INTERVISTA DOPPIA

PER UNA COPPIA CON ETÀ MATERNA AVANZATA, QUALI TEST SONO MAGGIORMENTE EFFICACI IN DIAGNOSI PREIMPIANTO E IN DIAGNOSI PRENATALE?

Human fertility is shaped by oocyte aneuploidy rate

RESEARCH

Science 2019

REPRODUCTIVE BIOLOGY

Chromosome errors in human eggs shape natural fertility over reproductive life span

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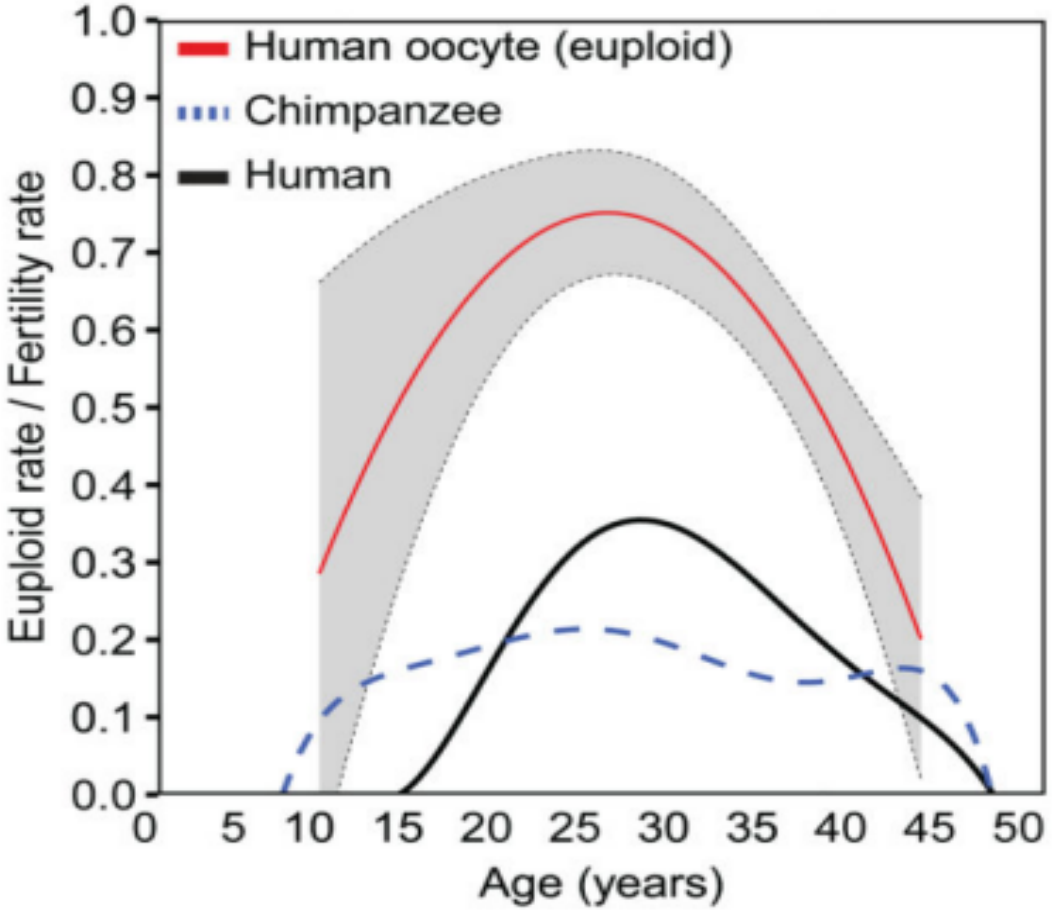
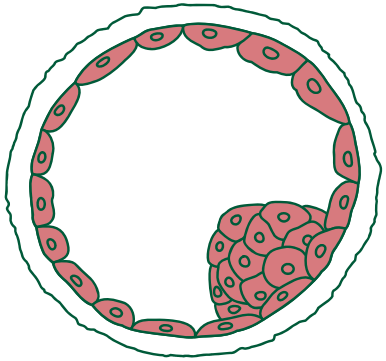


Grhun, et al. Science 2019; Capalbo et al., HRU 2017; Ottolini, Capalbo et al., Nat Prot 2016; Ottolini, Newman, Capalbo et al., Nat Gen 2015; McCoy, R. C. et al., HMG 2018; Hassold, T. J., & Hunt, P. A. PND 2021. **Origins of Aneuploidy Research Consortium.**

Non-Mosaic Aneuploidy Detection in the Preimplantation Embryo is Highly Predictive of Early Lethality

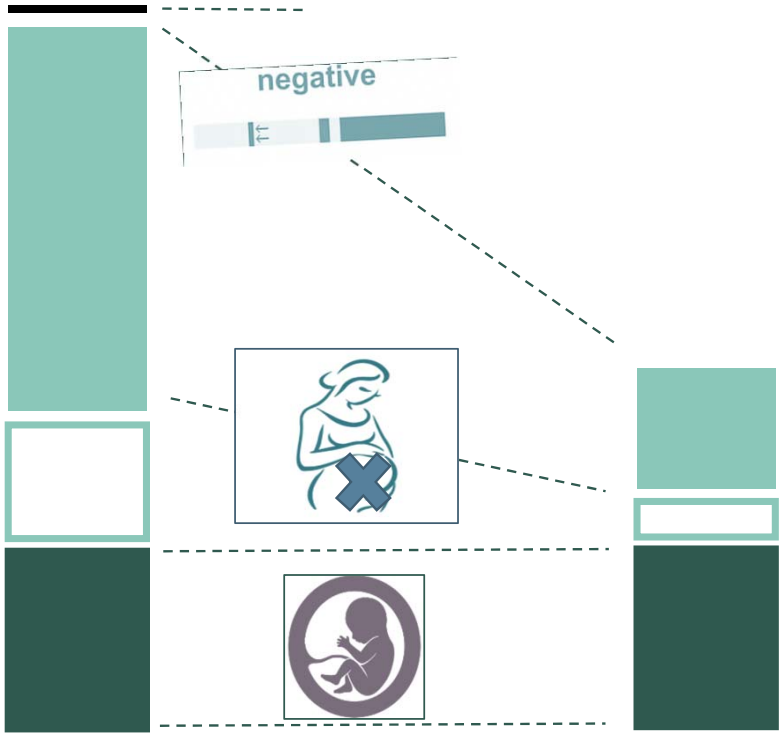
Antonio Capalbo, Maurizio Poli, Eric Forman, Chaim Jalas, Nathan R. Treff

American Journal Of Human Genetics 2022



Study	Design	Transfers of Uniformly Aneuploid Embryos n*	Miscarriage rate % (n, 95%CI)	Lethality rate % (n, 95%CI)
Scott et al 2012	blinded	95	33.3% (2/6) (4.3%-77.7%)˚	95.8% (91/95) (84.5%-99.4%)
Tiegs et al 2021	blinded	102	100% (24/24) (85.8%-100%)	100% (102/102) (96.5%-100%)
Wang et al. 2021	blinded	44	75.0% (6/8) (34.9%-96.8%)	95.5% (42/44) (84.5%-99.4%)
Yang et al., 2022	blinded	6	100% (6/6) (54.1%-100%)	100% (6/6) (54.1%-100%)
Barad et al., 2022	Unblinded	106	85.7% (6/7) (42.1%-99.6%)	99.1% (105/106) (94.9%-99.9%)
TOTAL		**353**	**86.3% (44/51) (73.7%-94.3%)**	**98.0% (346/353) (96.0%-99.2%)**

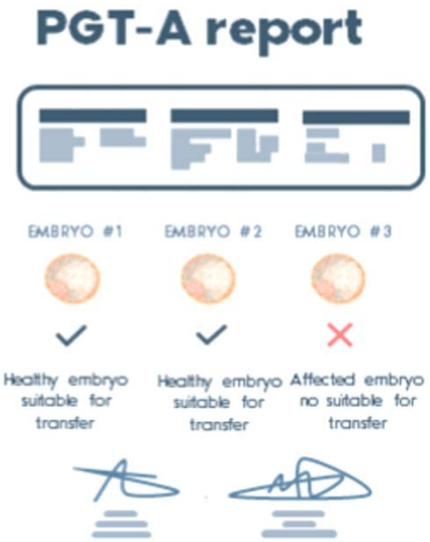
PGT-A: the theory



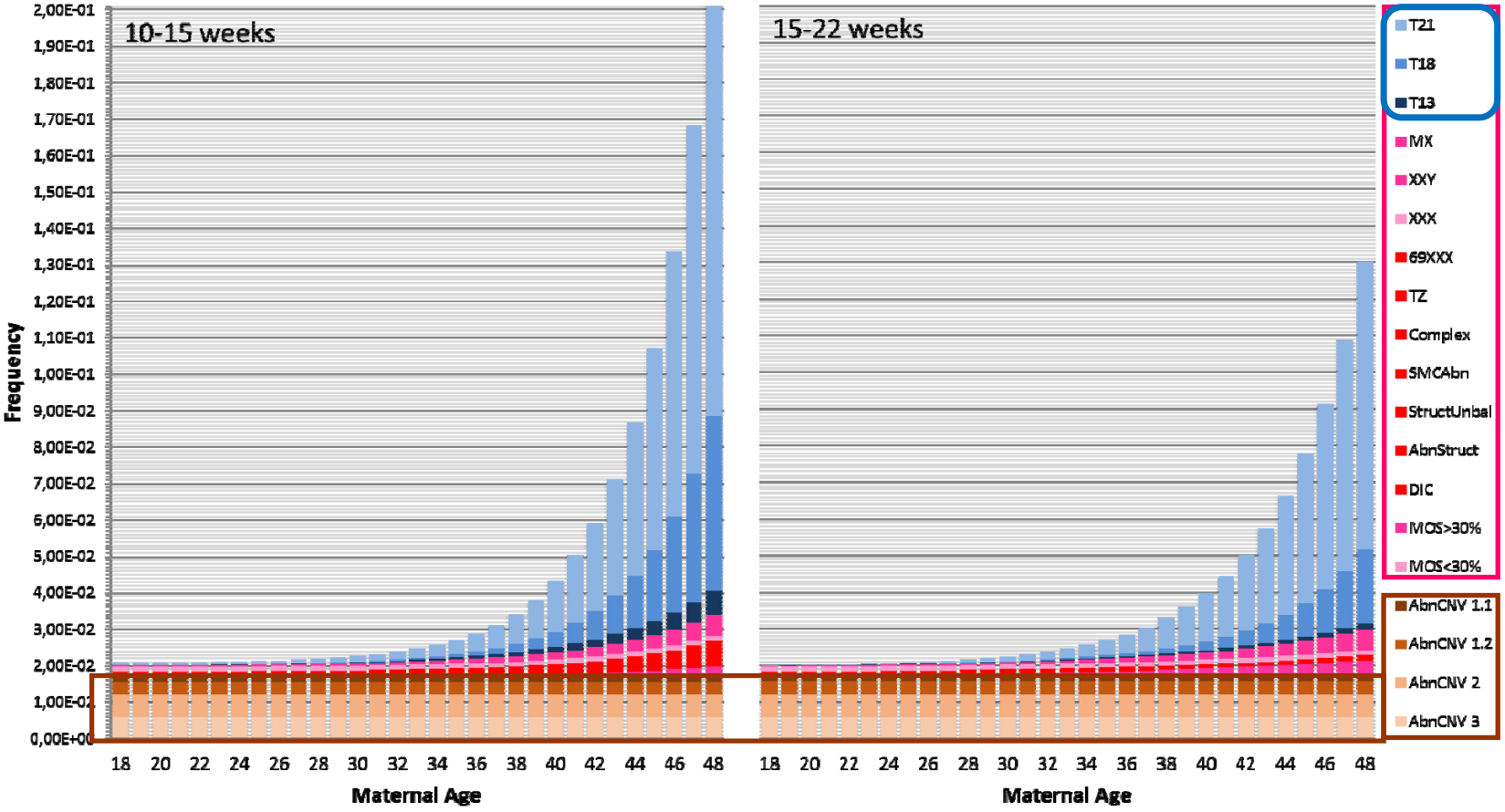
LIVE BIRTHS
Intention to treat

NO SELECTION

ANEUPLOIDY TESTING



A PRIORI RISK OF A WOMAN TO CONCEIVE A CHROMOSOMICALLY ABNORMAL FETUS



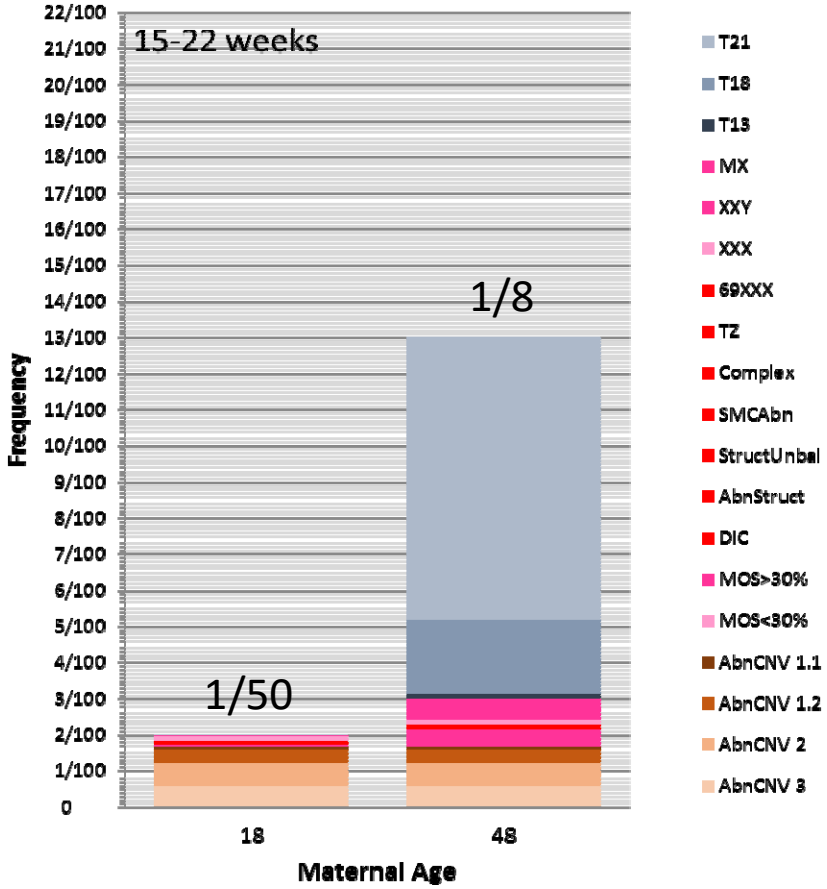
Common trisomies

Large chromosome abnormalities (karyotype)

Sub-microscopic chromosome abnormalities (chromosomal microarray)

Ferreira, Grati FR et al, Prenat Diagn. 2016 Dec;36(12):1146-1155; Wapner et al, N Engl J Med 2012;367(23):2175–2184

RISK



In older women age-dependent chromosome abnormalities (e.g.: T21,18,13) dominate fetal risk

Ferreira, Grati FR et al, Prenat Diagn. 2016 Dec;36(12):1146-1155

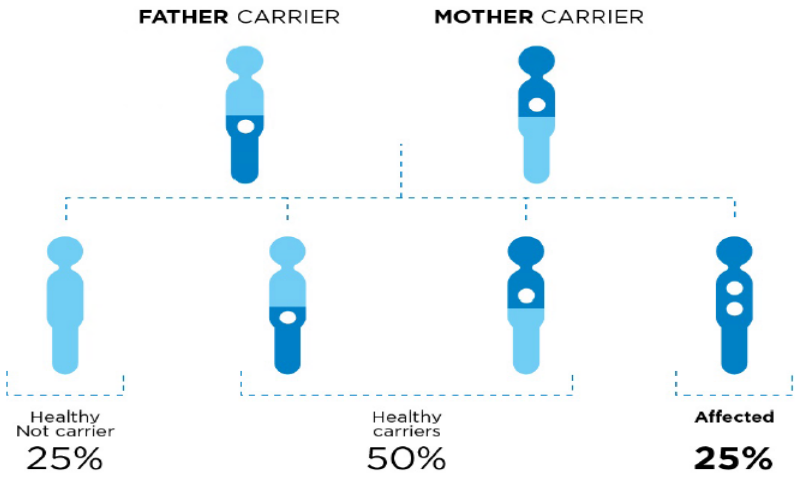
PER UNA COPPIA CON ETÀ MATERNA INFERIORE AI 35 ANNI, QUALI TEST SONO MAGGIORMENTE EFFICACI IN DIAGNOSI PREIMPIANTO E IN DIAGNOSI PRENATALE? E QUALE VA RITENUTO L'APPROCCIO MIGLIORE?

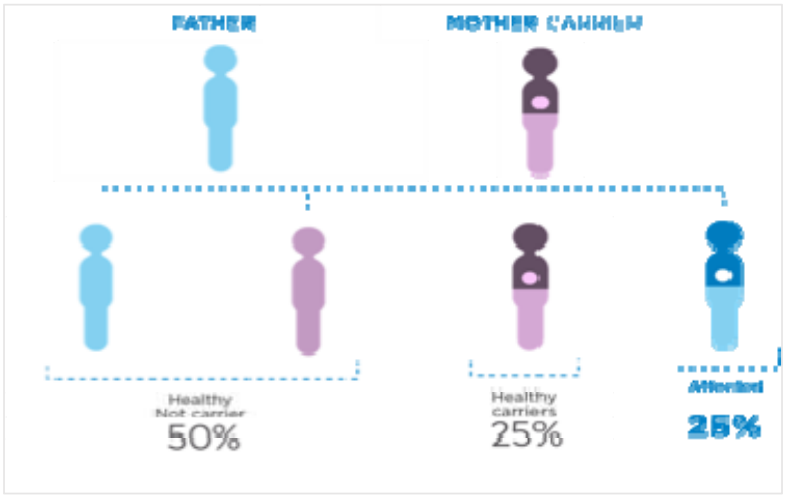
The burden of recessive single gene disorders: highly prevalent when considered as a group

4% Couples at risk of having a child affected with a recessive genetic condition.

20% Paediatric hospitalizations and mortality (developed countries)

88% children born with a genetic disease have no family history for the conditions





Parker SE, et al. *Birth Defects Res A Clin Mol Teratol.* 2010;88(12): 1008-1016; Franasiak et al., 2016; Martin et al., 2015;. **3.** American Thoracic Society website. https://www.thoracic.org/patients/patient-resources/breathing-in-america/resources/chapter-7-cystic-fibrosis.pdf. Accessed November 25, 2016. Sever JL, Ellenberg JH, Ley AC et al: Toxoplasmosis: Maternal and pediatric findings in 23,000 pregnancies. Pediatrics 82: 181– 192, 1988

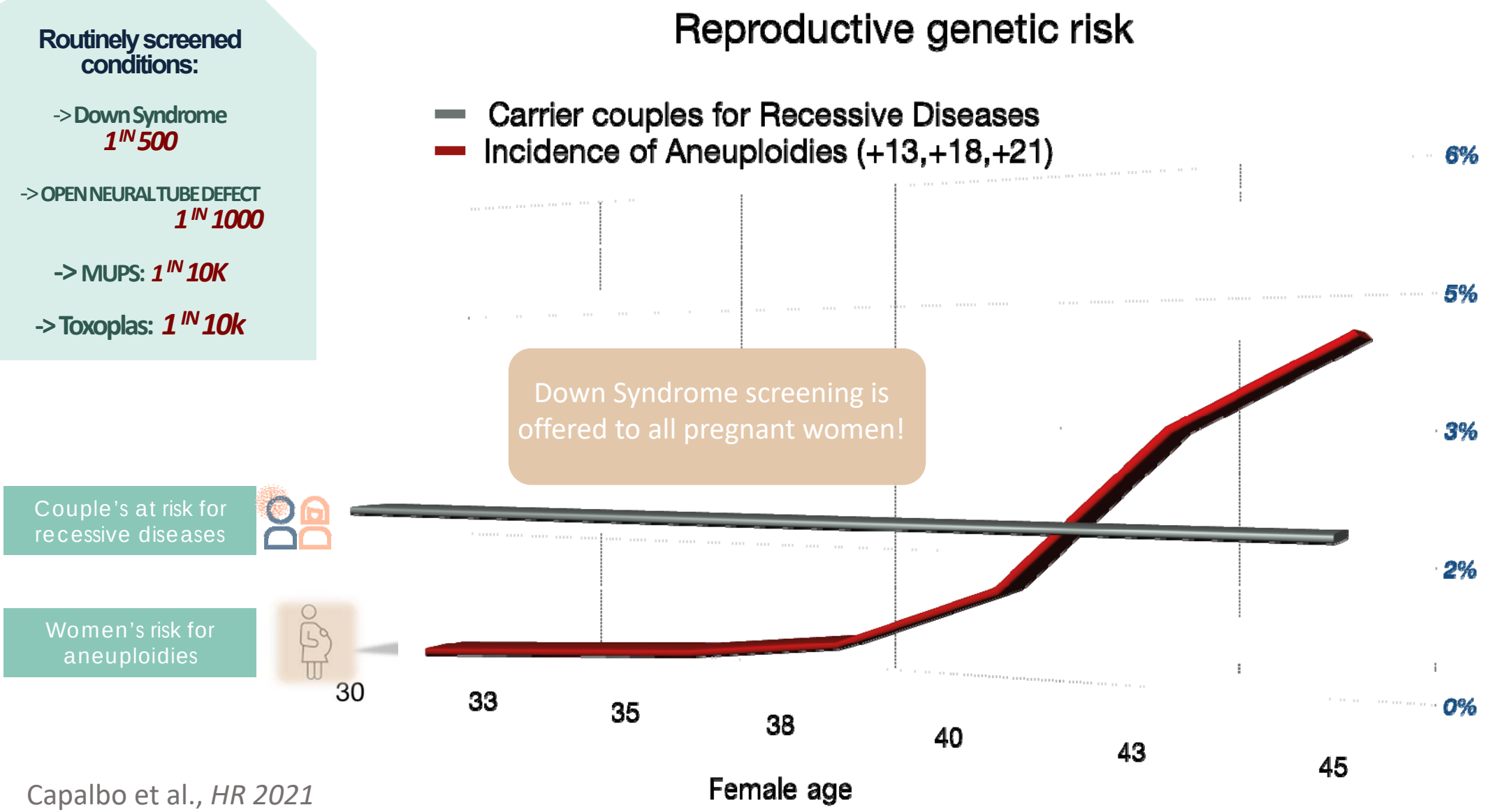
Routinely screened conditions:

-> Down Syndrome
1 IN 500

-> OPEN NEURAL TUBE DEFECT
1 IN 1000

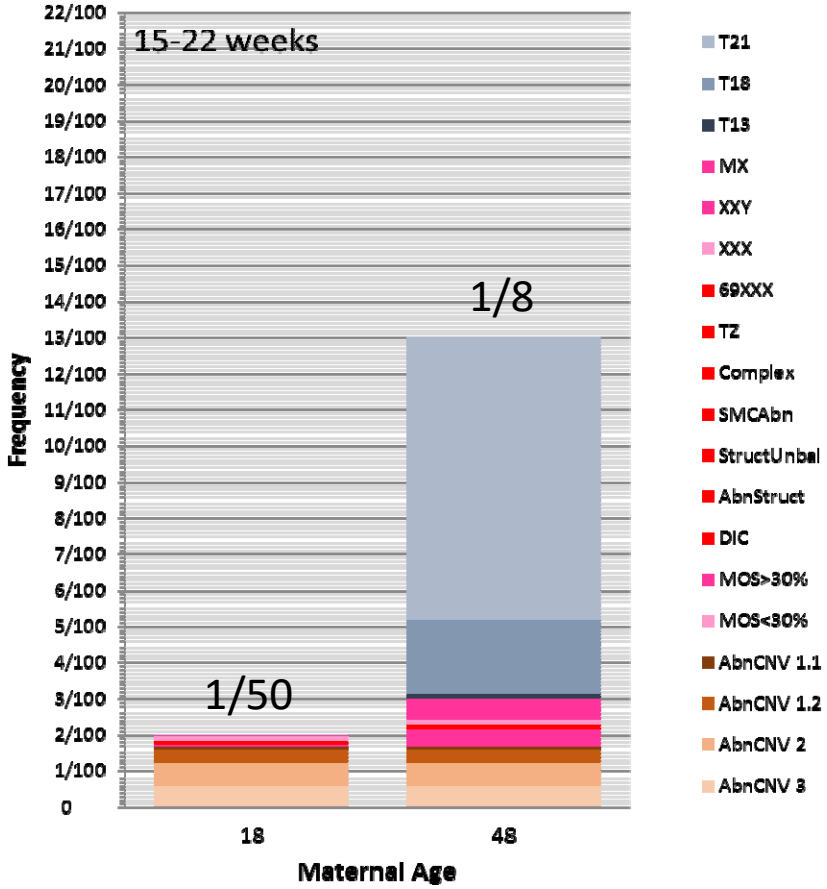
-> MUPS: *1 IN 10K*

-> Toxoplas: *1 IN 10k*



Capalbo et al., *HR 2021*

RISK

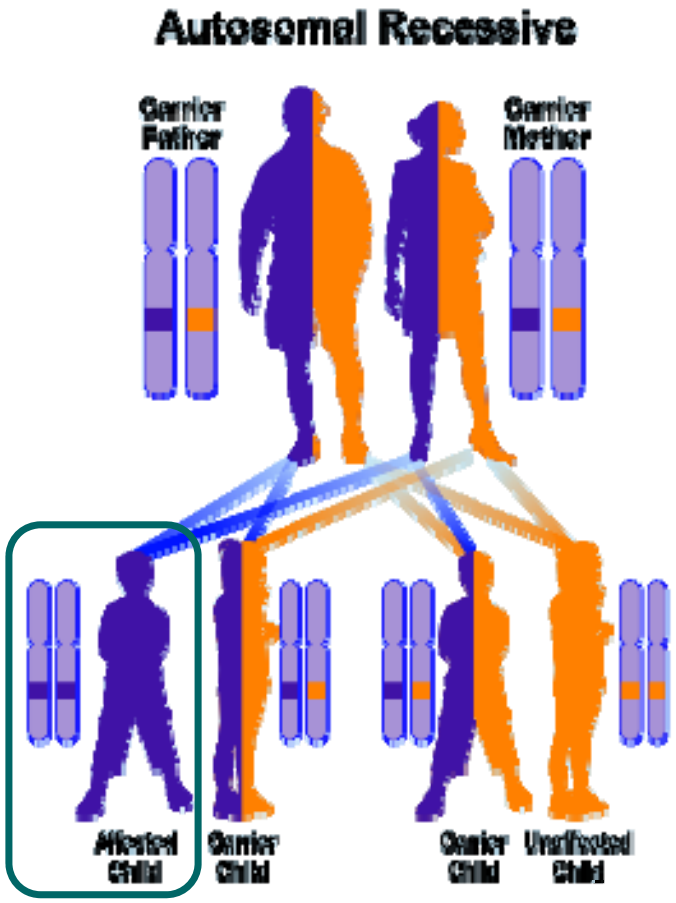


- In younger women the non-age-dependent pCNVs dominate fetal risk
- CNVs represent the main component of the a priori risk for fetal genomic abnormalities in younger women:
  - 80% of the risk in 18y
  - 15% of the risk in 48y

Ferreira, Grati FR et al, Prenat Diagn. 2016 Dec;36(12):1146-1155

PER UNA COPPIA PORTATRICE DI UNA CONDIZIONE AUTOSOMICA RECESSIVA, QUALE/I TEST È/SONO MAGGIORMENTE EFFICACI IN DIAGNOSI PREIMPIANTO E IN DIAGNOSI PRENATALE?

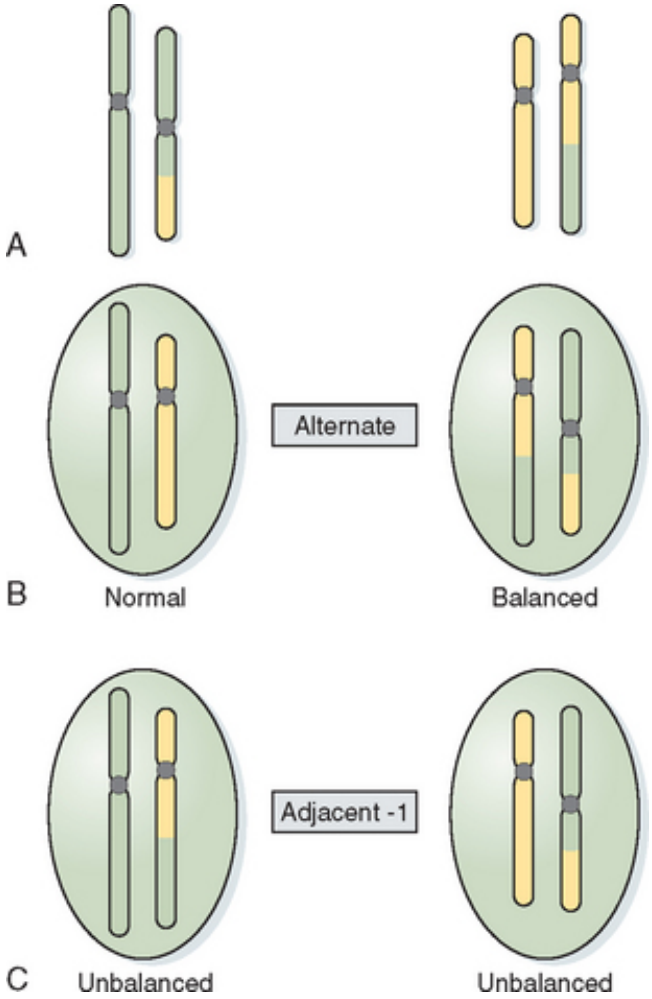
MEIOTIC SEGREGATION OF A COUPLE CARRIER OF AN AUTOSOMAL RECESSIVE DISORDER



25% risk of affected offpring

PER UNA COPPIA IN CUI UNO DEI MEMBRI È PORTATORE DI UNA TRASLOCAZIONE BILANCIATA QUALE/I TEST È/SONO MAGGIORMENTE EFFICACI IN DIAGNOSI PREIMPIANTO E IN DIAGNOSI PRENATALE?

TRANSLOCATION

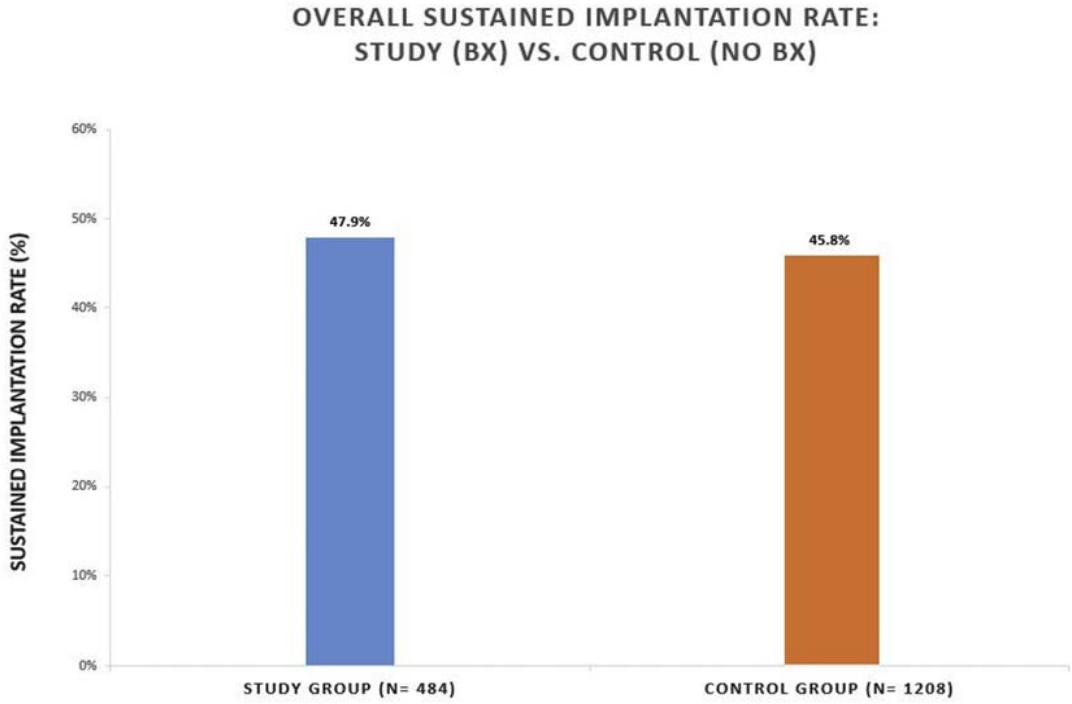


CI SONO DATI RECENTI CIRCA IL RISCHIO DI DANNEGGIARE LA BLASTOCISTI DURANTE LA BIOPSIA CELLULARE PER PGT E DATI CIRCA I RISCHI LEGATI ALLA DIAGNOSI PRENATALE INVASIVA?

The trophectoderm biopsy had no detectable adverse impact on sustained implantation: prospective non-selectio trial

484 single, frozen, blastocyst transfers

There was no difference in sustained implantation between the study group and an age-matched control group, where biopsy was not performed (47.9% vs. 45.8%).



Tiegs, Scott et al., 2020

- Gestational, perinatal and postnatal outcomes: no impact

World Journal of Pediatrics
https://doi.org/10.1007/s12519-018-0172-4

REVIEW ARTICLE

Pregnancy and child developmental outcomes after preimplantation genetic screening: a meta-analytic and systematic review

Misaki N. Natsuaki[1] · Laura M. Dimler[2]

Abstract

Background In in vitro fertilization (IVF) treatment, preimplantation genetic diagnosis/screening (PGD/S) attempts to detect chromosomal abnormalities in embryos before implantation. Using the meta-analytic and qualitative review approaches, this study aims to evaluate the effect of PGD/S on clinical pregnancy, live births, and childhood outcomes.

Methods We conducted a literature search using 1) PubMed and other search engines, and 2) an ancestry search by tracking references cited in prior work. After screening the studies, we extracted information pertinent to the meta-analysis. We calculated the effect sizes for clinical pregnancy and live birth rates, and performed a moderation analysis by maternal age, type of genetic screening, and timing of the biopsy. For childhood outcomes, we conducted a systematic review of studies reporting the anthropometric, psychomotor, cognitive, behavioral, and family functioning of PGD/S children.

Results We included 26 studies for clinical pregnancy and live births, and 18 studies for childhood outcomes. Results indicated that women who underwent comprehensive chromosome screening-based PGD/S had significantly higher clinical pregnancy rates (*rr* 1.207, 95% CI 1.017–1.431) and live birth rates (*rr* 1.362, 95% CI 1.057–1.755) than those whose IVF treatment did not include PGD/S. Early childhood outcomes of PGD/S children did not differ from those of non-PGD/S children.

Conclusions Comprehensive chromosome screening-based PGD/S can improve clinical pregnancy and live birth rates without adversely affecting functioning in childhood at least up to age 9. Results are discussed in the context of bioethical, financial, legal, and psychological issues surrounding PGD/S.

MISCARRIAGE

AMNIOCENTESIS

0,1%

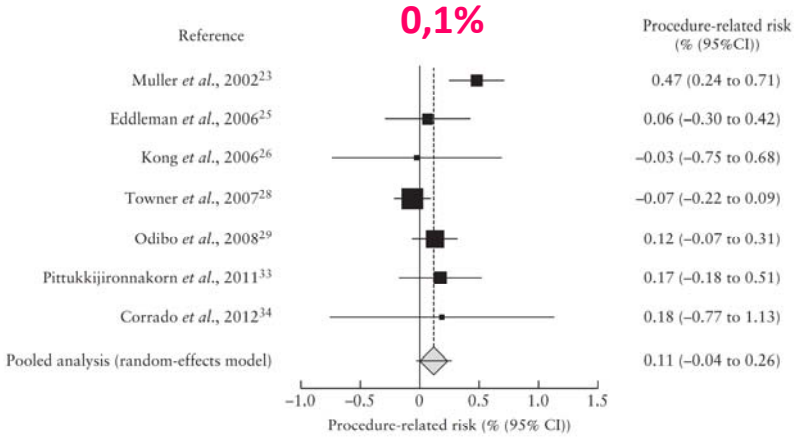


Figure 3 Forest plot showing estimated procedure-related risk of miscarriage before 24 weeks' gestation with 95% CIs derived from each of the controlled studies and weighted pooled summary estimate using a random-effects model and incidence–rate difference meta-analysis in women who underwent amniocentesis.

CHORIONIC VILLUS SAMPLING

0,2%

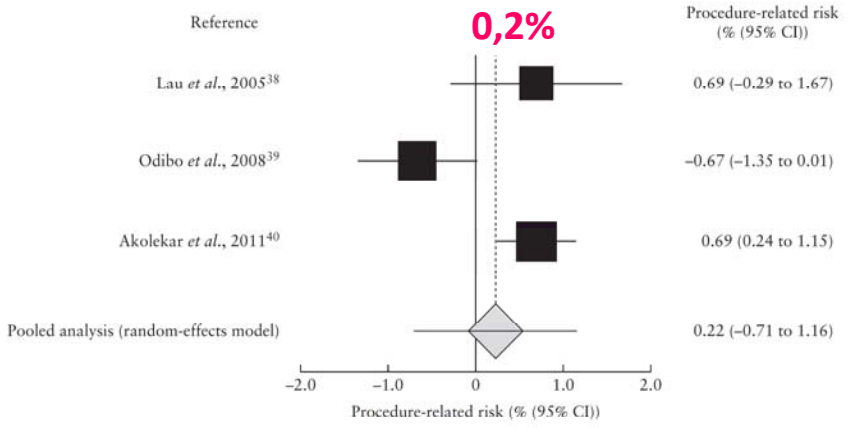


Figure 4 Forest plot showing estimated procedure-related risk of miscarriage before 24 weeks' gestation with 95% CIs derived from each of the controlled studies and weighted pooled summary estimate using a random-effects model and incidence–rate difference meta-analysis in women who underwent chorionic villus sampling.

- There is ***no significant difference in the risk of miscarriage*** before 24 weeks' gestation in women who undergo amniocentesis or CVS and in those who do not have any invasive testing.
- The procedure-related risks of miscarriage ***in specialist centers performing a large number of procedures are considerably lower*** than the figures that are currently given.
- The ***characteristics of the pregnancy*** (maternal age, FCT, …) play a role in determining the risks of miscarriage
- The added procedure-related risks of miscarriage following ***amniocentesis and CVS*** are in the region of ***0.1% and 0.2%,*** respectively.

Akolekar et al, Ultrasound Obstet Gynecol 2015; 45: 16–26