

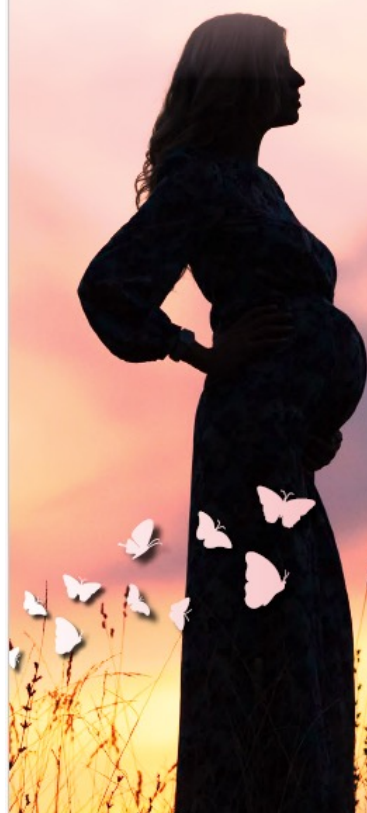


Du jeudi 11 au
vendredi 12 Juin
2026

PALAIS DES CONGRÈS
D'ANTIBES JUAN-LES-PINS
FRANCE

24^{ème}

CONGRÈS INTERNATIONAL
DE GYNÉCOLOGIE
OBSTÉTRIQUE
& REPRODUCTION
DE LA CÔTE D'AZUR



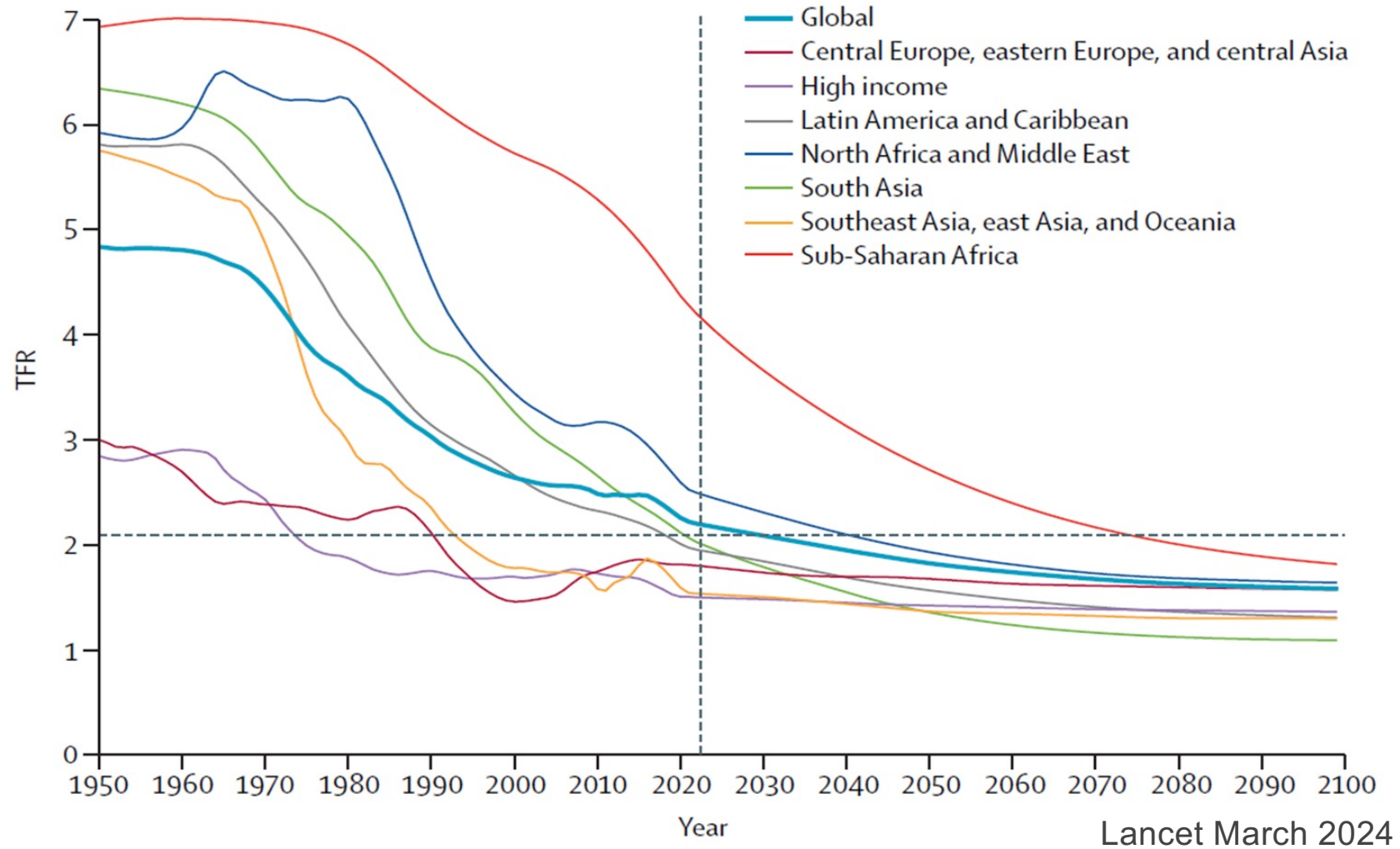
Résultats préliminaires d'expression génique
des spermés de 600 patients



Nino Guy Cassuto ART Unit Drouot Paris



Total Fertility Rate TFR, globally and by Global Burden of Diseases GBD 1950 – 2100



Reproductive epidemiology

Semen quality and lifespan: a study of 78 284 men followed for up to 50 years

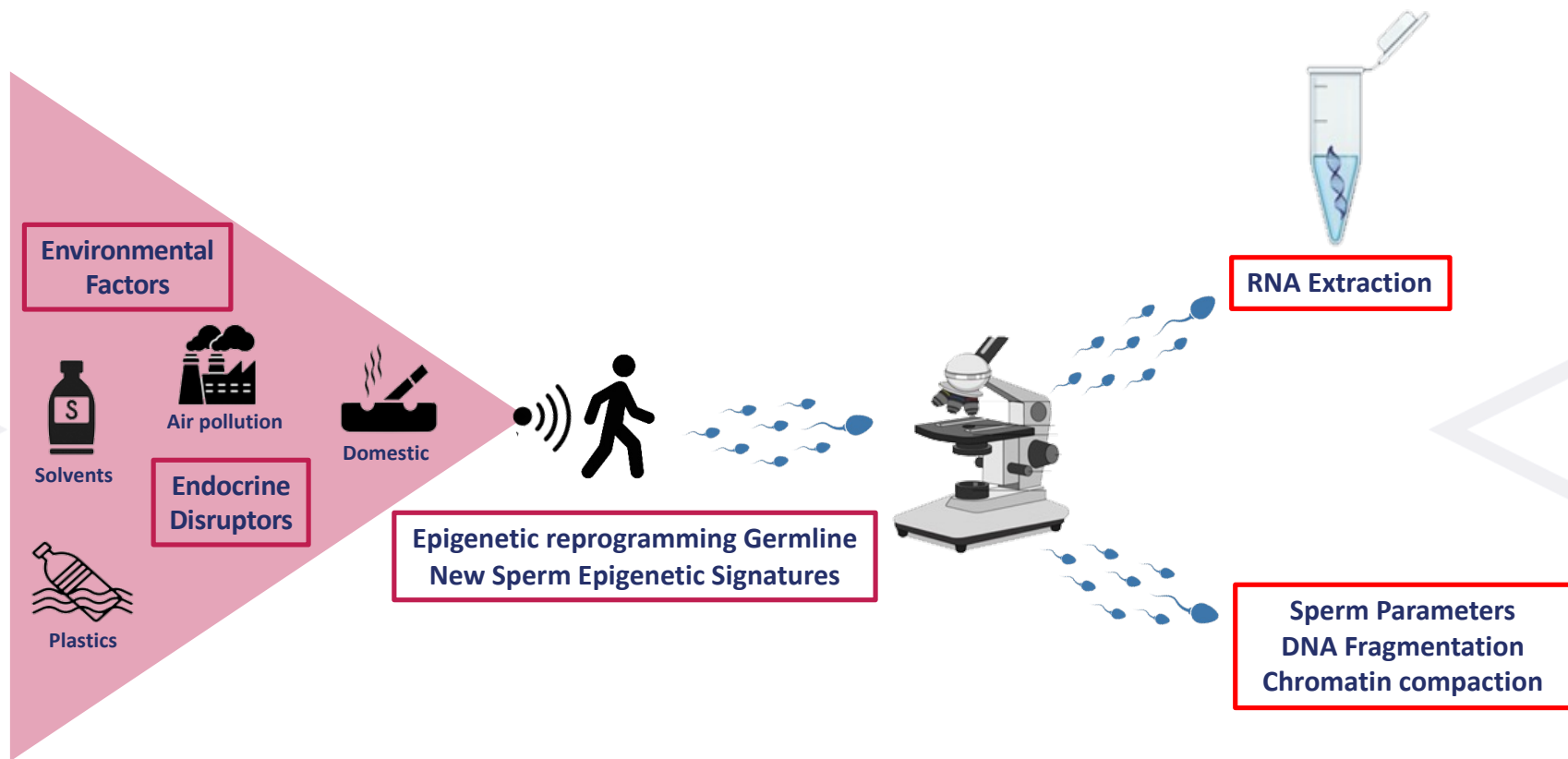
Men with a Total Motile Sperm count of > **120 million / Ejaculate**
could expect to live 2.7 years longer **(80.3 years)**
than men with total motile sperm count of > 0 – 5 million **(77.6 years)**

Semen quality was found to be a strong marker of mortality

Priskorn L. et al., March 2025



Effect of Environment on Sperm



Comparative overview of sperm diagnostic tests and complementarity with SFI

Tests	Target / Principle	Strengths	Limitations	Complementarity with SFI
Sperm Chromatin Structure Assay Blue Aniline	Chromatin Compaction Packaging	Well-established. Predicts some ART outcomes	Not assess functional pathways	Functional Gene Expression Level
DNA Fragmentation TUNEL Assay	DNA Fragmentation / Apoptosis	Sensitive detection of DNA breaks	Limited Predictive Power of the overall Sperm Function	Integrates Multiple Pathways: Sperm Fertilization, Embryo Development
Sperm Parameters (WHO)	Concentration, Motility, Morphology	Quantitative; Widely used	Limited Predictive Power of the overall Sperm Function	No predictive indication
Fluorescence In Situ Hybridization (FISH)	Detection of Aneuploidies Chromosomal Structure: Translocation	Nuclear Hybridization: Specific Probes	Labor-intensive. Not routinely	Idem
Karyotype	Chromosomal Abnormalities: Numerical and Structural	Detects Major Genetic causes of Infertility	Low resolution; does not identify submicroscopic defects	Idem
Y-Chromosome Microdeletions (AZF)	Azoospermia factor: Long Y AZFa, AZFb, AZFc	In Azoospermia and Severe Oligospermia	Limited to Specific Genetic Regions; does not Capture Functional Heterogeneity	Idem
Sperm MessengerSperm Functional Index	Combined Genes Expression AURKA, HDAC4, CARHSP1	Captures Functional Heterogeneity; Applicable to Normospermia	Requires RNA Extraction and qPCR Amplification	Predictive Indication in term: Natural Fecundity and ART





genes



The Combined Expression Profiles of Epigenetic Biomarkers Reveal Heterogeneity in Normospermic Human Sperm Samples



genes



Article

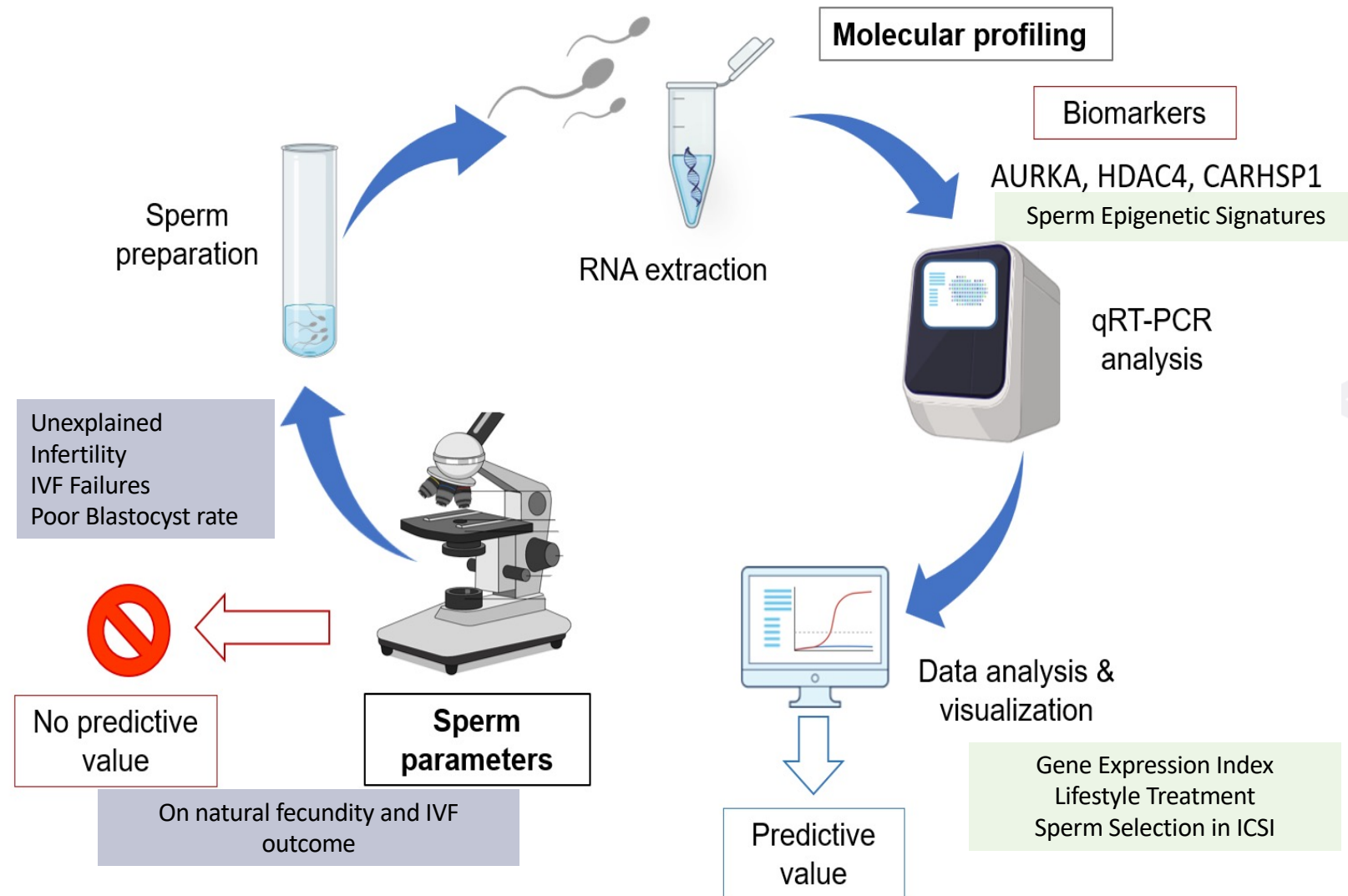
The combined expression profiles of epigenetic biomarkers reveal heterogeneity in normospermic human sperm samples

Nino Guy Cassuto ^{1, #}, Florence Boitrelle ², Léa Ruoso ¹, Omar Bouattane ³, Marion Bendayan ², Lina Abdiche ¹, Lionel Larue ⁴, Gwenola Keromnes ⁴, Nathalie Lédée ^{5, 6}, Laura Prat-Ellenber ⁵, Geraldine Dray ⁵, Alexandre Rouen ⁷, John De Vos ⁸, Said Assou ^{8, #}

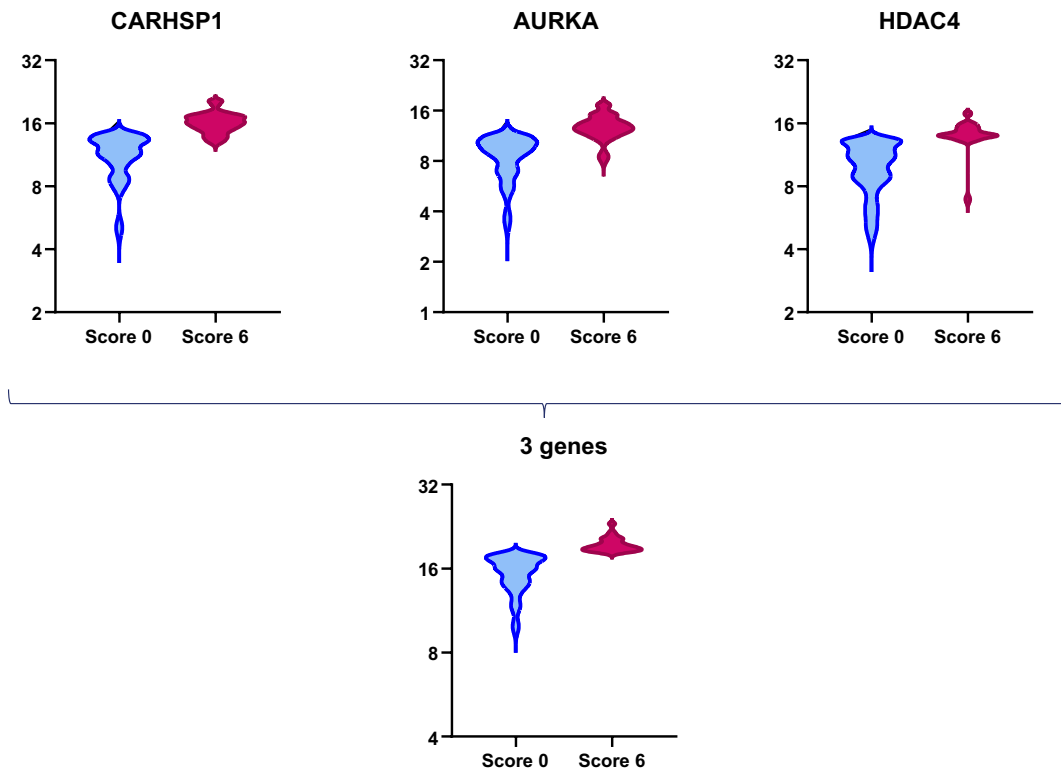
2 November 2025



Sperm Epigenetic Signatures - Study Design



Combined expression of the 3 target genes



Index Expression < 290
Under-expression

Index =290 < Expression < 320
Intermediate expression

Index Expression > 320
Normal expression



EXPRESSION OF TARGET GENES

AURKA (AURORA KINASE A)

- It is a key regulator of cell division and is involved in mitosis.
- Essential for the first mitotic spindle and chromosome segregation.
- Is involved in the early development of the embryo.

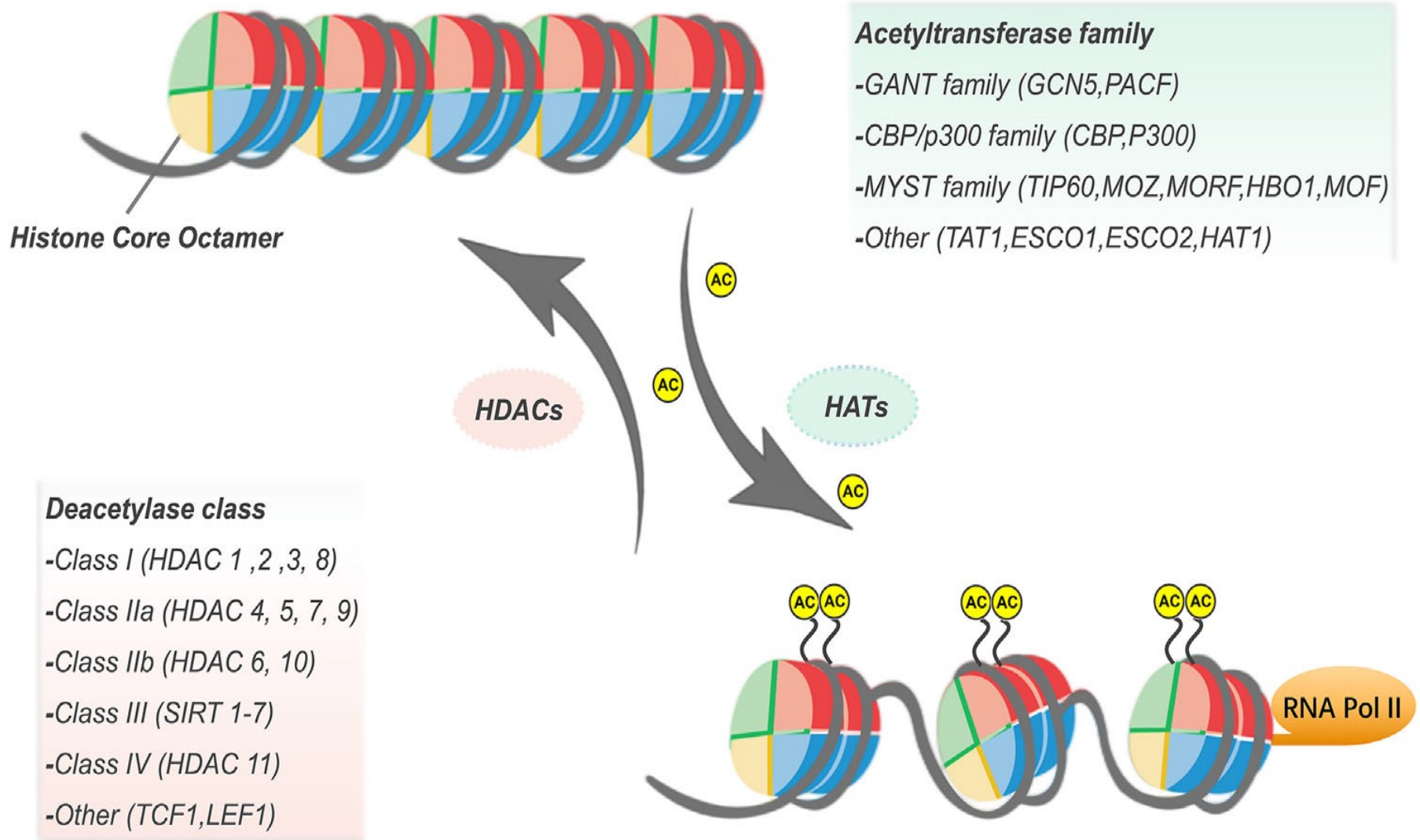
HDAC4 (HISTONE DEACETYLASE)

- Involved in the epigenetic regulation of gene expression through methylation profile.
- Playing a role in early embryonic development, regulating gene expression.

CARHSP1 (CALCIUM-REGULATED HEAT-STABLE PROTEIN)

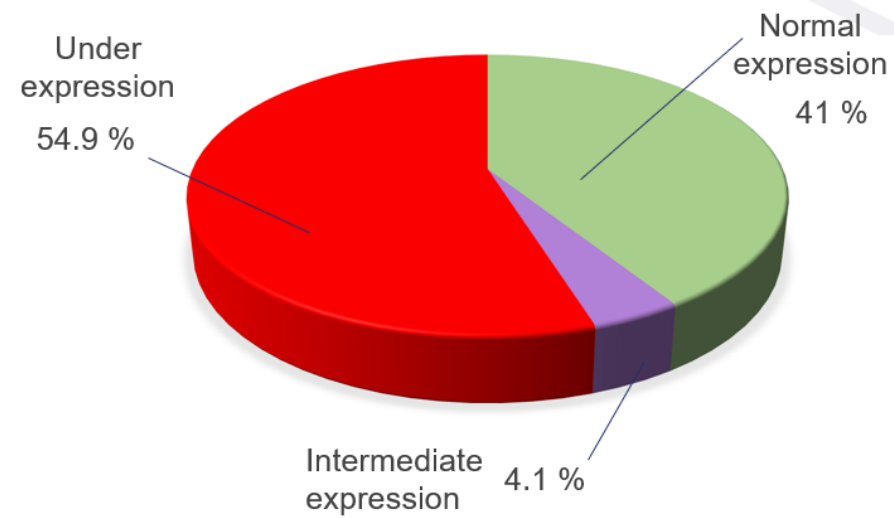
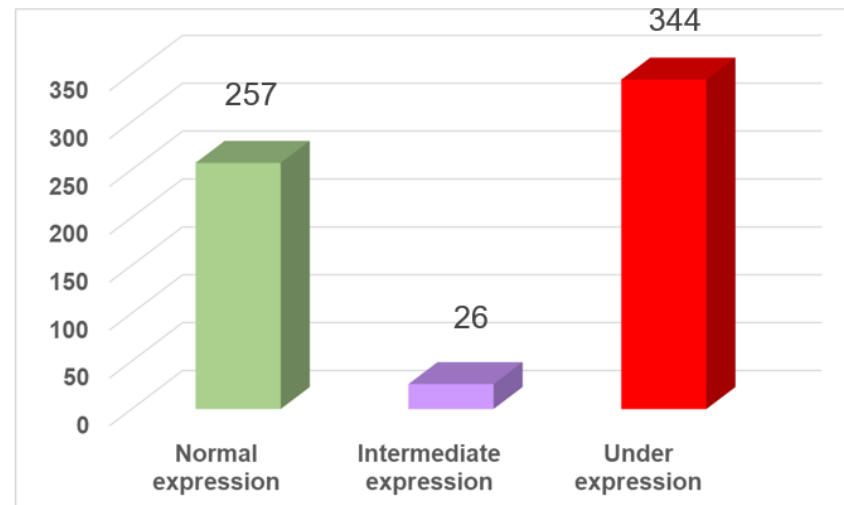
- Highly expressed in the early stages of embryonic development.
- Under-expression of CARHSP1 leads to chaotic cell division and arrested embryonic development.
- Its expression is significantly higher in blastocyst-developed embryos, associated with higher pregnancy rates.





Study population and genes expression (n=627)

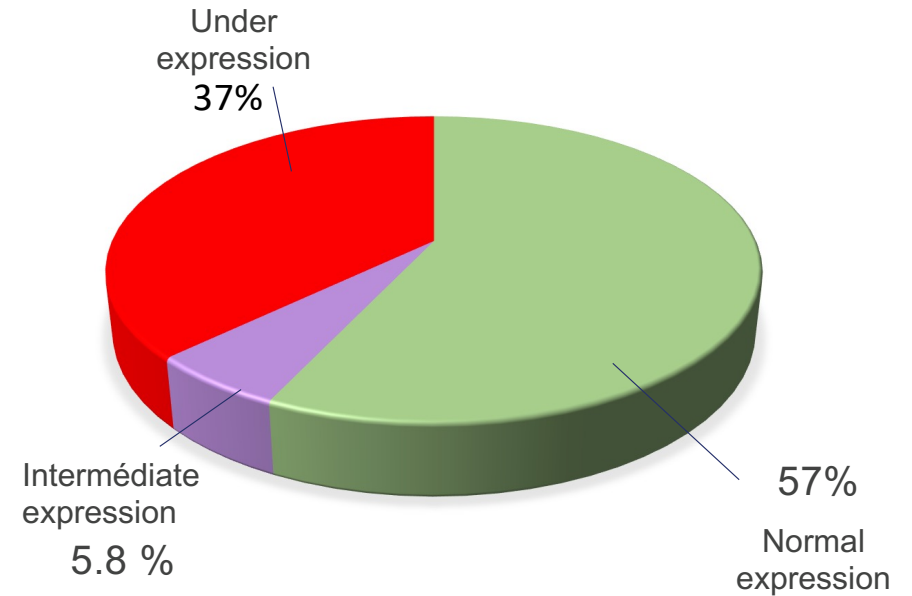
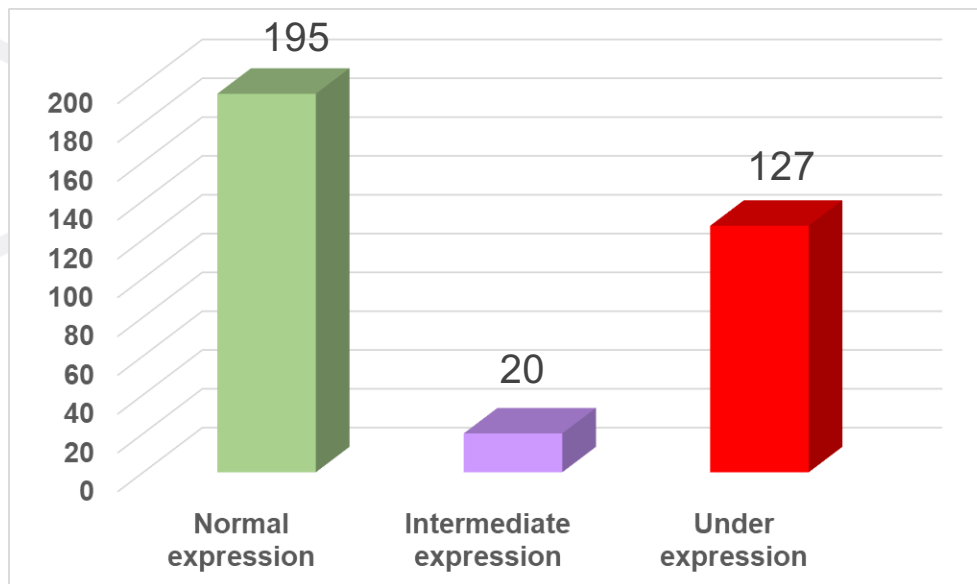
B



SFI variation in normal sperm samples according to the WHO criteria (n=342)

Cnc: ≥ 16 million/mL
Total Motility $\geq 42\%$, Progressive Motility $\geq 30\%$
Morphology $\geq 4\%$ Kruger

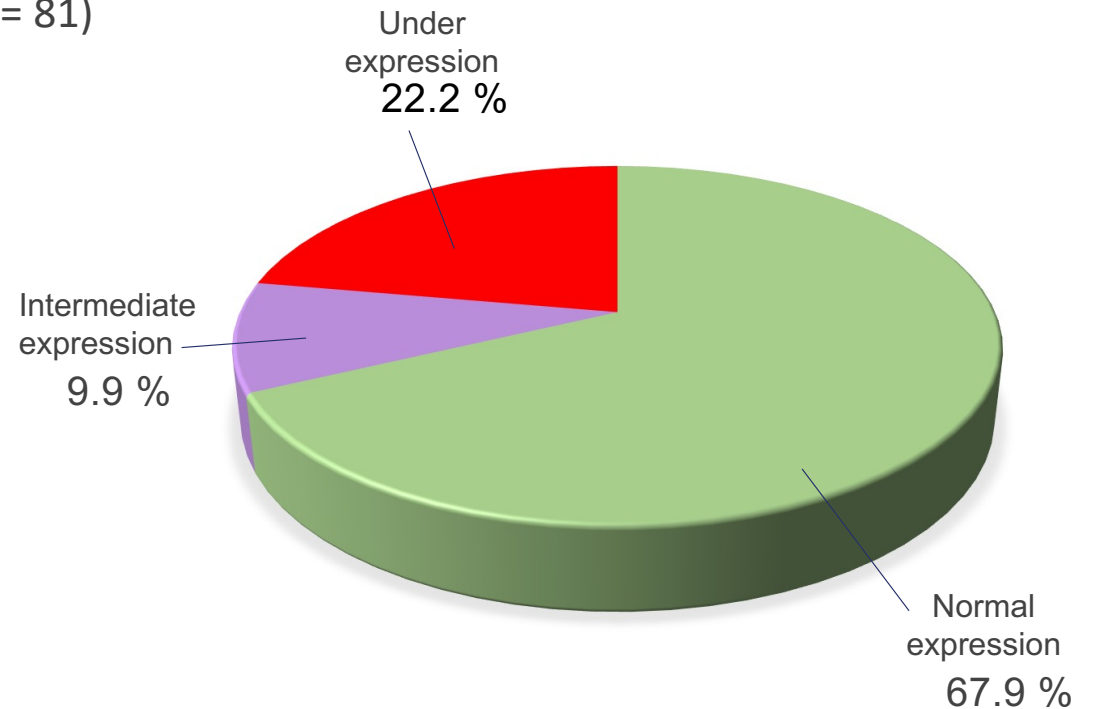
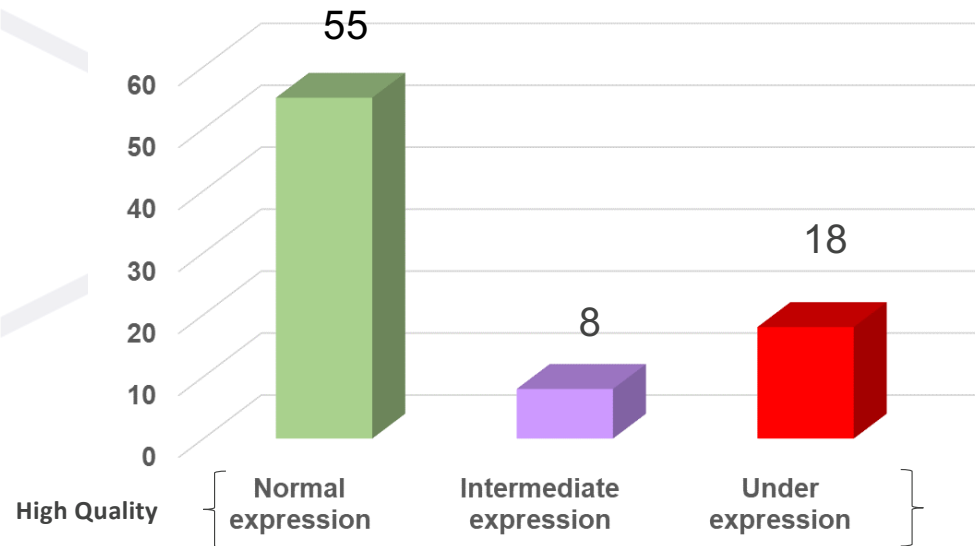
Population with normal WHO semen parameters and epigenetic biomarker expression (n = 342)



SFI variation in high-quality sperm samples according to the WHO criteria (n=81)

Cnc: ≥ 50 million/mL
Total Motility $\geq 50\%$, Progressive Motility $\geq 40\%$
Morphology $\geq 14\%$ Kruger

Population with high-quality semen parameters (n = 81)



Epigenetic determinants of reproductive potential augment the predictive ability of the semen analysis

Fertil Steril 4 November 2023

Ryan H. Miller, M.S.,^a Elizabeth A. DeVilbiss, Ph.D.,^b Kristin R. Brogaard, Ph.D.,^a Carter R. Norton,^c Chad A. Pollard, B.S.,^c Benjamin R. Emery, M.S.,^d Kenneth I. Aston, Ph.D.,^d James M. Hotaling, M.D., M.S.,^d and Tim G. Jenkins, Ph.D.^{c,d}

Significant differences in IUI pregnancy and live birth outcomes between the poor and excellent groups. Live birth outcomes from ICSI, were not found to be significantly different among any of the 3 groups: poor, average, and excellent sperm quality.

Methylation profile variability in a panel of 1233 gene promoters could augment the predictive ability of semen analysis and be a reliable biomarker for assessing IUI.

ICSI appears to overcome high levels of epigenetic instability in sperm





Epigenetic sperm quality testing for predicting fertility treatment success: a real-world and multi-site analysis

Kristin Brogaard¹ · Susan Hudson² · Carrie Bedient³ · Abby Eblen⁴ · Kristin Van Heertum⁴ · Emma Giuliani⁵ · Meghan Smith⁴ · Madeline Kaye² · Amy Schutt² · Lisa Hansard² · Valerie Shavell⁵ · Kaylen Silverberg² · Mili Thakur⁵ · Andrew Olson¹ · Ryan Miller⁶ · Lorry Schneider¹ · Derek Petersen¹ · Bryce Daines¹ · Lakingya Robinson⁷ · Alexis Reynolds⁷ · Nirvika Singh⁷ · Khalied Kaskar⁷ · Jordan Kassab⁸ · Larry Lipshultz⁸ · Matthew VerMilyea^{7,9}

Men with **abnormal sperm epigenetic profiles** had significantly lower pregnancy success rates with IUI compared to those with normal profiles, **despite similar SPZ motility and concentration**

Pregnancy rates did not differ between abnormal and normal profiles among couples undergoing ICSI, suggesting that **ICSI may overcome sperm epigenetic quality issues**.

Nevertheless, the findings:

Highlight the clinical value of epigenetic sperm assessment as part of male fertility evaluation;
and support to guide more effective personalized fertility treatment pathways.



Traitements

Consultation: Obésité (IMC), Diabète, Recherche d'une varicocèle, Activité professionnelle (Chaleur, Solvant), Environnement de vie (Pollution, Pesticide, Toxique) Life style: Alimentaire (Tabac, Alcool, Stress) ; Physique, Traitement antioxydant et/ou complément alimentaire.



Etude en cours, sur une petite cohorte, permet de voir une amélioration des profils d'expressions après 3 mois de traitement.



Couple en PMA : Eviter une IAC: Risque d'échec, ou FIV: Pauci fécondation ou d'Absence de Fécondation ; due à la sous expression de ces gènes impliqués dès les premières mitoses du développement embryonnaire



Prise en charge en ICSI en sélectionnant les spermatozoïdes de façon très précise avant injection: **S-ICSI**



Isitol® améliore significativement l'expression génique des répondeurs

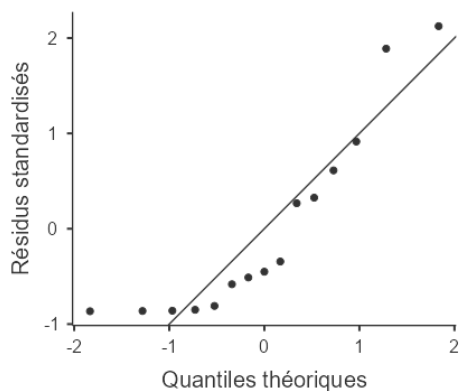
AURKA

→ 15/28 (53,5% des patients)

Statistiques descriptives

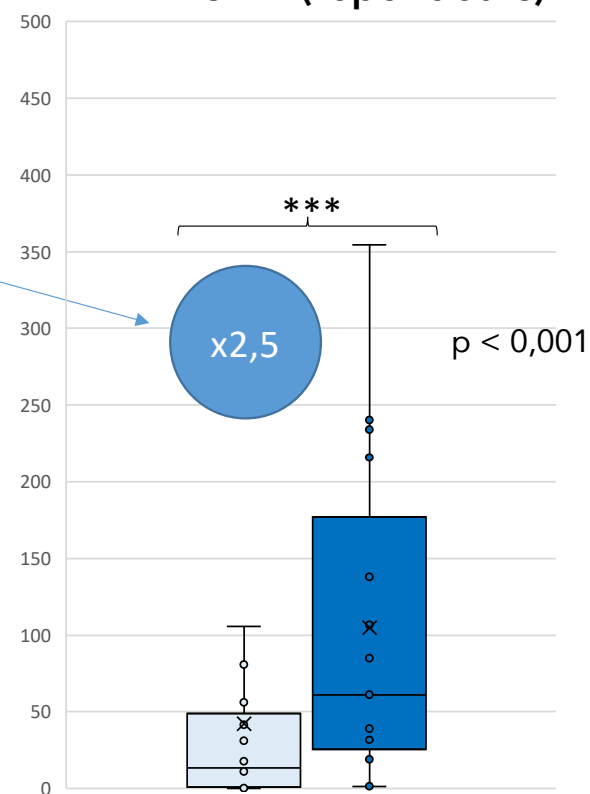
	Expression AURKA avant	Expression AURKA après
N	15	15
Moyenne	42.2	105
Médiane	13.3	61.2
Ecart-type	70.4	109

Diagramme Q-Q



Distribution ne suit pas une loi Normale
→ Test de Wilcoxon

Expression AURKA V1 vs V2 (répondeurs)



↗ de **148,3%** de l'expression du gène **AURKA** après 3 mois de traitement avec Isitol®



Isitol® améliore significativement l'expression génique des répondeurs

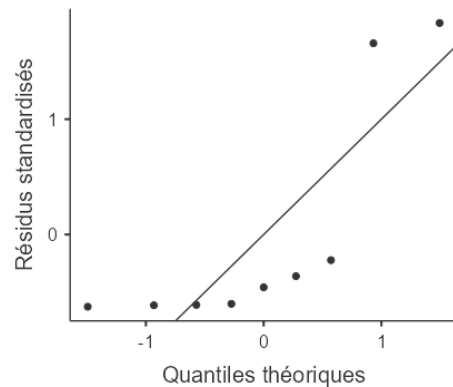
HDAC4

→ 9/28 (32,1% des patients)

Statistiques descriptives

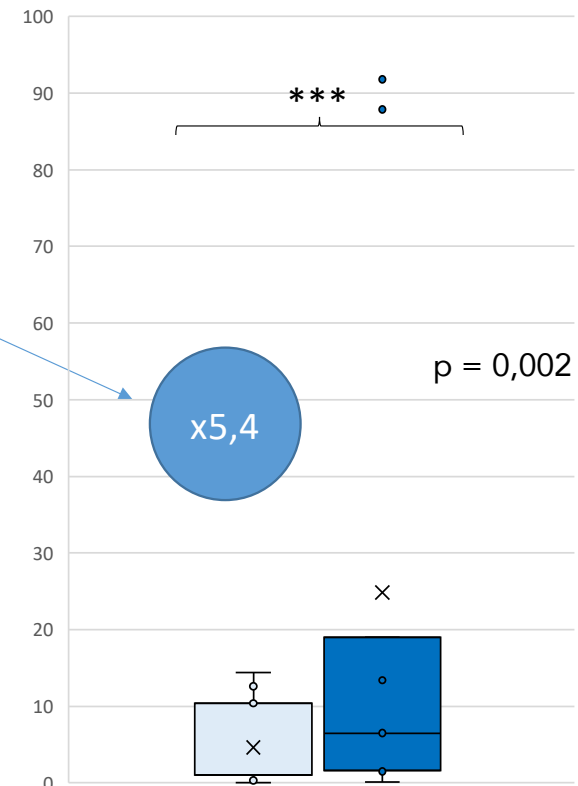
	Expression HDAC4 avant	Expression HDAC4 après
N	9	9
Moyenne	4.64	24.9
Médiane	1.00	6.50
Ecart-type	5.97	37.4

Diagramme Q-Q



Distribution ne suit pas
une loi Normale
→ Test de Wilcoxon

Expression HDAC4 V1 vs V2 (répondeurs)



⤴ de **435,8%** de l'expression du gène **HDAC4** après 3 mois de traitement avec Isitol®



Isitol® améliore significativement l'expression génique des répondeurs

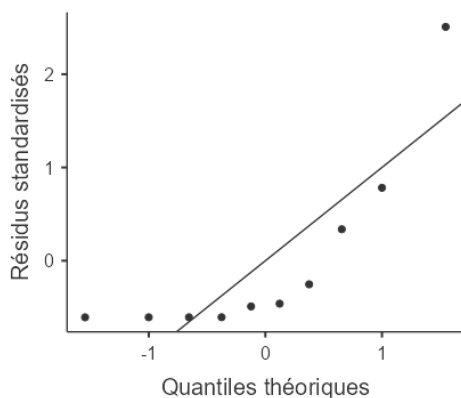
CARHSP1

→ 10/28 (37,5% des patients)

Statistiques descriptives

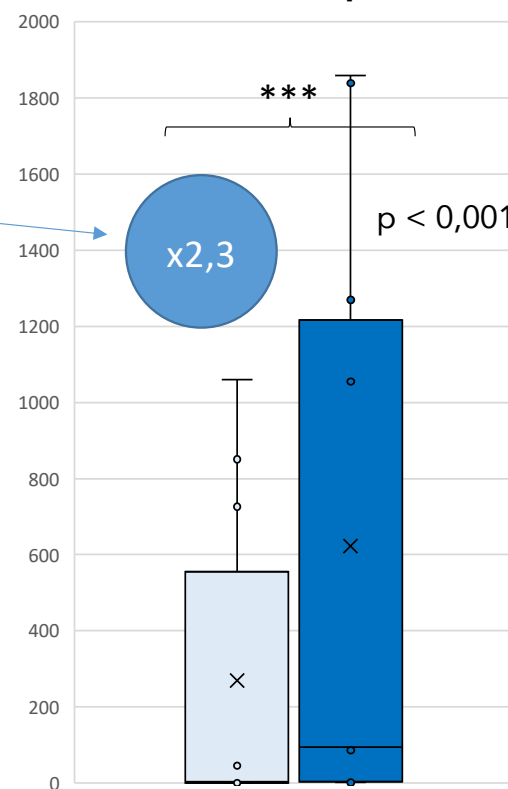
	Expression CARHSP1 avant	Expression CARHSP1 après
N	10	10
Moyenne	273	622
Médiane	20.9	93.8
Ecart-type	426	797

Diagramme Q-Q



Distribution ne suit pas
une loi Normale
→ Test de Wilcoxon

Expression CARHSP1 V1 vs V2 (répondeurs)



⤴ de **127,8%** de l'expression du gène **CARHSP1** après 3 mois de traitement avec Isitol®



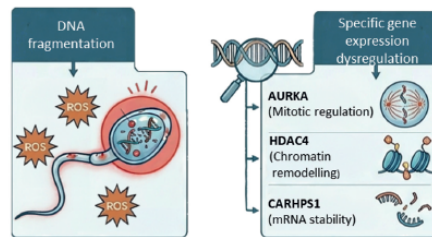
BEYOND SPERMOGRAM, A NUTRITIONAL STRATEGY CAN IMPROVE SPERM GENETICS

N-G Cassuto, ART Unit,
Drouot Laboratory, 75009 Paris, France

Impact of ROS* on sperm^{1,2,3,4,5}



Epigenetic/genetic aftermath



Consequences on sperm



Consequences on IVF outcomes



* Reactive Oxygen Species

Reducing sperm DNA fragmentation and optimizing the expression of critical genes through a combination of myo-inositol and an antioxidant complex

Population

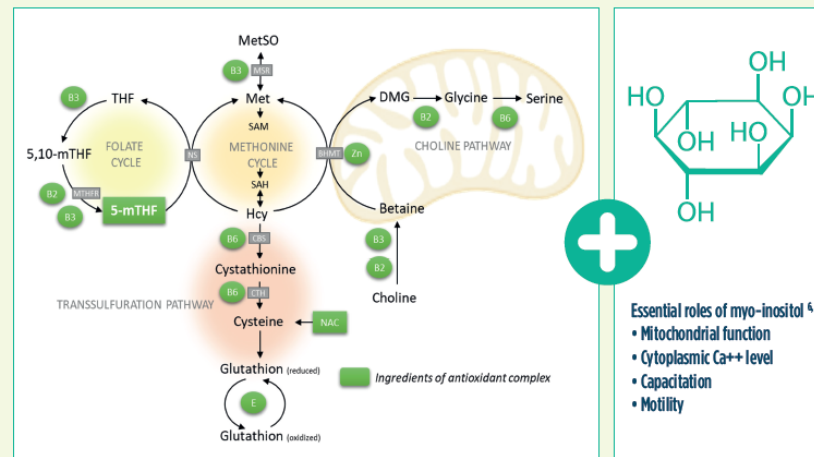
- n=28 men (20-45 yo) included in an IVF/ICSI project with a sperm DNA fragmentation rate $\geq 30\%$

Pre-Post study endpoints

- DNA fragmentation (TUNEL)
- Spermogram (WHO)
- mRNA AURKA, HDAC4, CARHSP1 (RT-qPCR)

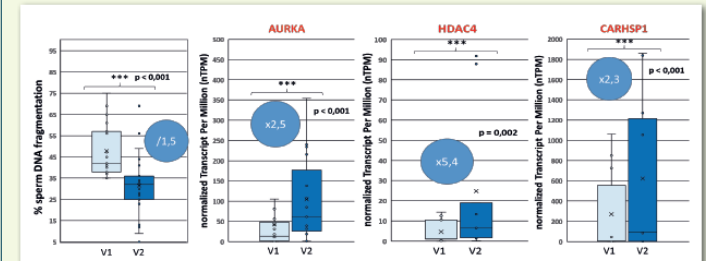
Intervention

- 4-month daily supplementation with myo-inositol (1g) + an antioxidant complex targeting the one-carbon metabolism^{7,8}

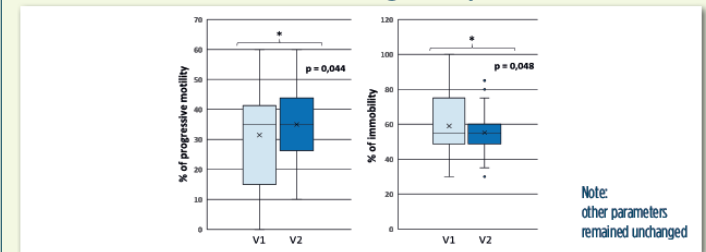


RESULTS

Improving DNA fragmentation & key genes expression



While increasing motility



CONCLUSIONS

A multi-targeted nutritional strategy that simultaneously addresses oxidative stress and epigenetic methylation processes can significantly reduce DNA fragmentation, improve the expression of genes critical for fertilization rate and early embryo development, and enhance gamete motility. This approach, which is not only widely accepted but also well tolerated, paves the way for new approaches to the treatment of male infertility. Concurrently, DNA fragmentation and gene expression should be taken into account in the evaluation of male infertility, along with the classical semen analysis. This pilot study will nevertheless need to be confirmed in a larger sample as part of a randomized trial.

Mandatory Col statement on behalf of all authors

- Wang Y, et al. Front Endocrinol 2025
- Nguyen HDK, et al. Reprod Med Biol 2025
- Nacholewski T, et al. Int J Mol Sci 2025
- Li F, et al. Sci Rep 2024
- Cassuto N-G, et al. Genes 2025
- Ghaemi M, et al. Food Sci Nutr 2024
- Viot, G, et al. J Assist Reprod Genet 2025
- Mohammadi P, et al. BJU Int 2018
- Salehi P, et al. Cryobiology 2024

Conclusions

Sperm Messenger™ is a new **tool exploring male infertility**.
Is a genomic signature assessing the potential sperm quality



This gene expression index **evaluates the sperm function**, giving a predictive value in terms of natural fecundity and IVF outcome



Permit to identify and **sort the sperm** normal parameters (WHO) with an under-expression index corresponding to a low spermatozoa functionality



Under-expression of target genes involved in fertilization, and early embryo development, may explain cases of:

Unexplained Infertility, IVF Failures, and Poor blastocyst rate



Conclusions

This epigenetic signature evaluates the sperm function, **non-invasive biomarker** to predict value in terms of natural fecundity; IVF success and offspring health



Sperm Messenger™ **is a tool exploring Male Infertility and Implantation Failure**

Abnormal methylation profile, Abnormal gene expression

show chaotic embryo development,

lower blastulation rates, lower success in ART, higher risk of birth defect, imprinting disease.



Under-expression of target genes **involved in fertilization, and early embryo development**, may explain cases of unexplained Infertility, poor blastocyst rate and Implantation Failure



Don't forget the sperm





MERCI

