SIGU - LIGURIA

titolo

Genova, 03 Maggio 2023

Esoma in diagnosi prenatale

Approximately **2–4%** of pregnancies are complicated by significant fetal structural anomalies.

Fetal congenital anomalies increase infant morbidity and mortality but also cause intangible suffering to the family

crucial adopt **timely** and **accurate** diagnoses

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prenatal testing strategy

Current options include:

- karyotype — d.r. **30%**
- chromosomal microarray analysis — d.r. **4-6%**
- targeted gene-specific molecular testing — d.r

- exome

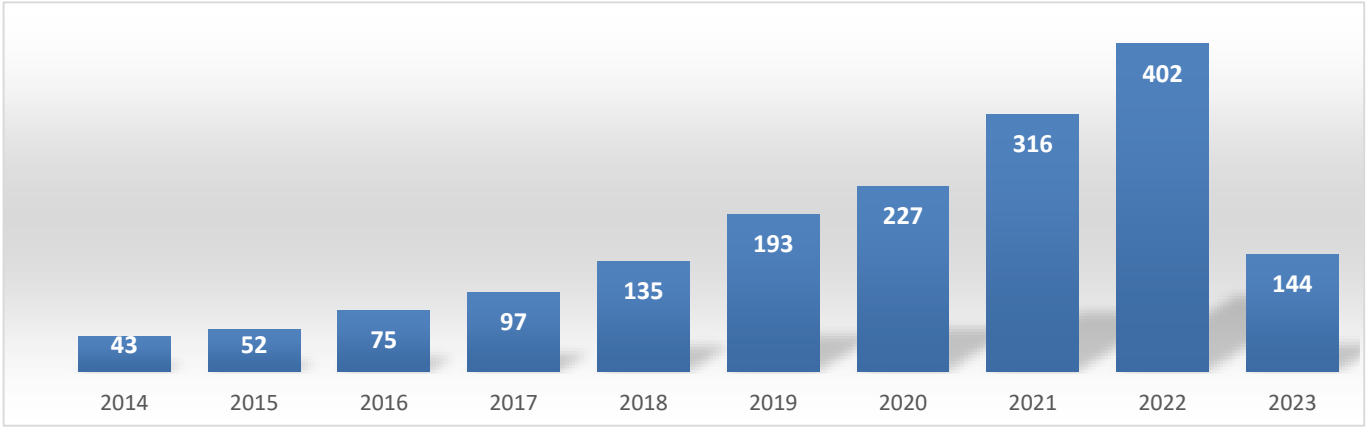

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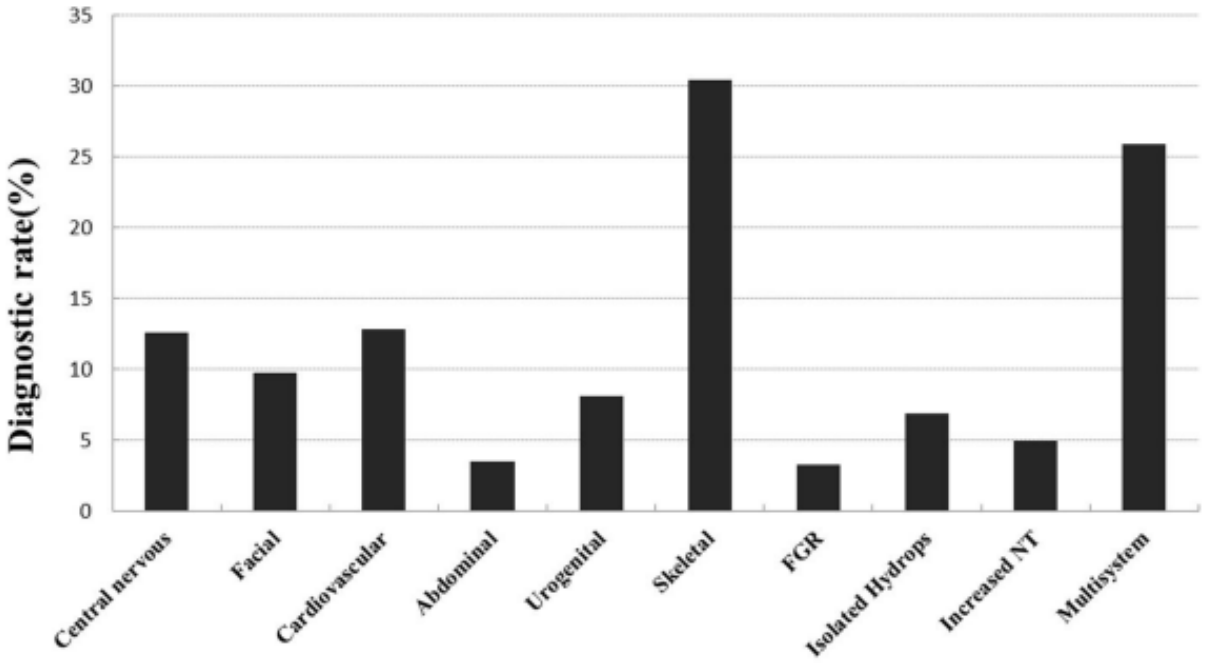
Table 1 The overall positive diagnostic and inconclusive rates in each analysis step

Analysis step	Diagnostic results	Inconclusive results
Step 1 (Genotype-driven)	**187/1618 (11.6%)**	**55/1618 (3.4%)**
Step 2 (Genotype-Phenotype correlation based on initial invasive indications)	**28/1618 (1.7%)** 19 due to genotype-phenotype correlations 9 due to family co-segregation	**68/1618 (4.2%)**
Step 3 (Reanalysis due to new phenotypes or physician's requests)	**14/1618 (0.9%)** 1 due to new phenotypes upgrading from VUS to LP 7 due to new phenotypes reclassified from IFs to positive diagnoses 3 due to new disease genes identified 2 with intragenic copy number variants 1 with focused Sanger analysis for a disease gene possessing pseudogene sequence	**8/1618 (0.5%)**
Total	**229/1618 (14.2%)**	**131/1618 (8.1%)**



Fu et al. Genome Medicine (2022) 14:123

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ACMG STATEMENT | Genetics inMedicine

The use of fetal exome sequencing in prenatal diagnosis: a points to consider document of the American College of Medical Genetics and Genomics (ACMG)

Kristin G. Monaghan, PhD[1], Natalia T. Leach, PhD[2], Dawn Pekarek, MD[3], Priya Prasad, MD[4] and Nancy C. Rose, MD[5]; on behalf of the ACMG Professional Practice and Guidelines Committee

Guidance document:

Rapid Exome Sequencing Service for fetal anomalies testing

NHS England and NHS Improvement

Clinical application of fetal genome-wide sequencing during pregnancy: position statement of the Canadian College of Medical Geneticists

Joanna Lazier [1], Taila Hartley,[2] Jo-Ann Brock,[3] Oana Caluseriu,[4] David Chitayat,[5,6] Anne-Marie Laberge,[7] Sylvie Langlois,[8] Julie Lauzon,[9,10] Tanya N Nelson,[11,12] Jillian Parboosingh,[9,10] Dimitri J Stavropoulos,[13] Kym Boycott,[1,2] Christine M Armour [1,14] On behalf of the Canadian College of Medical Geneticists

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Pretest considerations

- Clinical GWS should only be used to interrogate the genome for sequence variants in genes known to cause disease.

- Exome sequencing may be considered for a fetus with ultrasound anomalies when standard CMA and karyotype analysis have failed to yield a definitive diagnosis.
- Clinical GWS could be considered in fetuses with an abnormal phenotype suggesting a monogenic aetiology. Evidence supports the use of clinical GWS in the diagnostic investigation of congenital anomalies affecting more than one system. Rapid aneuploidy diagnosis must be completed prior to GWS. Chromosomal microarray should be completed in parallel, or prior to, GWS.

- Exome sequencing is a phenotype-driven test, therefore, the ordering health-care professional **should provide the testing laboratory with adequate information** required to generate the most accurate interpretation of results.
- Phenotyping is key in deciding if GWS is indicated and is critical to the interpretation of the data

- Trio analysis is preferred to singleton
- GWS trios should be performed

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Pretest considerations

- Pretest counseling is ideally provided by a genetics professional
- clinical GWS should only be ordered in pregnancy by a medical geneticist with expertise in prenatal diagnosis and care

- With the use of prenatal ES, the turnaround time has to be rapid to maintain all aspects of reproductive choice
- Timing of testing and the decision of whether to use ‘rapid’ GWS should be directed by the clinical presentation and the potential impact on pregnancy management

- maternal cell contamination that may interfere with the interpretation of fetal results must be excluded

- Testing should be performed in a laboratory with appropriate clinical accreditation for provision of clinical GWS

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Considerations for reporting

- report pathogenic and likely pathogenic variants in known disease genes consistent with the reported fetal phenotype
- As a general rule, only pathogenic and likely pathogenic variants associated with the identified anomalies should be reported

- Laboratories may have different policies with regard to reporting VUS in a fetal specimen

- Any variant identified in a candidate gene should be classified no higher than VUS, regardless of the applicable ACMG criteria

- Laboratories should have clear policies regarding whether prenatal ES analysis and reporting is limited to only known disease genes or could include candidate genes and this information should be communicated to the individual(s) consenting to the test.

- Highly penetrant pathogenic variants detected in genes unrelated to the fetal phenotype, but known to cause moderate to severe childhood onset disorders, are recommended to be reported
- Incidental findings unintentionally identified that show a pathogenic or likely pathogenic variant that reveals a fetal risk for a significant Mendelian paediatric-onset condition, whether or not medically actionable, should be reported

- variants without a known fetal or childhood phenotype not be reported

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Considerations for reporting

- fetal carrier status for autosomal recessive (male and female fetuses) and X-linked disorders (female fetuses) unrelated to the test indication not be reported
- Secondary findings should be discussed with the patient as part of the pretest informed consent discussion

Post-test considerations

- Post-test counseling is recommended, preferably a genetics professional
- The medical geneticist should review the report and incorporate the findings with other relevant medical considerations when discussing the results with the patient
- Counseling should also include a discussion of the possibility of an upgrade or a downgrade of the classification of reported variants over time.

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- **Analisi dell'esoma completo** (WES, Whole Exome Sequencing):
  questa analisi copre l'intero esoma umano, ovvero la parte del genoma che codifica per le proteine

- **Esoma clinico:**
  si analizzano gli esoni dei geni OMIM associati a malattie mendeliane

- **Esoma clinico mirato** (pannelli *in silico*)**:**
  lo studio è limitato all'insieme di geni noti che potrebbero giustificare i sintomi presenti nel paziente