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A review of a perinatal genetics and genomics service's role in prenatal diagnosis

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Abstract

Aims

The aim of this study was to review prenatal anomaly cases referred to the Department of Perinatal Genetics and Genomics at the National Maternity Hospital.

Methods

We conducted a retrospective review of all patients who were referred to the Department between August 2021 to April 2025. We included cases referred for consideration of further genetic testing because of a fetal anomaly where initial QF-PCR and chromosomal microarray studies did not reveal a genetic diagnosis.

Results

There were 109 patients who met our inclusion criteria. A molecular diagnosis was made in 56 (51.4%) of this cohort. These diagnoses were apparently de novo in 35 cases (62.5%) and inherited in 21 (37.5%). Pregnancy outcomes showed 31 cases (28.4 %) had a livebirth surviving the neonatal period.

Discussion

Our findings demonstrate the high diagnostic yield and clinical value of a dedicated Perinatal Genetics and Genomics service as part of the multi-disciplinary team for prenatal diagnosis. These cases all have a higher rate of recurrence in subsequent pregnancies compared to the empiric risk, indicating a need for ongoing genetics counselling in subsequent pregnancies. This data also indicates a high proportion of these patients experience a fetal or neonatal loss and that appropriate psychological input is needed.

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Introduction

Advances in imaging modalities such as high-resolution ultrasound and fetal MRI coupled with developments in genetic testing have significantly contributed to improvements in prenatal diagnosis in the last decade. While traditional cytogenetic techniques including G-band karyotyping have been available for almost 60 years, chromosomal microarray is now offered where there are congenital abnormalities and has increased the resolution to detect submicroscopic copy number variants. [1] In 6% of cases where the karyotype has not identified a diagnosis, the chromosomal microarray provides answers in cases of a congenital abnormality. [2]

The introduction of exome sequencing into clinical care provides a diagnosis in 6-80% of cases, depending on phenotype. [3] The prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE) study was a landmark study published in this field in 2019. This included 610 fetuses and identified a diagnostic genetic variant in 52 fetuses (8.5%) [4] A recent systematic review and meta-analysis found the diagnostic yield of exome sequencing in fetuses with multisystem anomalies to be 33% (95% CI 27%-40%). [5] A second systematic review and meta-analysis published the same year found the diagnostic yield for exome sequencing in fetal structural anomalies to be between 5% (95% CI -8 to 18%) and 89% (95% CI 72%-99%), with a pooled incremental diagnostic yield of 31 % (95% CI 26%-36%, p<0.0001). [6]

The Joint Position Statement from the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM) and the Perinatal Quality Foundation (PDF) on the use of genome wide sequencing for prenatal diagnosis in fetal structural anomalies was first published in 2018 and updated in 2022. [7,8] This emphasised a number of points regarding the use of exome sequencing in prenatal diagnosis including: its use when chromosomal microarray is uninformative, it is best done as a trio analysis, interpretation of results is highly complex and therefore pre-test and post-test counselling is paramount and should be done by someone with expertise in clinical and laboratory aspects of prenatal diagnosis. [7]

This study aimed to review the outcomes of the Department of Perinatal Genetics and Genomics Service since August 2021. There is a paucity of evidence of these outcomes from the Republic of Ireland. The development of this service has been crucial for prenatal diagnosis, allowing for timely decision making in pregnancy.

Methods

The National Maternity Hospital is a tertiary maternity hospital located in Dublin, Ireland with approximately 7000 deliveries per annum. The fetal medicine multi-disciplinary team includes sub-specialists in maternal and fetal medicine and clinical midwife specialists, a consultant

clinical geneticist with a special interest in Perinatal Genomics, perinatal pathology, paediatric cardiology and paediatric radiology with a provision of on-site fetal MRI. There is no publicly funded first trimester screening programme in Ireland, although patients can access this privately if they wish. The genetic testing pathway in an anomalous pregnancy is QF-PCR in the first instance, with a reflex to chromosomal microarray if no genetic diagnosis is revealed on QF-PCR.

We conducted a retrospective review of all patients who were seen in the Department of Perinatal Genetics and Genomics between August 2021 and May 2025. For this study, we included all cases referred to the genetics department for consideration of further genetic testing because of a fetal anomaly where QF-PCR and chromosomal microarray studies did not reveal a genetic diagnosis. Cases were identified via the integrated patient management system (iPMS) and data was collected from both electronic health records and paper charts.

Cases excluded included those for predictive testing because of a prior affected pregnancy or a family history of a genetic diagnosis, maternal medicine patients with a genetic diagnosis, neonatology referrals and reproductive counselling for patients who are known carriers of single gene disorders e.g. cancer predisposition genes.

All cases underwent detailed pre-test counselling prior to consenting for testing, to include potential testing options and outcomes, family implications, uncertainty, unexpected information, DNA and data storage, research and education. Trio testing, comprised of testing the fetus along with both parents, was performed in all cases of exome sequencing. This has the advantage of determining if the variant identified was inherited or apparently de novo. Rapid prenatal exome sequencing (R21) was carried out in all prenatal cases. This is exome sequencing of a nationally approved panel of genes that are known to cause prenatal onset genetic disorders. Only pathogenic and likely pathogenic variants were reported for a diagnosis as they are clinically relevant and actionable.

Variables extracted and analysed included referral indication, imaging modalities, phenotypic findings, genetic testing performed, whether a molecular diagnosis was ultimately made and pregnancy outcomes.

Data was collected and descriptive statistical analysis was performed using SPSS v.28.0. Ethical approval was granted by the National Maternity Hospital Ethics Research Committee (Ref EC21.2023).

Results

Of the 898 families (1592 individuals) seen in the department, 109 patients met our inclusion criteria. The majority of patients were referred prenatally (73.4%, n=80), while 26.6% (n=29)

were referred after pregnancy. All cases in the postnatal cohort were referred based on prenatal findings who either had an intrauterine death or termination of pregnancy before they were seen in the genetics clinic. Half (52.3%, n=57) of women were in their first pregnancy. The average number of appointments in the index pregnancy per patient was three (SD 1.2; range 2-7). Importantly, the majority of these patients have had subsequent pregnancies which required additional consultations. These are not included here.

Referring locations and indications

Nearly all patients had their first appointment in person (97.2%, n=106). The reason for this was to allow for phenotypic assessment of the parents, which can inform testing interpretation. To minimise travel, the genetics appointment was coordinated to coincide with another hospital appointment on the same day in nearly half of these patients (46.7%, n=51). This included an ultrasound in 41.3% (n=45), fetal MRI in 2.8% (n=3) and a Neonatal review in 2.8% (n=3).

Fetal anomaly was the most common indication for referral (92.7%, n=101), followed by fetal death (4.6%, n=5) and neonatal death (2.8%, n=3). In all cases of perinatal death, there were fetal anomalies identified prenatally on ultrasound. The vast majority of patients did not have a family history of a known genetic condition which they were aware of at the time of referral (95.4%, n=104). The most common phenotypes seen by system were multisystem anomalies in 45% (n=49), musculoskeletal in 22% (n=24), neurological in 11.9% (n=13), fetal hydrops in 6.4% (n=7), cardiac in 4.6% (n=5), cystic hygroma in 3.7% (n=4), gastrointestinal in 3.7% (n=4), renal in 1.8% (n=2) and face in 0.9% (n=1).

Diagnostic modalities

All patients had a prenatal ultrasound. Fetal MRI was performed in 38.5% (n=42). Deep phenotyping occurred in 31.2% (n=34). This was a comprehensive multi-disciplinary analysis of the fetal phenotype by ultrasound, MRI or a combination of the two.

Invasive prenatal testing was performed in the majority of patients, with 65.1% (n=71) having an amniocentesis and 13.8% (n=15) having chorionic villous sampling. In 16.5% (n=18) of cases, genetic testing was done on products of conception. The remaining five patients (4.6%) had non-invasive prenatal diagnosis (NIPD) performed.

Of the cohort, 85 patients (78%) had trio-exome sequencing, 13 (11.9%) had single gene sequencing and 15 (13.8%) had a gene panel done.

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Molecular diagnosis

A molecular diagnosis was made in 51.4% of patients this cohort (n=56). This diagnosis was made through exome sequencing in 66.0% (n=37), a gene panel in 19.6% (n=11) and single gene sequencing in 14.3% (n=8) of cases. The diagnostic yield by phenotype system is described in Table 1. These diagnoses were apparently de novo in 62.5% of cases (n=35) and inherited in 37.5% (n=21). Of the inherited cases, 11 showed autosomal recessive inheritance (19.6% of cohort), 9 were autosomal dominant (16.1%) and 1 was X-linked (1.8%).

Table 1.

Phenotype	Molecular diagnosis made (%)	Genes with P/LP variant
Cystic hygroma	1/4 (25%)	RIT1
Fetal hydrops	5/7 (71.4%)	CFTR, RAF-1, PTPN11
Neurological	5/13 (38.5%)	CSPP1, EPG5, PIK3CA, OFD1, NFIA
Cardiac	3/5 (60%)	FLT4, JAG1, NOTCH1, TSC1
Musculoskeletal	16/24 (66.7%)	ACTA1, CHRNG, COL1A1, EBP, FGFR3, MIA3, COL1A2, RUNX2, TRIP11
Renal	0/2 (0%)	
Gastrointestinal	0/4 (0%)	
Face	1/1 (100%)	IRF6
Multisystem	25/49 (51%)	BRAF, CHRNG, COL2A1, COL4A1, CEP290, CRB-2, FANCC, FGFR2, FGFR3, FLNA, FLNB, CHD7, KMT2D, MAPK1, MYH3, PIGN, PKD1L1, PTPN11, RTEL1TCTN3

Pregnancy outcomes

The mean gestational age at first appointment was 25+1 weeks' gestation (SD 5+4 weeks). Mean age at diagnosis was 27+6 weeks' gestation (SD 5+1 weeks) and mean age at delivery was 29+2 (SD 8 weeks) weeks gestation.

Of the 109 patients in this cohort, pregnancy outcomes were available for 108 patients, detailed in Figure 1. 28.4% (n=31) had a livebirth surviving past the neonatal period, 18.3% (n=20) had a termination of pregnancy in Ireland, 17.4% (n=19) had a termination outside of Ireland, 12% (n=14) had a pregnancy loss greater than 23 weeks' gestation, 1.9% (n=2) had a pregnancy loss less than 23 weeks' gestation and 20.4% (n=22) had a neonatal death.

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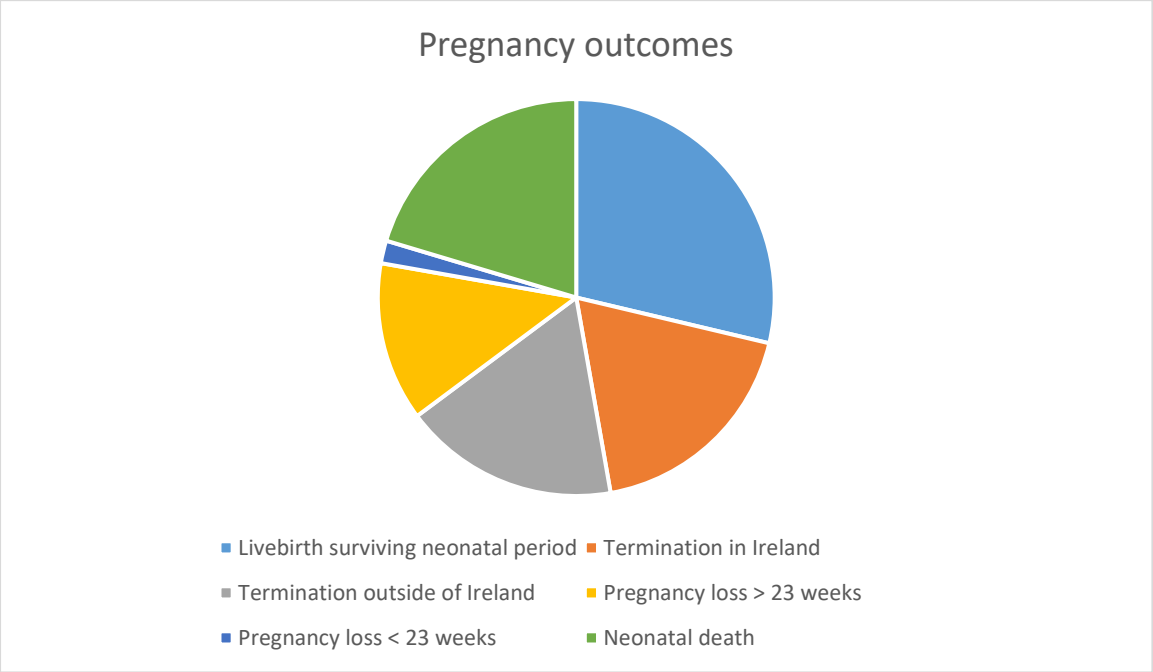
Figure 1.



Discussion

This study represents the first retrospective review of prenatal cases referred to a dedicated Perinatal Genetics and Genomics Service in Ireland for further investigation of prenatal anomalies where QF-PCR and chromosomal microarray have been non-diagnostic.

The diagnostic yield of 51.4% in this cohort ranks favourably internationally, exceeding figures reported in recent systematic review and meta-analyses which estimate a diagnostic yield of 31-33%. [5,6] We defined a diagnosis by the detection of a pathogenic or likely pathogenic variant known to be associated with the observed prenatal phenotype. The notably high diagnostic yield highlights the important role of genetic input in these rare and complex cases. In such cases, genetics expertise is essential for pre-test counselling, careful case selection for consideration of further testing and interpretation of complex results. The mean number of appointments of three (range 2-7), reflects the complexity of genetic counselling in the diagnostic process. This level of engagement with the service highlights the time and expertise needed in managing such challenging cases. Nearly half of our cohort had multisystem involvement, which is associated with a greater likelihood of identifying an underlying monogenic aetiology. [6]

From a logistical perspective, nearly half of patients (47.2%) had their genetics appointment coordinated with another hospital appointment on the same day. This is particularly

beneficial for the 28.4% of patients referred from outside our catchment area. This would indicate a national demand for such specialised services.

The majority of diagnoses in this cohort was made using trio exome sequencing. As discussed previously, the advantage of using this approach is to allow for comparison between fetal and parental DNA to determine if a pathogenic or likely pathogenic variant is apparently de novo or inherited and for interpretation of novel variants. In our cohort, 37% of variants were inherited and therefore associated with a high recurrence risk, consistent with previous studies. [10] Autosomal recessive inheritance accounted for 19.6% of this cohort and carries a recurrence risk of 25%. Autosomal dominant inheritance was observed in 16% of cases, and X-linked dominant in 1.8%, both with a recurrence risk of 50%. Even in cases where the pathogenic or likely pathogenic variant was de novo, the recurrence risk remains higher than that of the general population due to the possibility of parental gonadal mosaicism.

All patients are offered an appointment for reproductive counselling following their pregnancy. Based on the identified recurrence risk, discussions include reproductive options and testing options available for future pregnancies. This may include preimplantation genetic testing for a monogenic condition (PGT-M), prenatal invasive testing for the known variant or the development of a bespoke NIPD assay for use in future pregnancies. Patients are encouraged to self-refer early in subsequent pregnancies to enable discussion of predictive testing options and to facilitate timely planning if they choose to pursue this. Reproductive decision making in this setting is complex and emotionally challenging. [11,12] These considerations are essential in guiding future service development and resource allocation.

In this cohort, only 28.7% of patients seen had a baby who survived beyond the neonatal period while 71.3% had a bereavement. This reflects the complexity and severity of fetal anomalies managed within this service. Over a third of patients (36.1%) opted for a termination of pregnancy. Under the Health (Regulation of Termination of Pregnancy) Act 2018, termination of pregnancy is legal in Ireland: under 12 weeks after a mandatory 3-day waiting period, or after 12 weeks if there is a risk to the life, or serious harm to the health, of the pregnant woman or there is a condition affecting the fetus which is likely to lead to the death of the fetus either in utero or within 28 days of birth. [9] Prenatal diagnosis can have a profound impact on clinician and parental decision making in these cases. The addition of a genetic diagnosis with a known fatal prognosis aid in multi-disciplinary clinician decision making around if a condition is a fatal fetal abnormality and therefore meets criteria for a termination of pregnancy in Ireland. It also helps parents decision making around pregnancy options and to be better prepared for multi-disciplinary management that may be required after birth. These findings highlight the importance of timely and accurate information to support informed choices during pregnancy and in future reproductive planning is key.

The high rate of bereavement (71.3%) within this cohort illustrates the significant emotional burden experienced by affected families. Despite this, the service lacks access to dedicated psychological support which is a critical need for this vulnerable cohort. At present, patients are signposted to external charities who provide support. This highlights a gap in service provision and is important in considering resource allocation for this service in the future.

Strengths of this study include one of the first publications detailing the outcomes of a dedicated perinatal genetics service in Ireland. Limitations include the retrospective data collection.

Our findings demonstrate the high diagnostic yield and clinical value of a dedicated Perinatal Genetics and Genomics service as part of the multi-disciplinary team for prenatal diagnosis in Ireland. The careful selection of cases, pre- and post-test counselling and expert interpretation of results, led by a Clinical Geneticist, is essential. Expansion of such services nationally, with appropriate funding and support will be essential to allow for equitable access to genetic testing in prenatal care in Ireland.

Declarations of Conflicts of Interest:
None declared.

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