CERPO
Centro de Referencia Perinatal Oriente
Facultad de Medicina, Universidad de Chile

Rol exoma prenatal en Hidrops fetal no inmune

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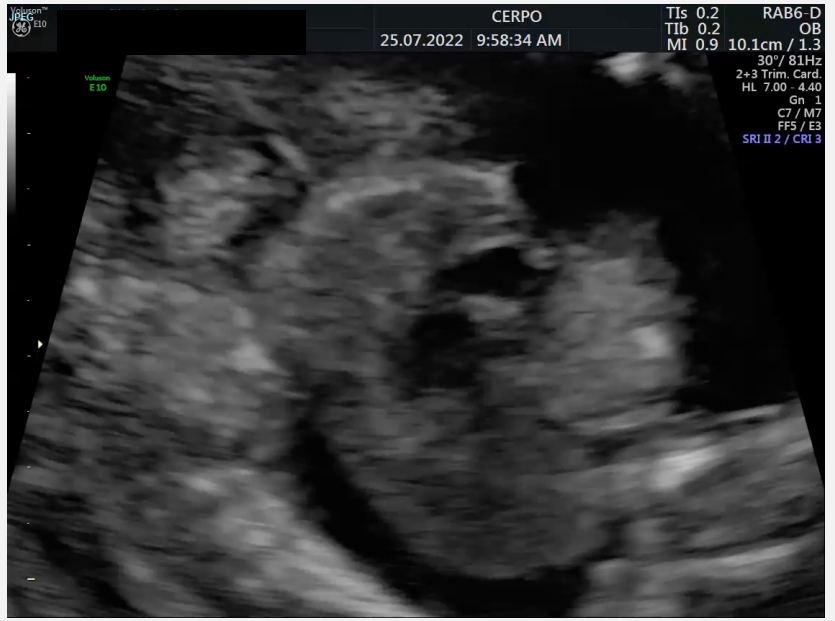
Hidrops fetal no inmune

Trastorno que afecta 1 a 1700 – 3000 embarazos

Mayor riesgo de MFIU, parto prematuro y morbimortalidad perinatal

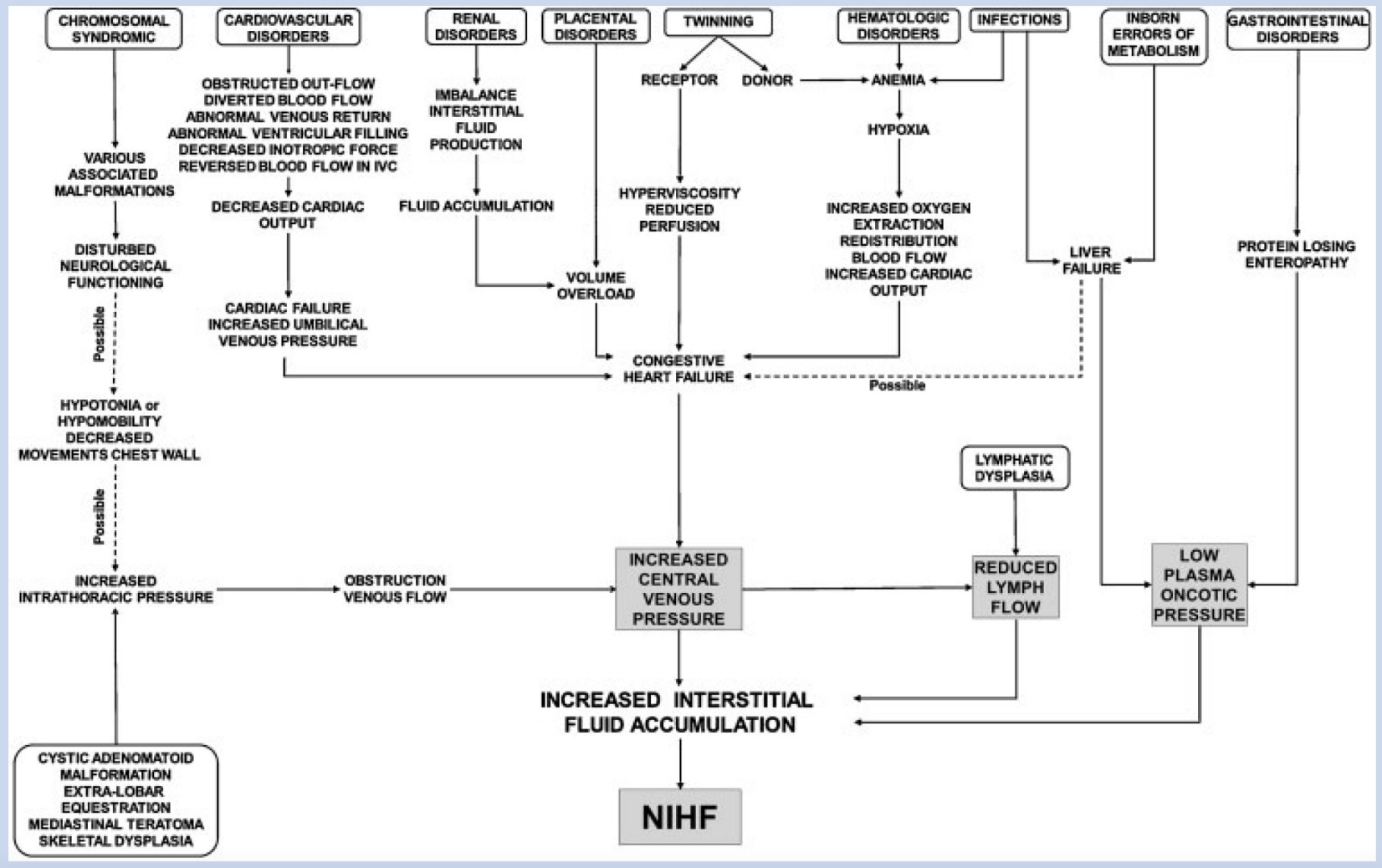
El estudio genético habitual solo detectaría causa hasta 25% de los casos

Las causas monogénicas son potenciales contribuciones a la etiología



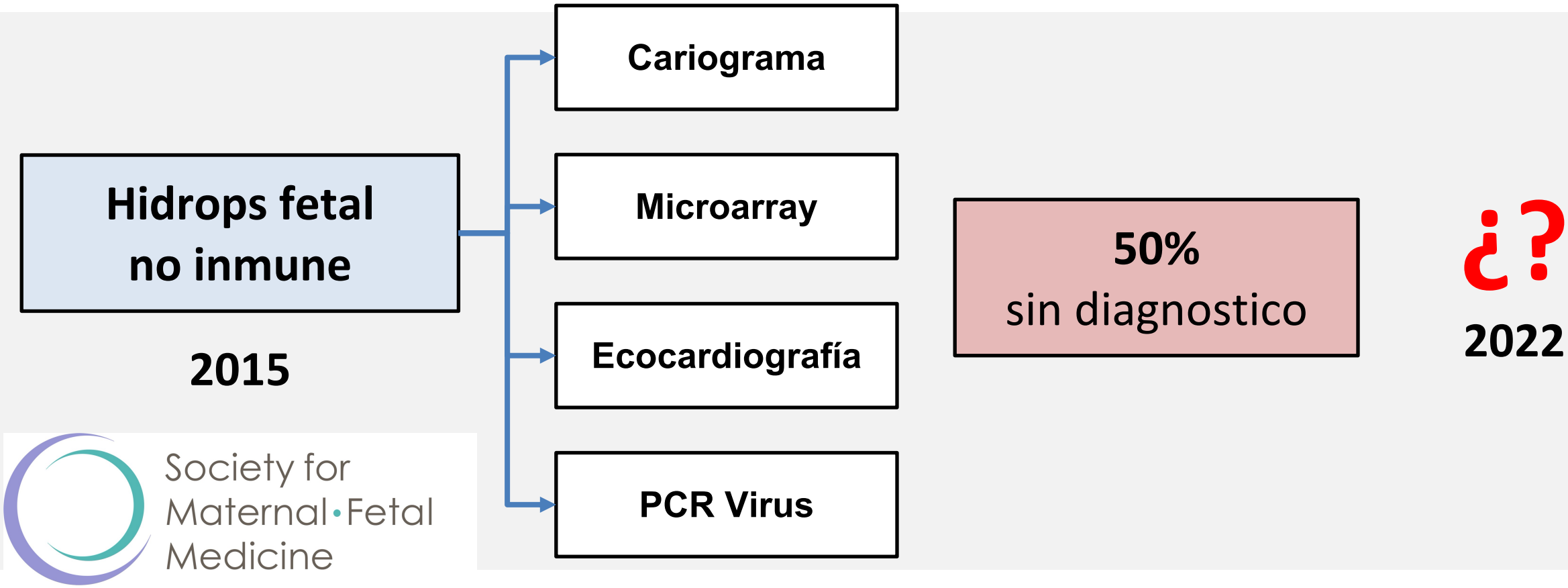
Sparks et al. Exome sequencing for prenatal diagnosis in Non-immune hydrops fetalis. NEJM 2020.

Hidrops fetal no inmune



Bellini, Hennekam. Non-inmune hydrops fetalis: a short review of etiology and pathophysiology. American Journal of medical genetics. 2012

Protocolo estudio HFNI



Quinn et al. A systematic review of monogenic etiologies of nonimmune hydrops fetalis. Genetics in medicine. January 2021

Resolución limitada de cariograma y microarray

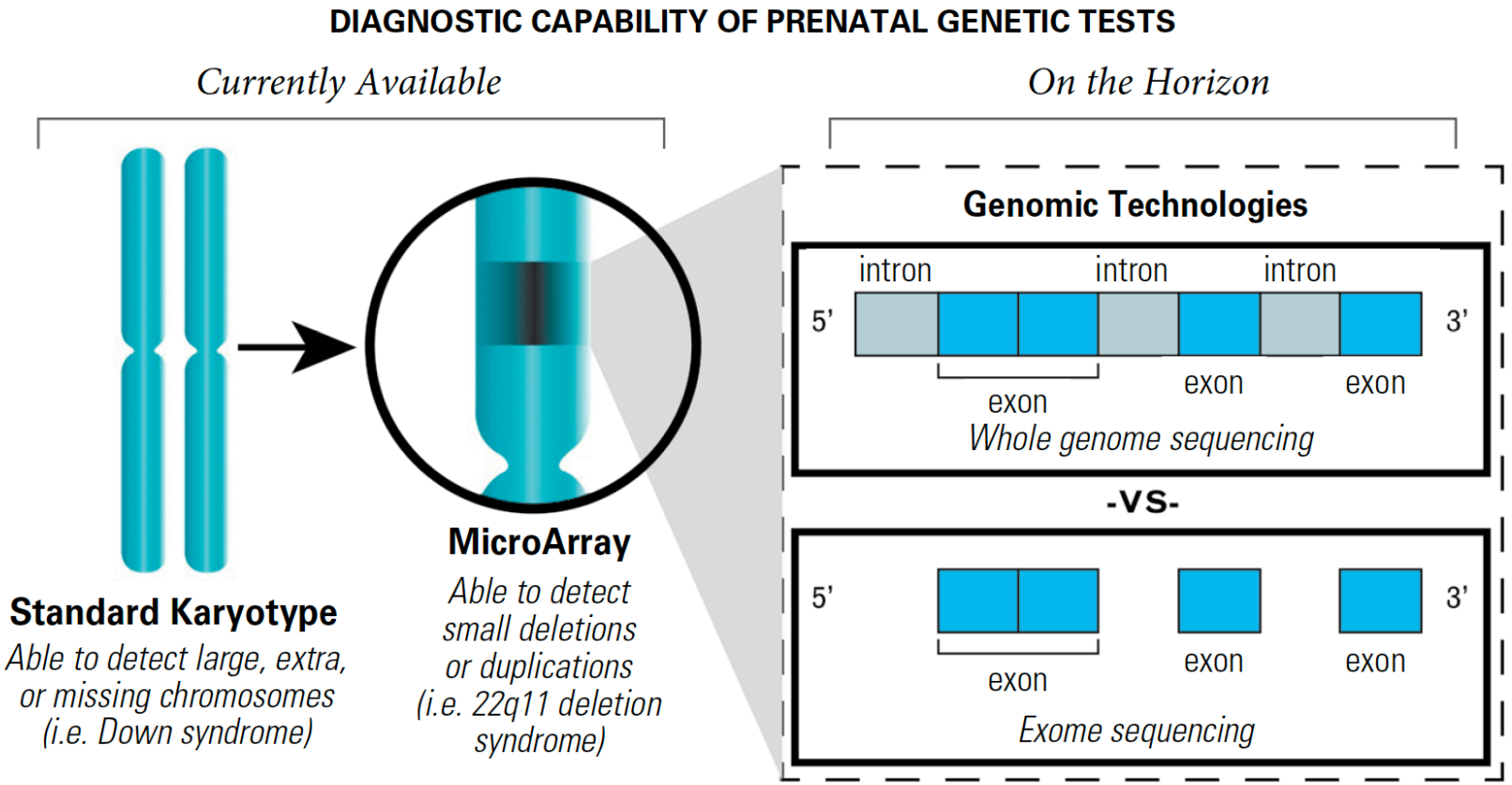


Figure 1. Diagnostic capability of prenatal genetic tests. (Reprinted from Hardisty EE, Vora NL. Advances in genetic prenatal diagnosis and screening. Curr Opin Pediatr 2014;26:634–8.) ⇦

Quinn et al. A systematic review of monogenic etiologies of nonimmune hydrops fetalis. Genetics in medicine. January 2021

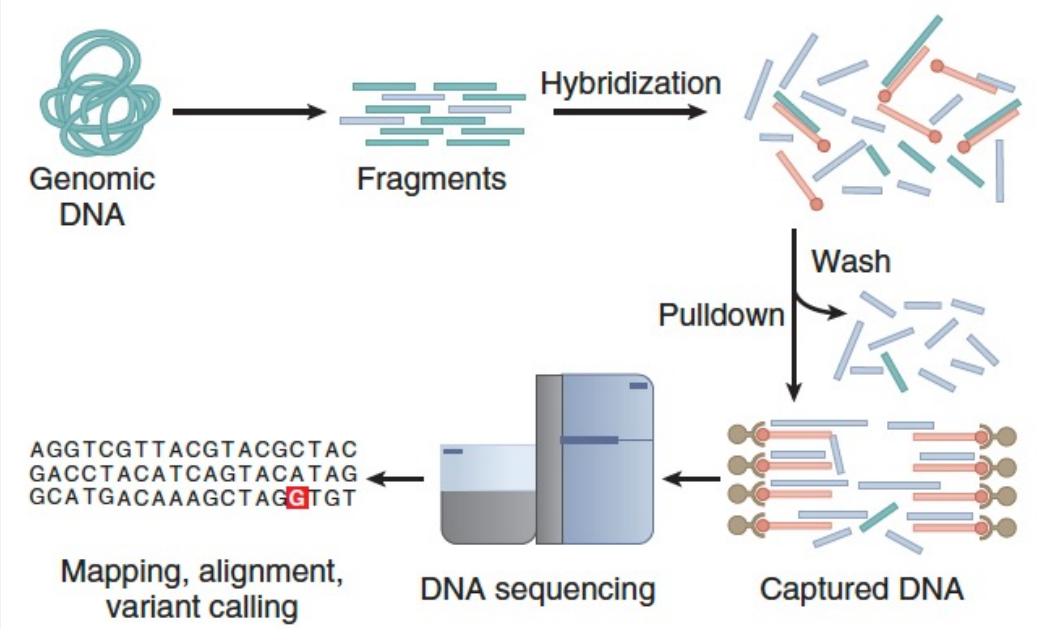
¿Qué es un exoma?

Exoma corresponde a todas las regiones del DNA que codifican para proteínas

Es aproximadamente 1% del genoma

Contiene aproximadamente 85% de variantes que causan enfermedad

Método de estudio basado en NGS



Quinn et al. A systematic review of monogenic etiologies of nonimmune hydrops fetalis. Genetics in medicine. January 2021

Recomendaciones de uso CMA y ES prenatal

Professional body	Recommendations for CMA	Recommendations for ES
American College of Medical Genetics and Genomics	(1) Has applications in prenatal specimens	Considered in fetus with one or more significant anomalies when routine prenatal methods are negative
American College of Obstetricians and Gynecologists and The Society of Maternal-Fetal Medicine	(1) Fetuses with structural abnormalities or fetal demise, CMA replaces karyotyping (2) Structurally normal fetuses undergoing invasive testing, CMA or karyotype could be performed	Not currently recommended outside the context of clinical trials
Canadian College of Medical Genetics & Society of Obstetricians and Gynaecologists of Canada	(1) Normal RAD and multiple fetal abnormalities (2) Increased NT $\geq$3.5 mm (3) Stillbirth after RAD with or without congenital anomalies	NA
Royal College of Obstetricians and Gynaecologists & The Royal College of Pathologists	(1) Fetuses with one or more structural anomalies (2) Increased NT at least 3.5 mm (3) Fetuses with sex chromosomal abnormality that is unlikely to explain the ultrasound anomalies	NA
International Society for Prenatal Diagnosis	NA	The routine use of prenatal sequencing as a diagnostic test cannot currently be supported due to insufficient validation data and knowledge about its benefits and pitfalls Currently ideally done in a research setting/protocol Case by case basis when a genetic disorder is suspected for confirmatory genetic testing by exome sequencing.
Chinese Medical Association	(1) Fetuses with one or more structural anomalies (2) Stillbirth after normal karyotype	NA

CMA, chromosomal microarray analysis; NT, nuchal translucency; RAD, rapid aneuploidy detection.

Chau, Choy. The role of chromosomal microarray and exome sequencing in prenatal diagnosis. Curr Opin Obstet Gynecol 2021

Recomendaciones de uso CMA y ES prenatal

Table 2. Additional diagnostic rates of prenatal chromosomal microarray analysis over conventional karyotyping stratified by prenatal ultrasound structural abnormality

Ultrasound structural abnormality	Additional diagnostic yield of CMA[a]	Additional diagnostic yield of ES[b]
Isolated to a single anatomical system	% (positive case/cohort size)	% (positive case/cohort size)
Cardiac	4.6 (30/650)	13.9 (16/115)
Respiratory	5.5 (6/109)	0.0 (0/23)
CNS	5.7 (37/652)	12.7 (17/134)
Facial	4.3 (8/185)	10.2 (5/49)
Musculoskeletal	6.9 (25/364)	17.3 (13/75)
Gastrointestinal	5.5 (8/145)	2.0 (1/50)
Urogenital	4.8 (9/186)	23.1 (6/26)
Increased NT	1.8 (6/334)	3.2 (3/93)
Cystic hygroma	4.0 (12/300)	–
Multiple abnormalities	9.1 (104/1139)	23.7 (93/392)

The diagnostic yields shown include abnormalities isolated to a single anatomical system and multiple systems. CMA, chromosomal microarray; CNS, central nervous system; ES, exome sequencing; NT, nuchal translucency.
[a]Additional diagonstic yield of CMA after exclusion over abnormal karyotype data were modified from de Wit *et al.* [24] and Hui *et al.* [25▪] (pooled data).
[b]Additional diagnostic yield of ES after exclusion of aneuploidies and pathogenic CNVs data were modified from Pratt *et al.* [26▪▪].

Chau, Choy. The role of chromosomal microarray and exome sequencing in prenatal diagnosis. Curr Opin Obstet Gynecol 2021

Importancia del diagnostico molecular

CERPO

Definir tratamiento específico

Asesoramiento sobre resultados a corto y a largo plazo

Beneficio psicológico a los padres

Estimar el riesgo de recurrencia

Quinn et al. A systematic review of monogenic etiologies of nonimmune hydrops fetalis. Genetics in medicine. January 2021

Etiología monogénica de HFNI

Table 2 Etiology of non-immune fetal hydrops in 243 singleton pregnancies that underwent invasive testing, according to gestational age at initial diagnosis

Etiology	*≤ 13 + 6 weeks (n = 63)*	*14 to 24 + 6 weeks (n = 106)*	*≥ 25 weeks (n = 74)*	P
Chromosomal abnormality	44 (69.8)	22 (20.8)	3 (4.1)	< 0.001
Single-gene disorder	2 (3.2)	8 (7.5)	6 (8.1)	0.44
Cardiovascular abnormality*	8 (12.7)	9 (8.5)	17 (23.0)	0.02
Other structural abnormality	3 (4.8)	8 (7.5)	8 (10.8)	0.41
Congenital infection	0 (0)	21 (19.8)	5 (6.8)	< 0.001
Hematologic etiology	0 (0)	3 (2.8)	7 (9.5)	0.01
Placental chorioangioma	0 (0)	1 (0.9)	5 (6.8)	0.02
Fetomaternal hemorrhage	0 (0)	1 (0.9)	0 (0)	0.52
Unknown etiology	6 (9.5)	33 (31.1)	23 (31.1)	0.003

Data are given as *n* (%). *Structure/rhythm.

Sileo et al. Non-immune fetal hydrops: etiology and outcome according to gestational age at diagnosis. Ultrasound Obstet Gynecol 2020; 56: 416–421

Exoma en Hidrops fetal

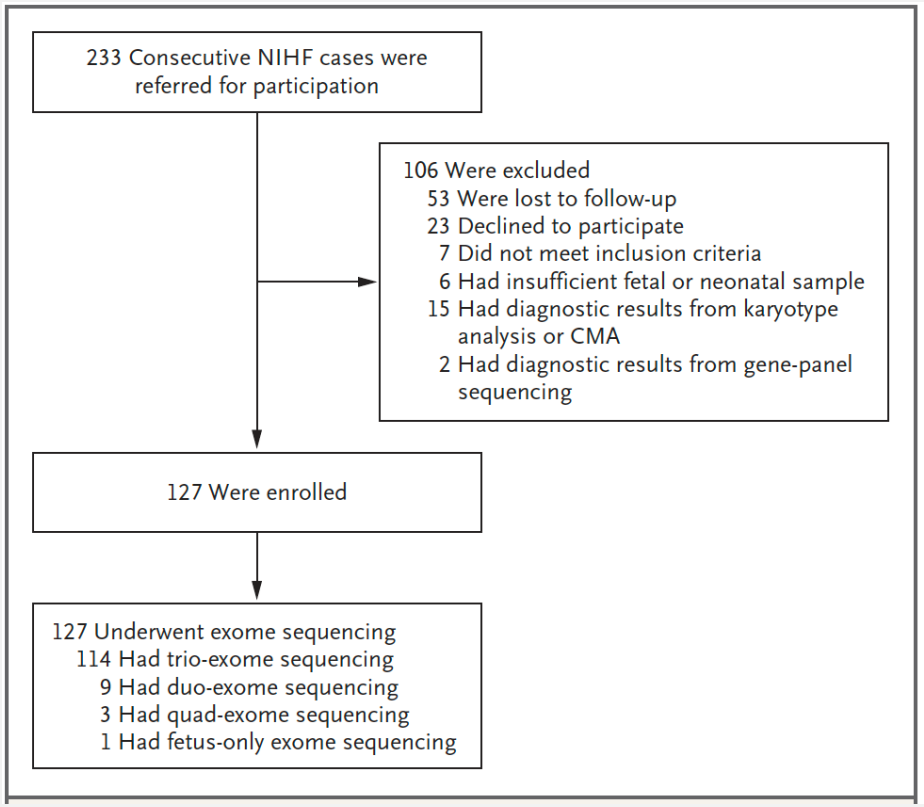


Table 1. Demographic Characteristics, Phenotypic Features, and Pregnancy Outcomes.*

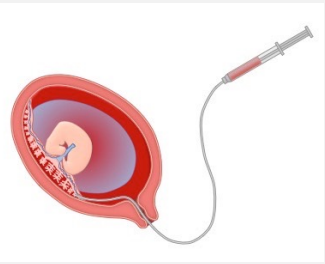
Characteristic	Value (N=127)
Median maternal age (IQR) — yr	32 (29–35)
Nulliparous — no. (%)	57 (45)
Use of assisted reproductive technology — no. (%)†	12 (9)
Median gestational age at diagnosis of NIHF (IQR) — wk	20.0 (13.4–24.6)
Previous pregnancy with NIHF — no. (%)	10 (8)
Biologic parents consanguineous — no. (%)	4 (3)
Prenatal phenotype at enrollment — no. (%)‡	
Increased nuchal translucency or cystic hygroma	29 (23)
Isolated increased nuchal translucency or cystic hygroma	15 (12)
Concurrent structural anomaly	9 (7)
>1 additional abnormal fluid collection	5 (4)
Single abnormal fetal fluid collection	21 (17)
Isolated single abnormal fetal fluid collection	4 (3)
Concurrent structural anomaly	17 (13)
≥2 abnormal fetal fluid collections	77 (61)
Isolated abnormal fetal fluid collections	39 (31)
Concurrent structural anomaly	38 (30)

Sparks et al. Exome sequencing for prenatal diagnosis in Non-immune hydrops fetalis. NEJM 2020.

Exoma en Hidrops fetal

Estudio genético previo

- Cariograma 4%
- Microarray 34%
- Ambos 62%



Exoma

- Trio 90%
- Duo 7%
- Solo probando 1%

Sparks et al. Exome sequencing for prenatal diagnosis in Non-immune hydrops fetalis. NEJM 2020.

Exoma en Hidrops fetal

Diagnostico variantes 29%

RASopatias corresponden al 30%

PTPN11, KRAS y RIT1

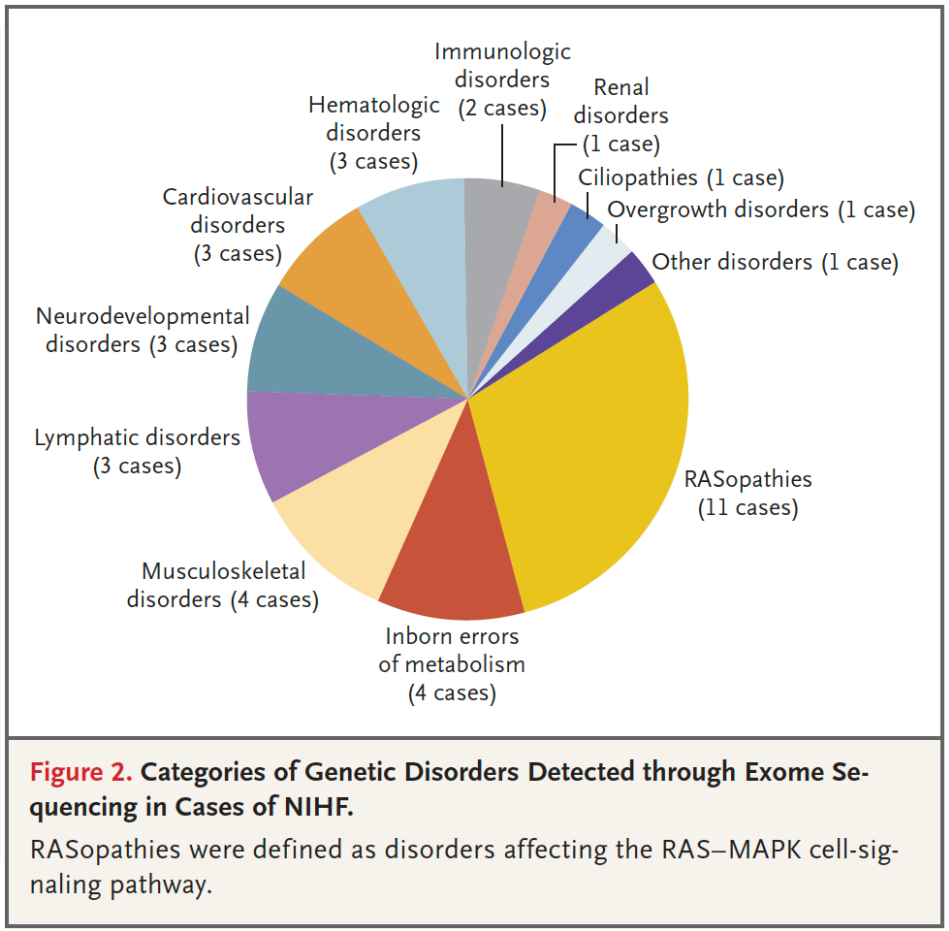


Figure 2. Categories of Genetic Disorders Detected through Exome Sequencing in Cases of NIHF.

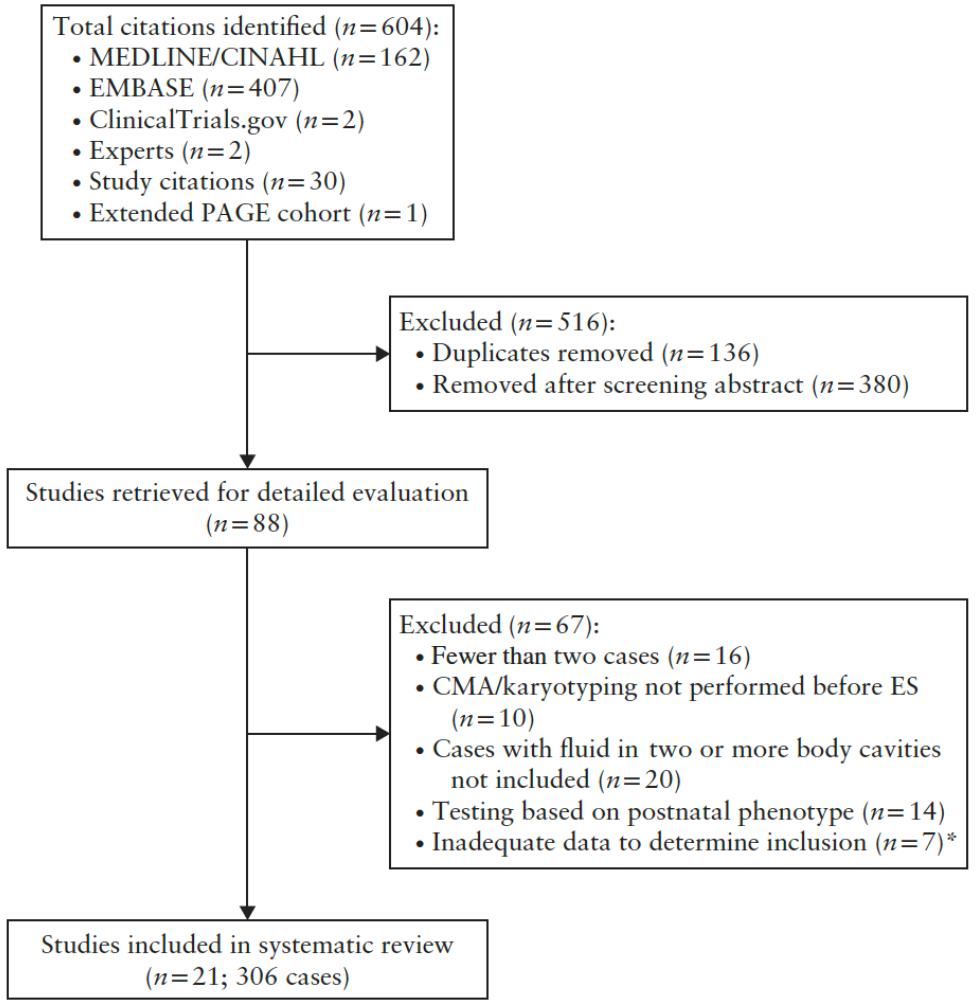
RASopathies were defined as disorders affecting the RAS–MAPK cell-signaling pathway.

Sparks et al. Exome sequencing for prenatal diagnosis in Non-immune hydrops fetalis. NEJM 2020.

Exoma en Hidrops fetal

Objetivo:
Evaluar el aumento en capacidad diagnostica de ES sobre CMA o Cariograma para HFNI

(1) Todos HFNI
(2) HFNI aislado
(3) HFNI asociado a anomalía estructural
(4) HFNI según severidad



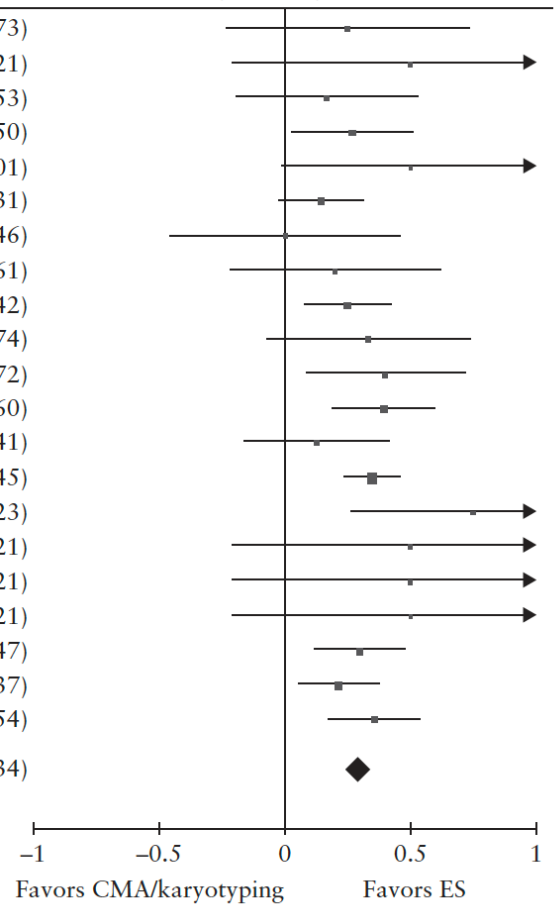
Mone et al. Fetal hydrops and the incremental yield of next-generation sequencing over standard prenatal diagnostic testing (FIND) study: propsective cohohrt study and meta-análisis. Ultrasound Obstet Gynecol 2021.

Exoma en Hidrops fetal

Study or subgroup	ES Events	ES Total	CMA/karyotyping Events	CMA/karyotyping Total	Weight	Incremental yield M–H, random, 95% CI
Becher (2020)[26]	1	4	0	4	1.2%	0.25 (–0.23, 0.73)
Boissel (2018)[18]	1	2	0	2	0.5%	0.50 (–0.21, 1.21)
Corsten-Janssen (2020)[32]	1	6	0	6	2.1%	0.17 (–0.19, 0.53)
Croonen (2013)[33]	4	15	0	15	4.8%	0.27 (0.03, 0.50)
Deden (2020)[27]	2	4	0	4	1.0%	0.50 (–0.01, 1.01)
Deng (2020)[19]	3	21	0	21	9.9%	0.14 (–0.02, 0.31)
Greenbaum (2019)[28]	0	3	0	3	1.3%	0.00 (–0.46, 0.46)
Jelin (2020)[20]	1	5	0	5	1.6%	0.20 (–0.21, 0.61)
Lord (2019)[8]	7	28	0	28	9.7%	0.25 (0.08, 0.42)
Mone (2020)[34]	2	6	0	6	1.7%	0.33 (–0.07, 0.74)
Normand (2018)[21]	4	10	0	10	2.7%	0.40 (0.08, 0.72)
Petrovski (2019)[16]	9	23	0	23	6.5%	0.39 (0.19, 0.60)
Sparks (2019)[29]	1	8	0	8	3.3%	0.13 (–0.16, 0.41)
Sparks (2020)[2]	27	78	0	78	23.7%	0.35 (0.24, 0.45)
Stals (2018)[23]	3	4	0	4	1.2%	0.75 (0.27, 1.23)
Vora (2017)[22]	1	2	0	2	0.5%	0.50 (–0.21, 1.21)
Westerfield (2015)[30]	1	2	0	2	0.5%	0.50 (–0.21, 1.21)
Westphal (2019)[24]	1	2	0	2	0.5%	0.50 (–0.21, 1.21)
Yang (2012)[31]	8	27	0	27	8.6%	0.30 (0.12, 0.47)
Yates (2017)[25]	6	28	0	28	10.6%	0.21 (0.06, 0.37)
Zhou (2020)[17]	10	28	0	28	8.2%	0.36 (0.18, 0.54)
Total (95% CI)		306		306	100.0%	0.29 (0.24, 0.34)
Total events	93		0			

Heterogeneity: $tau^2 = 0.00$; $chi^2 = 16.52$, df = 20 ($P = 0.68$); $I^2 = 0\%$

Test for overall effect: $Z = 10.98$ ($P < 0.00001$)



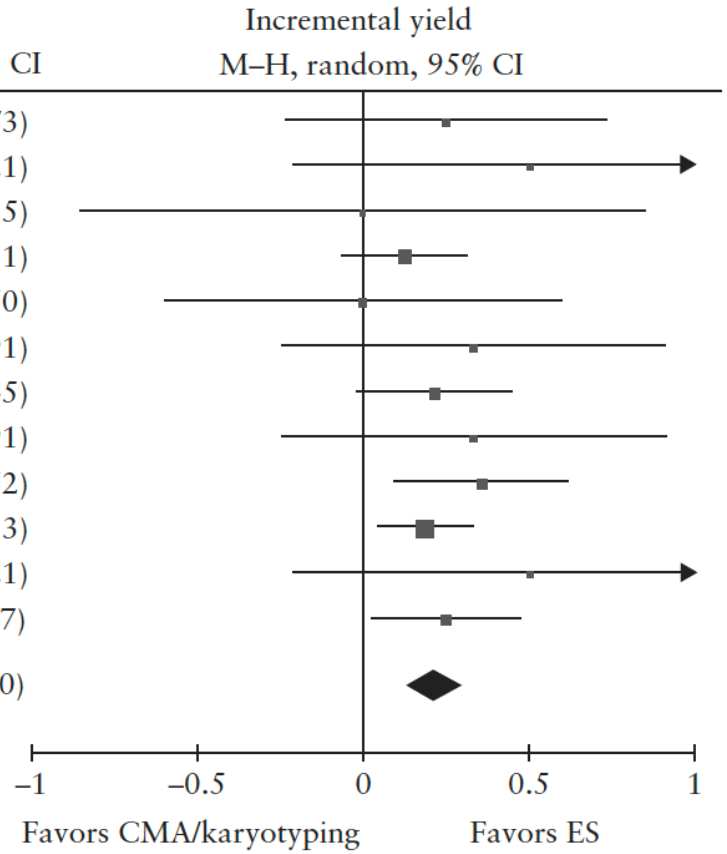
Mone et al. Fetal hydrops and the incremental yield of next-generation sequencing over standard prenatal diagnostic testing (FIND) study: propsective cohohrt study and meta-análisis. Ultrasound Obstet Gynecol 2021.

Exoma en Hidrops fetal

Study or subgroup	ES Events	ES Total	CMA/karyotyping Events	CMA/karyotyping Total	Weight	Incremental yield M–H, random, 95% CI
Becher (2020)[26]	1	4	0	4	2.9%	0.25 (–0.23, 0.73)
Corsten-Janssen (2020)[32]	1	2	0	2	1.3%	0.50 (–0.21, 1.21)
Deden (2020)[27]	0	1	0	1	0.9%	0.00 (–0.85, 0.85)
Deng (2020)[19]	2	16	0	16	19.2%	0.13 (–0.06, 0.31)
Greenbaum (2019)[28]	0	2	0	2	1.9%	0.00 (–0.60, 0.60)
Jelin (2020)[20]	1	3	0	3	2.0%	0.33 (–0.24, 0.91)
Lord (2019)[8]	3	14	0	14	12.3%	0.21 (–0.02, 0.45)
Mone (2020)[34]	1	3	0	3	2.0%	0.33 (–0.24, 0.91)
Petrovski (2019)[16]	5	14	0	14	9.8%	0.36 (0.10, 0.62)
Sparks (2020)[2]	6	32	0	32	33.1%	0.19 (0.05, 0.33)
Vora (2017)[22]	1	2	0	2	1.3%	0.50 (–0.21, 1.21)
Zhou (2020)[17]	4	16	0	16	13.2%	0.25 (0.03, 0.47)
Total (95% CI)		109		109	100.0%	0.21 (0.13, 0.30)
Total events	25		0			

Heterogeneity: tau²=0.00; chi²=4.75, df=11 (P=0.94); I^2=0%

Test for overall effect: Z=5.15 (P<0.00001)



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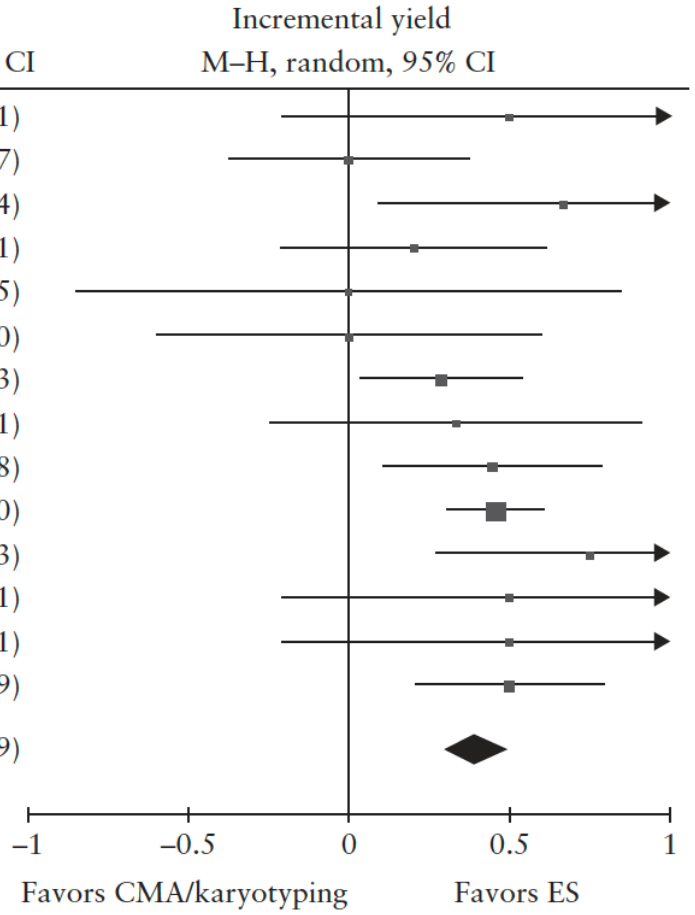
Exoma en Hidrops fetal

Study or subgroup	ES Events	ES Total	CMA/karyotyping Events	CMA/karyotyping Total	Weight	Incremental yield M–H, random, 95% CI
Boissel (2018)[18]	1	2	0	2	1.8%	0.50 (–0.21, 1.21)
Corsten-Janssen (2020)[32]	0	4	0	4	6.3%	0.00 (–0.37, 0.37)
Deden (2020)[27]	2	3	0	3	2.6%	0.67 (0.09, 1.24)
Deng (2020)[19]	1	5	0	5	5.2%	0.20 (–0.21, 0.61)
Greenbaum (2019)[28]	0	1	0	1	1.2%	0.00 (–0.85, 0.85)
Jelin (2020)[20]	0	2	0	2	2.5%	0.00 (–0.60, 0.60)
Lord (2019)[8]	4	14	0	14	13.8%	0.29 (0.04, 0.53)
Mone (2020)[34]	1	3	0	3	2.6%	0.33 (–0.24, 0.91)
Petrovski (2019)[16]	4	9	0	9	7.6%	0.44 (0.11, 0.78)
Sparks (2020)[2]	21	46	0	46	38.9%	0.46 (0.31, 0.60)
Stals (2018)[23]	3	4	0	4	3.8%	0.75 (0.27, 1.23)
Westerfield (2015)[30]	1	2	0	2	1.8%	0.50 (–0.21, 1.21)
Westphal (2019)[24]	1	2	0	2	1.8%	0.50 (–0.21, 1.21)
Zhou (2020)[17]	6	12	0	12	10.2%	0.50 (0.21, 0.79)
Total (95% CI)		109		109	100.0%	0.39 (0.30, 0.49)
Total events	45		0			

Heterogeneity: tau²=0.00; chi²=13.13, df=13 (P=0.44); I^2=1%

Test for overall effect: Z=8.23 (P<0.00001)



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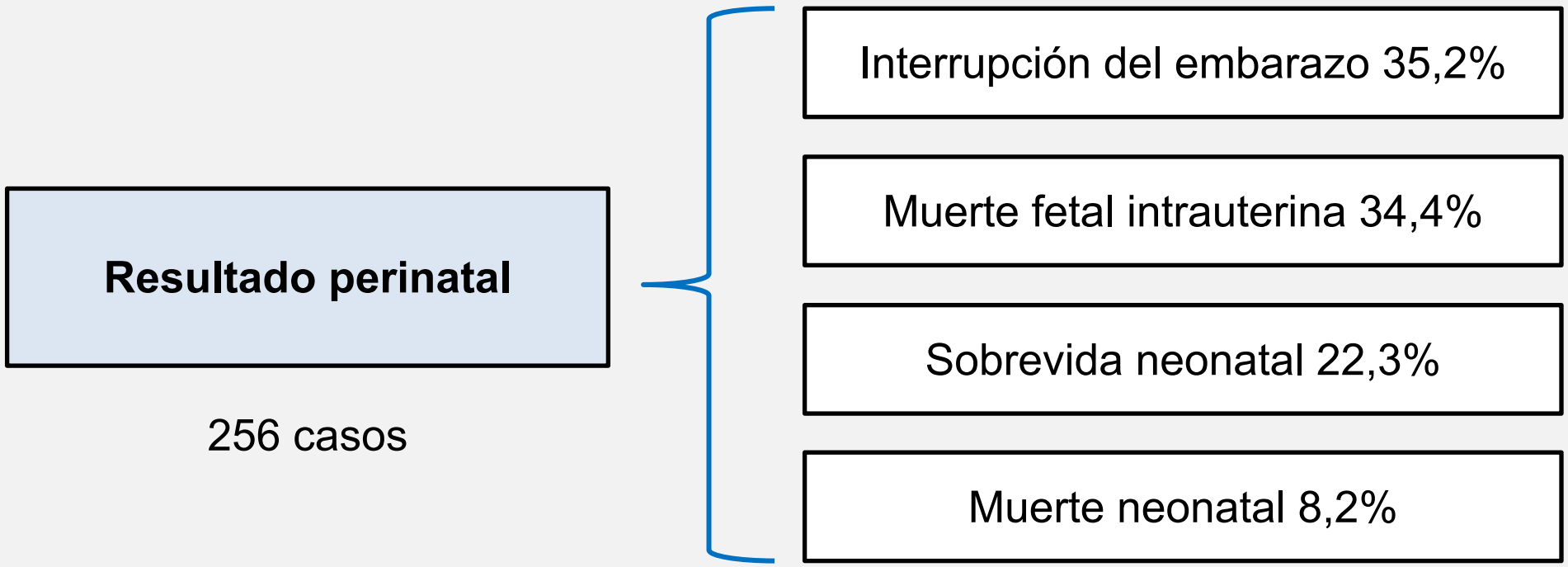
Exoma en Hidrops fetal



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Exoma en Hidrops fetal

RASopatías (30,3%)	**Trastornos musculoesqueléticos (14,6%)**	**Errores innatos del metabolismo (12,4%)**

Autosómica dominante (57,3%)	***De novo* (86,3%)**

Mone et al. Fetal hydrops and the incremental yield of next-generation sequencing over standard prenatal diagnostic testing (FIND) study: propsective cohohrt study and meta-análisis. Ultrasound Obstet Gynecol 2021.

Exoma vs panel genético

Objetivo:
Comparar capacidad diagnostica del ES con la aplicación simulada de paneles genéticos comerciales en HFNI

Análisis secundario de ES en HFNI
61% compromiso de ≥ 2 cavidades
17% solo 1 cavidad
50% tenían anomalía estructural

TABLE 1
Demographics of exome cohort

Demographic	Value (N=127)
Median maternal age (IQR), y	32 (29–35)
Nulliparous (%)	45 (57/127)
Median gestational age at diagnosis of NIHF (range), wk	20.0 (13.4–24.6)
Any concurrent anomaly (%)	50 (64/127)
Maternal race and ethnicity (%)	
White	58 (74/127)
Asian	15 (19/127)
Multiracial	14 (18/127)
Hispanic or Latina	9 (12/127)
Black	2 (3/127)
Unknown	1 (1/127)
Type of abnormal fetal effusion (%)	
Early onset (increased NT or cystic hygroma)	23 (29/127)
Single abnormal fetal effusion	17 (21/127)
Traditionally defined NIHF with ≥2 abnormal effusions	61 (77/127)

Data are presented as median (IQR) or percentage (number), unless otherwise indicated.

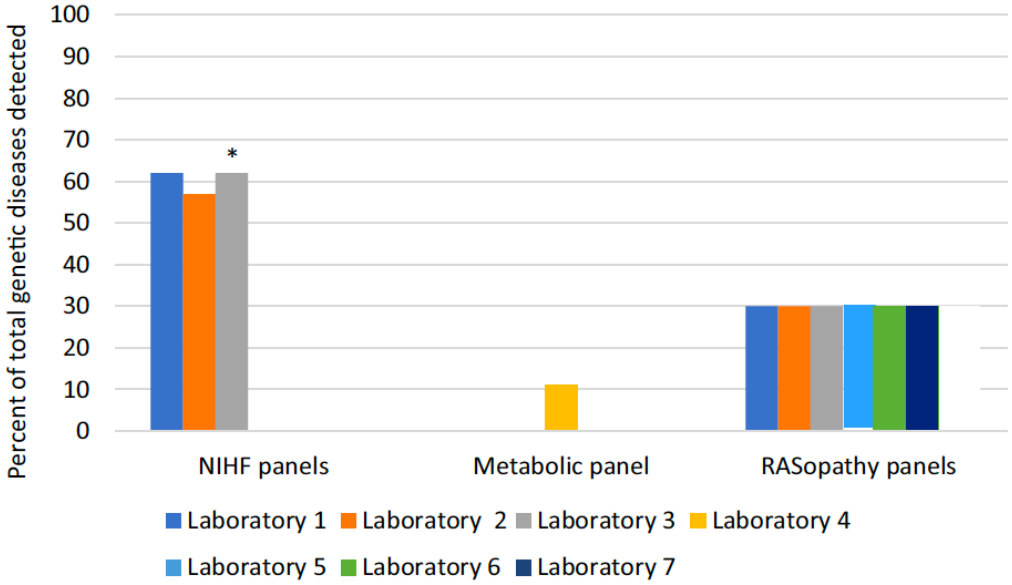
IQR, interquartile range; *NIHF*, nonimmune hydrops fetalis; *NT*, nuchal translucency.

Norton et al. Panels vs exomes for nonimmune hydrops. Am J Obstet Gynecol 2021.

Mone et al. Fetal hydrops and the incremental yield of next-generation sequencing over standard prenatal diagnostic testing (FIND) study: propsective cohohrt study and meta-análisis. Ultrasound Obstet Gynecol 2021.

Exoma vs panel genético

FIGURE
Genetic diseases detected by targeted gene panels and exome sequencing



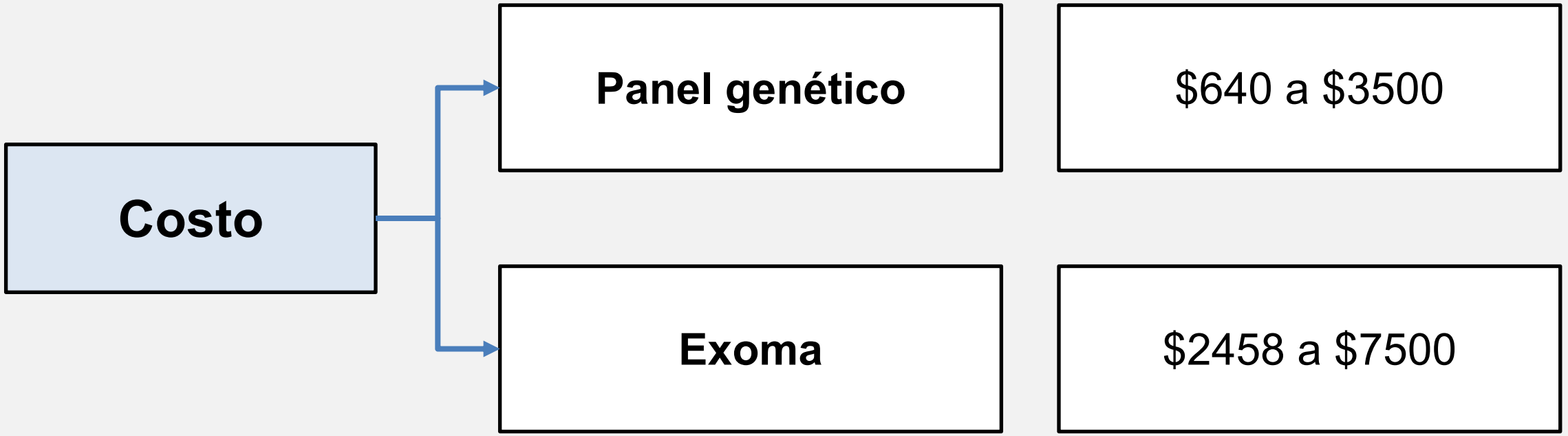
The *asterisk* represents that this NIHF panel was updated to include additional genes after publication of our primary analysis.[4] After this update, the percent of total genetic diseases that would have detected by this panel was 100%, including the full list of genes we reported (in the text).

NIHF, nonimmune hydrops fetalis.

Norton et al. Panels vs exomes for nonimmune hydrops. Am J Obstet Gynecol 2021.

Mone et al. Fetal hydrops and the incremental yield of next-generation sequencing over standard prenatal diagnostic testing (FIND) study: propsective cohohrt study and meta-análisis. Ultrasound Obstet Gynecol 2021.

Exoma vs panel genético



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Exoma vs panel genético

Exoma posee mayor capacidad diagnostica que panel genético en HFNI, pero con un eventual mayor costo

Un panel genético no estaría indicado en fenotipos poco diferenciados

Panel es limitado en descubrir nuevas variantes patogénicas asociadas a HFNI

Mone et al. Fetal hydrops and the incremental yield of next-generation sequencing over standard prenatal diagnostic testing (FIND) study: propsective cohohrt study and meta-análisis. Ultrasound Obstet Gynecol 2021.

Conclusiones

HFNI es un síndrome heterogéneo que precisa de diagnostico molecular

Exoma prenatal tiene capacidad diagnostica de un 29% en casos ya estudiados con cariograma y microarray

Por ahora se debe preferir estudio con exoma por sobre panel genético

Mone et al. Fetal hydrops and the incremental yield of next-generation sequencing over standard prenatal diagnostic testing (FIND) study: propsective cohohrt study and meta-análisis. Ultrasound Obstet Gynecol 2021.

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Rol exoma prenatal en Hidrops fetal no inmune

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