phenotypic spectrum [19].

Demographic information, phenotypic data, and genomic findings for patients for whom no diagnosis was established via the RAPIDOMICS ES pipeline are shown in Table 2. Two patients had abnormal CMA findings that explained their clinical phenotypes, either partially or completely (R08 and R26). Another patient was found to have an inherited likely pathogenic variant in *TP63* by concurrent clinical exome sequencing; this variant was not identified by our initial pipeline, which did not include inherited autosomal dominant variants. Subsequent to this analysis (R09), we modified the pipeline to include inherited autosomal dominant disorders.

A total of 34 discrete and immediate medical decisions were identified for 15 of the 18 diagnosed patients (Table 3). Most of these decisions were oriented toward further investigation for possible occult complications and the development of monitoring protocols. Specifically, decisions were made to screen for visual or hearing impairments, hormonal deficiencies, malignancy, additional anomalies, or immunodeficiency. Two patients presented primarily with epilepsy, in whom *KCNT1* and *KCNQ2* de novo variants were identified, respectively; specific decisions regarding seizure treatment were made to either introduce a new agent or continue the same. A refined prognosis informed several decisions made in this window: for example, it was decided to place a gastrostomy feeding tube in one newborn (*ZMYND11* de novo variant) when it became more clear

Table 1 Demographic, clinical, and exome findings of RAPIDOMICS patients with definite/probable variants from research ES pipeline

R#	Sex	Age (days)	Primary presenting phenotype	Exome findings: gene/variant(s), ACMG classification from clinical laboratory Sanger validation, Inheritance	Clinical diagnosis
R01	F	1	Bilateral cataracts, cardiomyopathy, nondysmorphic	*AGK* NM_018238:exon7:c.409C>T:p.R137X NM_018238:exon12:c.841C>T:p.R281X ACMG—pathogenic/pathogenic Autosomal recessive	Sengers syndrome
R03	F	31	Enlarged cystic kidneys, postaxial polydactyly of all four extremities, low-set ears	*BBS4* NM_033028:exon4:c.220+1G>C NM_033028:exon8:c.513T>A:p.Y171X ACMG—pathogenic/pathogenic Autosomal recessive	Bardet–Biedl syndrome
R05	M	18	Enlarged liver, large anterior fontanelle, wide internipple distance, dysmorphic features: downslanting palpebral fissures; low set, small ears; large nuchal fold, right ventricular hypertrophy, jittery, short stature	*RAF1* NM_002880:exon7:c.770C>T:p.S257 L ACMG—pathogenic Autosomal dominant de novo	Noonan syndrome
R06	M	31	Intractable seizures, nondysmorphic	*KCNT1* NM_020822:exon13:c.1283G>A:p.R428Q ACMG—pathogenic Autosomal dominant de novo	Early infantile epileptic encephalopathy
R10	M	1	Multiple congenital anomalies: single right kidney, atrial septal defect, absent septum pellucidum, choanal atresia, coloboma, simple, abnormal ears, triphalangeal thumbs	*CHD7* NM_017780:exon33:c.6994dup: p.W2332LfsX5 ACMG—pathogenic Autosomal dominant de novo	CHARGE syndrome
R11	M	19	Central hypotonia, peripheral hypertonia, contractures, hydrocephalus, relative macrocephaly, dysplastic left hip, undescended right testis	*SMARCB1* NM_001007468:exon2:c.110G>A:p.R37H ACMG—variant of unknown significance (Coffin–Siris syndrome 3) Autosomal dominant de novo	Kleefstra syndrome
R12	F	58	Premature delivery at 32 weeks gestation, choanal atresia, H-type tracheal esophageal fistula, minor dysmorphic features	*EFTUD2* NM_004247:exon8:c.579del C:p.G195EfsX15 ACMG—pathogenic Autosomal dominant de novo	Mandibulofacial dysostosis, Guion–Almeida type
R14	F	7	Seizures, extensive polymicrogyria of the right hemisphere involving the lateral frontal lobe, parietal lobe, superolateral temporal lobe and superior insular cortex, nondysmorphic	*KCNQ2* NM_172107:exon15:c.1687G>A:p.D563N R—definite ACMG—likely pathogenic Autosomal dominant de novo	Epileptic encephalopathy, early infantile 7
R15	F	82	Premature delivery at 28 weeks gestation, severe fetal growth retardation involving length, weight and head circumference from 18 weeks gestation, subsequent failure to thrive with weight <<< 3rd %, and head circumference 3rd %, posteriorly positioned big toes, very long second toes, minor dysmorphic features: overfolded helix of left ear, wide nasal bridge, tapering digits of hands and hyperconvex nails	*SAMD9* NM_017654:exon3:c.2920G>A:p.E974K ACMG—likely pathogenic Autosomal dominant de novo	MIRAGE syndrome
R16	M	1	Polyhydramnios detected at 20 weeks gestation, intracranial cysts identified at 30 weeks gestation, multiple cysts on the superior surface of the cerebellum, small left cerebellar hemisphere, periventricular/basal ganglia/thalamus calcifications	*COL4A1* NM_001845:exon11:c.634G>A:p.G212S ACMG—likely pathogenic Autosomal dominant de novo	Porencephaly
R17	M	35	Premature delivery at 33 weeks gestation, hypoventilation, truncal hypotonia	*PHOX2B* NM_003924:exon2:c.245C>T:p.P82L ACMG—likely pathogenic	Congenital hypoventilation syndrome

Table 1 (continued)

R#	Sex	Age (days)	Primary presenting phenotype	Exome findings: gene/variant(s), ACMG classification from clinical laboratory Sanger validation, Inheritance	Clinical diagnosis
				Autosomal dominant Parental mosaicism	
R18	F	2	Premature delivery at 27 5/7 weeks gestation, significant polyhydramnios detected at 23 weeks gestation, elbow contractures, reduced muscle bulk in arms, flexion deformities of both hands and wrists, overlapping fingers, prominent heels, reduced overall tone, hepatomegaly	*HRAS* NM_005343:exon2:c.35_36delGCinsTT:p.G12V ACMG—pathogenic Autosomal dominant de novo	Costello syndrome
R22	F	38	Low birth weight, low tone, reduced respiratory effort, perineal groove, bilateral hip dislocation, retrognathia, low-set protruding ears, telecanthus	*ZMYND11* NM_006624:exon15:c.1798C>T:p.R600W ACMG—pathogenic Autosomal dominant de novo	Autosomal dominant mental retardation 30
R23	M	1	Respiratory distress, query seizures at birth, hyopotonia, poor suck, club feet, large anterior fontanelle, ocular hypertelorism, micro/retrognathia, small, low-set ears, extra nuchal skin	*SLC12A5* NM_001134771:exon8:c.943C>A:p.R315S ACMG—variant of unknown significance Autosomal dominant de novo Patient subsequently diagnosed on a peroxisomal disorders gene panel: *PEX1* NM_000466.2: c.2383c>T p.(Arg795*) NM_000466.2: c.2097dupT,p.(Ile700Tyrfs*42) (latter variant was missed by Ion Torrent Variant Caller software) ACMG—pathogenic/pathogenic Autosomal recessive	Epileptic encephalopathy, early infantile, type 34 (partial) Zellweger syndrome
R24	M	104	Premature delivery at 25 weeks gestation, prolonged hyperbilirubinemia, recurrent distal bowel obstruction, large patent ductus arteriosis, electrolyte abnormalities, height, weight and head circumference all < 3rd centile (corrected), plagiocephaly, high anterior hair line, high and narrow palate, low-set, posteriorly rotated ears with large lobules, thin inverted lips, clinodactyly of 5th fingers, deep crease between first and second metatarsals, sacral dimple, right inguinal hernia, liver biopsy showed neonatal hepatitis, cholestasis and mild portal fibrosis	*KMT2D* NM_003482:exon48:c.14878C>T:p.R4960X ACMG—pathogenic Autosomal dominant de novo	Kabuki syndrome

that severe feeding difficulties were likely to be ongoing for an extended period, and similarly, a diagnosis of congenital central hypoventilation (*PHOX2B*) informed long-term respiratory support planning. For three newborns, the genomic diagnosis confirmed a suspected poor prognosis, and a decision was made to change goals of care to emphasize comfort. At the conclusion of the study, 8 newborns had died from their genetic disorders.

Discussion

Of 30 families who met our entry criteria and were approached, 25 (83%) agreed to participate. In a previously reported NICU study [6], approximately half of families eligible for rapid GWS enrolled. Reasons for not enrolling included unavailability of one or more biological parents, parents younger than 18 years of age, and parents refusing to participate. In a more recent study of 129 infants eligible for a randomized controlled trial for rapid whole-genome sequencing in critically ill infants, 17 parents declined (13%) [7]. In our cohort, families were not approached unless both parents were determined to be available, as the availability of both parents was an inclusion criterion.

The importance of availability of genetic counselling for rapid GWS has previously been discussed [4]. Petrikin et al. noted the challenges of obtaining informed consent for GWS in a NICU/PICU setting [7]. In our study, there was effective communication between the clinical staff in NICU, the clinical genetics consultant, and the study staff, with flexibility of the genetic counsellor's availability to

Table 2 Demographic, clinical, and genomic findings for RAPIDOMICS patients in whom no variants suspected to cause the patient's phenotype were detected from research ES pipeline

R#	Sex	Age (days)	Primary presenting phenotype	Investigations and diagnosis
R02	F	24	Fetal growth retardation, microcephaly, right hydronephrosis, hepatosplenomegaly, persistent thrombocytopenia, transient hypotension, patent ductus arteriosus (resolved), transient hypoglycemia	CMA—normal Clinical exome: negative; heterozygous for a *FECH* M267I variant (variant of uncertain significance), homozygous for *DNASE2* C347Y variant (variant of uncertain significance)
R07	F	2	Multiple pterygia, vertebral anomalies, diaphragmatic hernia, macrocephaly, hypertelorism, low-set ears, webbed neck, arthrogryposis, scoliosis	CMA—normal
R08	M	28	Multiple intestinal atresias, ventricular septal defect, ectopic kidney, bilateral renal cystic dysplasia, severe combined immune deficiency, nondysmorphic	CMA—abnormal 13 kb deletion including *TTC7A* -involving exons 12–14 Subsequent targeted comparative genomic hybridization analysis identified two deletions, (arr(hg19) 2p21(47,246,165-47,261,576) and 2p21(47,255,251-47,257,997) resulting in a deletion of both copies exon 15 **Diagnosis: gastrointestinal defects and immunodeficiency syndrome** **Autosomal recessive** **Partial diagnosis**
R09	F	7	Dextrocardia and situs inversus totalis, bilateral venae cavae, prominent trabeculations of right sided left ventricle, perimembranous ventricular septal defect with outlet extension, superior vena cava abnormality, patent ductus arteriosus, midline liver, bilateral cleft lip, and palate	CMA—copy gain at 5q11.1 (684.8 kb)—unclear significance region includes 2 RefSeq genes (*EMB, PARP8*) and no OMIM disease genes Clinical exome—*TP63* p.R393X c.1177C>T ACMG—Likely pathogenic **Diagnosis: ectrodactyly, ectodermal dysplasia, and cleft lip/palate (EEC) syndrome—3** **Autosomal dominant** **Partial diagnosis** Inherited from parent with dystrophic nails but no other sign of EEC syndrome
R13	M	23	Premature delivery at 32 4/7 weeks gestation, fetal growth retardation and oligohydramnios noted at 32 weeks gestation, gestational diabetes, craniosynostosis, atrial septal defect, ventricular septal defect, hypospadias	CMA—normal
R19	F	3	Fetal growth retardation (birth weight and length < 3rd centile, head circumference 10th centile), Tetralogy of Fallot with pulmonary atresia, ectopic left kidney, bilateral pre-auricular pits, anteriorly placed anus with low sacral dimple, short toes with small nails	CMA—normal
R20	F	2	Fetal growth retardation, mild polyhydramnios, echogenic bowel grade 2, single umbilical artery, right multicystic kidney, and distended bowl loops noted on prenatal ultrasound examination, born at 32 weeks gestation, pre-axial polydactyly of left upper extremity, small right ear with skin tag, multiple vertebral, and rib anomalies	CMA—normal
R21	M	7	Decreased fetal movement, small for gestational age, respiratory distress and hypoglycemia, dysmorphic features: micro/retrognathia, low-set ears, barrel shaped chest, undescended testicles, high anterior hair line, elbow contractures, clenched hands, dislocated left hip, rocker bottom feet, small appearing nails, gracile ribs and clavicles, bilateral grade IV intraventricular hemorrhage with significant cortical, periventricular and basal ganglia involvement, echogenic kidneys, thrombocytopenia, hypertension	CMA—normal

Table 2 (continued)

R#	Sex	Age (days)	Primary presenting phenotype	Investigations and diagnosis
R25	F	13	Ocular hypertelorism, upslanting palpebral fissures, depressed nasal bridge, retrognathia, low-set ears, microtia, bilateral hip dysplasia, small atrial septal defect, dysgenesis of the corpus callosum, absent splenium and possible decreased volume of the posterior body, colpocephaly, periventricular heterotopias	CMA—normal
R26	M	2	Severe fetal growth retardation involving head and body with onset at 19 weeks gestation, born at 37 5/7 weeks, high-pitched cry, hyperextensible knees bilaterally, short left palpebral fissure, rocker bottom feet, prominent heels, short first metatarsals	CMA—abnormal 4.52 Mb copy loss of maternal 15q26.2q26.3 that includes 36 RefSeq genes and 7 OMIM genes **Diagnosis: 15q26-qter deletion syndrome (OMIM 612626)**

ensure appropriate pre-test genetic counselling was provided to accommodate the parents. For some families, the parents were counselled separately.

Patients with multiple congenital anomalies comprised the largest group enrolled in our study (56%), followed by infants with suspected neurologic anomalies (28%). Multiple congenital anomalies and suspected neurologic disorders were frequent indications in other rapid GWS studies [4, 6, 7].

With our pipeline and review by the RAPIDOMICS research team, 15 patients were identified as having a variant that was suspected of being pathogenic that was subsequently Sanger validated in a clinical laboratory (Table 1). Seven patients had a suspected neurologic disorder, and six had multiple congenital anomalies. One patient, who had a suspected metabolic disorder, had Sengers syndrome (cardiomyopathic mitochondrial DNA depletion syndrome-10). A patient with fetal growth retardation and minor anomalies had MIRAGE syndrome (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotype, and enteropathy).

Of the ten remaining patients in our study (Table 2), eight had multiple congenital anomalies, and two had fetal growth retardation with minor anomalies. Within this group, two patients had abnormal CMA findings. Patient R08 had a copy loss in *TTC7A* detected by CMA. Subsequent targeted array comparative genomic hybridization analysis identified a second smaller deletion in *TTC7A* in the other allele. This patient was, therefore, deleted for both copies of exon 15, which represented a partial diagnosis for this patient, explaining the severe combined immunodeficiency and gastrointestinal findings, but not the cardiac and renal findings. Patient R26 had a 4.52-Mb copy loss at 15q26.2q26.3 that explained the phenotype (15q26-qter deletion syndrome; OMIM 612626), but this result was not reported until 3 months after the CMA was requested. Patient R09 was found to be heterozygous for a likely pathogenic variant in *TP63*, which can explain the orofacial clefting. This patient also had a heart defect that may be related to her heterotaxy (which is not known to be associated with *TP63* variants); cardiac defects have occasionally been reported in patients with pathogenic *TP63* variants [20].

Our study had a diagnostic yield of partial or full diagnoses in 60% of the patients tested. Kingsmore's group performed rapid GWS in 35 critically ill neonates and diagnosed a genetic disorder in 57% through GWS compared to 9% by conventional genetic testing, with results available as early as five days [6]. In a retrospective study of infants tested within the first 100 days of life, diagnostic rates of 51% and 32% were achieved in 63 infants who underwent rapid trio ES and 176 infants who underwent singleton ES, respectively [2]. A study of ES and CMA involving 23 critically ill babies younger than 12 months of age had an associated diagnostic rate of 30% [5]. Forty patients undergoing rapid singleton whole exome sequencing from two pediatric tertiary centers had an associated diagnostic rate of 52% [4]. Twelve (80%) of the 15 patients in our study were

Table 3 Patients for whom the genomic diagnosis had an impact on medical decision-making

R#	Primary presenting phenotype/clinical diagnosis	Medical decisions
R01	Bilateral cataracts, cardiomyopathy, nondysmorphic/**Sengers syndrome**	Change to comfort care; extubation and discontinuation of cocktail, vasopressors, TPN; Family utilized information for subsequent prenatal diagnosis
R03	Enlarged cystic kidneys, postaxial polydactyly of all four extremities, low-set ears/**Bardet–Biedl syndrome**	Continue intensive care (with ventilation for pneumothoraces); peritoneal catheter placed; audiology screen; ophthalmology screen
R05	Enlarged liver, large anterior fontanelle, wide internipple distance, dysmorphic features: downslanting palpebral fissures; low set, small ears; large nuchal fold, right ventricular hypertrophy, jittery, short stature/**Noonan syndrome**	Ophthalmology referral; coagulation profiling
R06	Intractable seizures, nondysmorphic/**early infantile epileptic encephalopathy**	Quinidine trialed for improved seizure control
R08	Multiple intestinal atresias, ventricular septal defect, ectopic kidney, bilateral renal cystic dysplasia, severe combined immune deficiency, nondysmorphic/**gastrointestinal defects and immunodeficiency syndrome**	Immunological testing; antibiotic prophylaxis;, CMV precautions; scope for inflammatory bowel disease; consultation with international experts regarding transplantation options
R10	Multiple congenital anomalies: single right kidney, atrial septal defect, absent septum pellucidum, choanal atresia, coloboma, simple, abnormal ears, triphalangeal thumbs/**CHARGE syndrome**	Discharge to local hospital as a result of having a definitive and survivable diagnosis and stable prognosis
R12	Premature delivery at 32 weeks gestation, choanal atresia, H-type tracheal esophageal fistula, minor dysmorphic features/**mandibulofacial dysostosis**, **Guion–Almeida type**	Audiology consultation; referral to local developmental therapy service
R14	Seizures, extensive polymicrogyria of the right hemisphere involving the lateral frontal lobe, parietal lobe, superolateral temporal lobe and superior insular cortex, nondysmorphic/**epileptic encephalopathy**, **early infantile 7**	Affirmed continuation of phenobarbital for seizure management
R15	Premature delivery at 28 weeks gestation, severe fetal growth retardation involving length, weight and head circumference from 18 weeks gestation, subsequent failure to thrive with weight <<< 3rd %, and head circumference 3rd %, posteriorly positioned big toes, very long second toes, minor dysmorphic features: overfolded helix of left ear, wide nasal bridge, tapering digits of hands and hyperconvex nails/**MIRAGE syndrome**	Cortisol levels checked; Endocrinology consultation; check for myelodysplasia/monosomy 7 and hematology consultation; consider central hypoventilation; consult Gastrointestinal Service for possible enteropathy; infection prophylaxis
R16	Polyhydramnios detected at 20 weeks gestation, intracranial cysts identified at 30 weeks gestation, multiple cysts on the superior surface of the cerebellum, small left cerebellar hemisphere, periventricular/basal ganglia/ thalamus calcifications/**porencephaly**	Avoid blood pressure extremes; avoidance of blood thinning agents; consult ophthalmology
R17	Premature delivery at 33 weeks gestation, hypoventilation, truncal hypotonia/**congenital hypoventilation syndrome (CCHS)**	Approach decision-making for long-term, ongoing ventilation needs according to prognosis of CCHS; neuroblastoma screening
R18	Premature delivery at 27 5/7 weeks gestation, significant polyhydramnios detected at 23 weeks gestation, elbow contractures, reduced muscle bulk in arms, flexion deformities of both hands and wrists,, overlapping fingers, prominent heels, reduced overall tone, hepatomegaly/**Costello syndrome**	Change to comfort care
R22	Low birth weight, low tone, reduced respiratory effort, perineal groove, bilateral hip dislocation, retrognathia, low-set protruding ears, telecanthus/**autosomal dominant mental retardation 30**	Proceed with gastrostomy tube; audiology consultation
R24	Premature delivery at 25 weeks gestation, prolonged hyperbilirubinemia, recurrent distal bowel obstruction, large patent ductus arteriosis, electrolyte abnormalities, Ht, Wt, OFC, all <3rd centile (corrected), plagiocephaly, high anterior hair line, high and narrow palate, low-set, posteriorly rotated ears with large lobules, thin inverted lips, clinodactyly of 5th fingers, deep crease between first and second metatarsals, sacral dimple, right inguinal hernia, liver biopsy showed neonatal hepatitis, cholestasis and mild portal fibrosis/**Kabuki syndrome**	Diagnosis-related prognosis influenced decision-making to limit the degree of invasive airway management and/or resuscitation in the setting of severe pulmonary compromise
R26	Severe fetal growth retardation involving head and body with onset at 19 weeks gestation, born at 37 5/7 weeks, high-pitched cry, hyperextensible knees bilaterally, short left palpebral fissure, rocker bottom feet, prominent heels, short first metatarsals/**15q26-qter deletion syndrome (OMIM 612626)**	Referral to endocrinology for growth hormone therapy; cardiac echocardiogram; renal imaging

identified as having de novo disorders, illustrating the importance of trio-based analysis.

Rapid GWS in the NICU setting has the capacity to identify the underlying genetic disorder in as little as 26 hours [21]. The average time to preliminary diagnosis in our study was 7.2 days. Variant interpretation occurred virtually, and results were communicated to the healthcare team virtually in most cases. Sanger confirmation in a clinical laboratory of variants considered to be definitely or probably causal of the patient's phenotype was pursued in 15 patients. The mean turnaround time was 13 days for rapid trio ES, 51 days for standard trio ES, and 95 days for standard singleton ES in another study [2]. A study of whole genome sequencing in critically ill newborns achieved a provisional diagnosis in 50 hours [6]. Sanger sequencing was used to confirm all likely causative genotypes, and the median interval from enrollment to report was 23 days, with a range of 5–912 days [6].

Receipt of the clinical Sanger confirmation report took more than 8 weeks in some cases in our study. Other investigators have recognized that confirmatory Sanger sequencing, the clinically accepted standard, can delay timely return of GWS diagnoses [7]. Removing mandatory Sanger sequencing to improve turnaround time has been discussed [5]. In our study, most treating physicians considered our preliminary research results in their clinical management, but other physicians were reluctant to do so, reducing the benefit of rapid sequencing in these cases. Mosaicism identified by ES of *PHOX2B* (congenital hypoventilation syndrome) in one parent (R17) was presumably too low to be detected by Sanger sequencing, revealing the importance of an ES result for post-test genetic counselling.

The inherited likely pathogenic *TP63* variant in patient R09 was missed in our analysis because our initial bioinformatic pipeline excluded heterozygous variants inherited from one of the parents on the assumption that the parents of these severely ill infants were unlikely to be affected with the same condition. Although there was a family history of orofacial clefting of patient R09, the affected parent only demonstrated dystrophic nails. This case illustrates the importance of obtaining a detailed family history and including shared heterozygous variants in the analysis, particularly for disorders with variable expressivity or incomplete penetrance.

A diagnosis of Zellweger syndrome was missed in our analysis of the ES data from patient R23, who was subsequently found to be a compound heterozygote for pathogenic *PEX1* variants. One of the *PEX1* variants was not called by the Ion Torrent Variant Caller software, even though visual inspection of the BAM files confirmed the presence of the variant in the raw data. This patient also had a heterozygous de novo VUS in *SLC12A5*.

This pilot project demonstrated that rapid ES in a translational research setting resulted in a diagnostic rate of 60% and provided preliminary results within 1 week. Patient selection was on a case-by-case basis involving a neonatologist and clinical geneticist, with approval by the research team. In our center, a team approach to identifying appropriate pediatric patients for exome sequencing contributes to higher diagnostic rates [22]. Personnel from clinical genetics (clinical geneticists and genetic counsellors) involved in our pediatric GWS initiative (CAUSES) [22] were also part of the clinical research team of RAPIDOMICS with protected time to participate in this study. Therefore, patient selection, pre- and post-genetic counselling, and genomic interpretation were handled by health professionals with expertise in these domains. Genetic counselling issues unique to this study have been reported [23].

In total, 18/25 (72%) of the patients enrolled had a genomic diagnosis achieved through ES, multi-gene panel or CMA, a high diagnostic yield, demonstrating the importance of genetic consultation and careful patient selection prior to pursuing ES. Challenges included the delay in obtaining the clinical Sanger report and limitations with the Ion Torrent Caller software. The importance of including inherited variants (shared heterozygotes) in the pipeline was a lesson learned, after missing a *TP63* variant, and is particularly important for disorders with reduced penetrance. Our observation that ES can detect parental mosaicism that may not be detected by Sanger sequencing has important consequences for accurate post-test genetic counselling and demonstrates the importance of communication within the research and clinical teams.

Immediate (within 1 week of diagnosis) impact on medical decision making was demonstrated in 83% of patients who obtained a genomic diagnosis in our cohort. A diagnosis was helpful in providing prognosis, despite the fact that most genetic disorders featured a broad range of expression and outcomes. At the least, the diagnosis allowed an estimated best-possible and worst-possible scenario for long-term outcomes, assuming that the medical problems keeping the infant in the NICU could be overcome. Invasive interventions judged likely to be futile were discontinued for some infants, and for others, decisions to maintain, add, or increase interventions were made. During the course of the study, nearly a third of the cohort died, reflecting the overall severity of genetic illnesses that tend to present in the neonatal period.

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Authors' contributions Dr. Elliott conceptualized and designed the study; was involved in data acquisition, analysis, and interpretation; drafted the initial manuscript; and revised the manuscript.

Ms. du Souich, Dr. Lehman, and Dr. Horacio Osiovich conceptualized and designed the study, were involved in data acquisition and analysis and interpretation of the data, reviewed and revised the manuscript.

Dr. Friedman conceptualized and designed the study, was involved in analysis and interpretation of the data, and reviewed and critically revised the manuscript.

Dr. Guella, Mr. Evans, Ms. Candido, Ms. Tooman, and Dr. Farrer conceptualized and designed the study, were involved in data analysis and interpretation, and reviewed and revised the manuscript.

Drs. Armstrong, Clarke, Gibson, Gill, Lewis, McKinnon, Nikkel, Patel, and van Allen were involved in data collection and interpretation of the data and critically revised the manuscript.

Drs. Lavoie, Solimano, Synnes, and Ting were involved in data collection and interpretation and critically revised the manuscript.

Dr. Christilaw conceptualized and designed the study, facilitated data acquisition, and provided revision of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the University of British Columbia (UBC)/BC Children's and Women's Clinical Research Ethics Board (REB H15-02750).

Informed consent Informed consent was obtained from all individual participants included in the study.

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