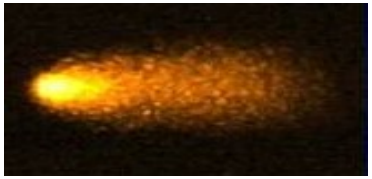
NOVEL MEASURES OF SPERM DNA DAMAGE INCREASE ITS USEFULNESS TO DIAGNOSE MALE INFERTILITY AND PREDICT LIVE BIRTHS FOLLOWING BOTH IVF AND ICSI

Nicopoullos J, Lewis S, Lee K, Larsen P, Ramsay J & Minhas S



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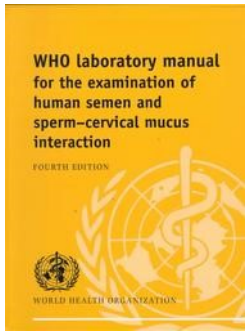


The effect of the new 2010 World Health Organization criteria for semen analyses on male infertility

Katie S. Murray, D.O.,[a] Andrew James, M.D.,[a] James B. McGeady, M.D.,[b] Michael L. Reed, Ph.D.,[c] Wayne W. Kuang, M.D.,[b,d] and Ajay K. Nangia, M.B.B.S.[a]

[a] Department of Urology, University of Kansas Medical Center, Kansas City, Kansas; and [b] University of New Mexico, [c] Center of Reproductive Medicine of New Mexico, and [d] Southwest Fertility Center for Men, Albuquerque, New Mexico

Semen analysis has limited diagnostic value for male infertility and prognostic value for ART

The New England Journal of Medicine

SPERM MORPHOLOGY, MOTILITY, AND CONCENTRATION IN FERTILE AND INFERTILE MEN

DAVID S. GUZICK, M.D., PH.D., JAMES W. OVERSTREET, M.D., PH.D., PAM FACTOR-LITVAK, PH.D., CHARLENE K. BRAZIL, B.S., STEVEN T. NAKAJIMA, M.D., CHRISTOS COUTIFARIS, M.D., PH.D., SANDRA ANN CARSON, M.D., PAULINE CISNEROS, PH.D., MICHAEL P. STEINKAMPF, M.D., JOSEPH A. HILL, M.D., DONG XU, M.PHIL., AND DONNA L. VOGEL, M.D., PH.D., FOR THE NATIONAL COOPERATIVE REPRODUCTIVE MEDICINE NETWORK*

Counting sperm does not add up any more: time for a new equation?

Linda Lefièvre[1], Kweku Bedu-Addo[2], Sarah J Conner[1], Gisela S M Machado-Oliveira[3], Yongjian Chen[4], Jackson C Kirkman-Brown[5], Masoud A Afnan[5], Stephen J Publicover[3], W Christopher L Ford[1] and Christopher L R Barratt[1]

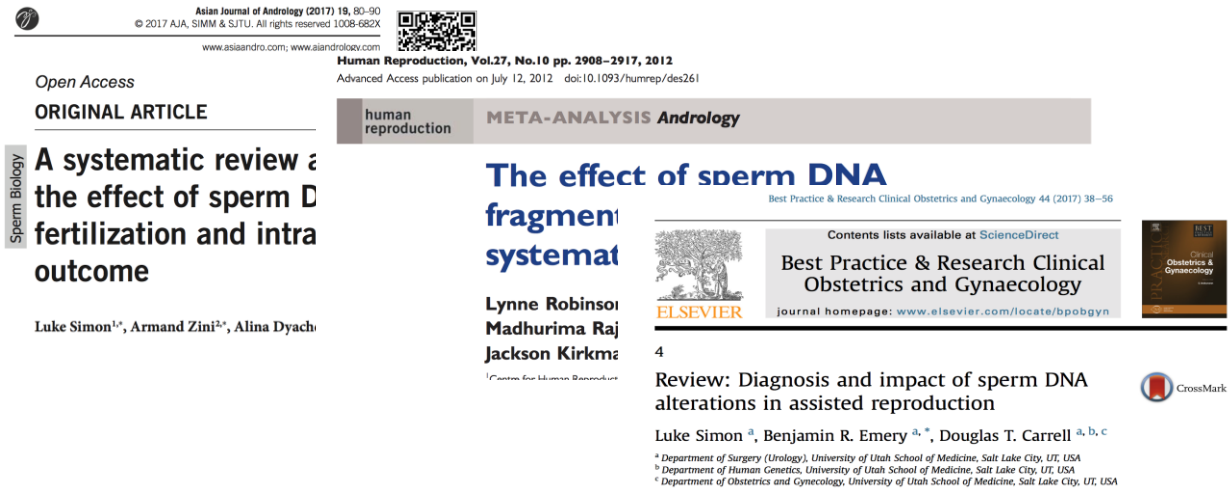
Focus on Determinants of Male Fertility

Is sperm evaluation useful in predicting human fertility?

Sheena E M Lewis

SPERM DNA TESTING

- Diagnostic of male infertility *(Zini et al, Urol 2002: Simon et al, FS 2011)*
- Increased time to conception *(Evenson et al, HR 1999)*
- Poor embryo development *(Simon et al, HR 2014)*
- Poor IVF and ICSI outcomes *(Simon et al, BPRCOG, 2017)*
- Increased miscarriage rate *(Robinson et al, HR 2012)*



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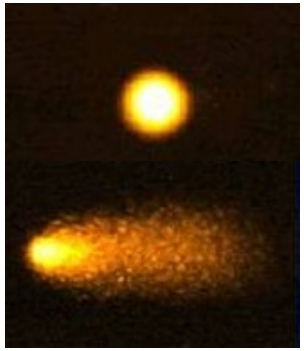
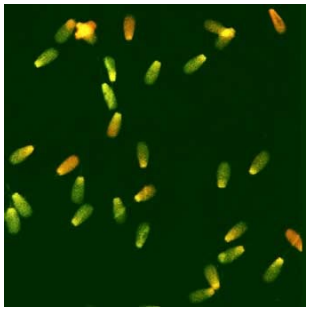
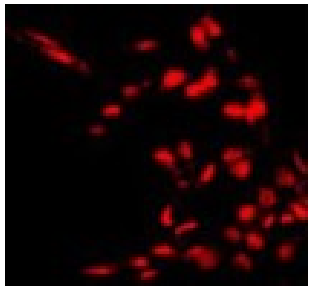
DETECTION OF SPERM DNA DAMAGE



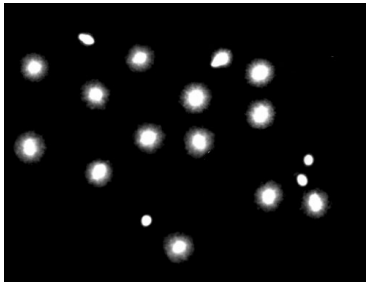
Comet assay
(Hughes *et al*., 1996)



Sperm Chromatin Structure assay
(Evenson *et al*., 1999; SPZ LAB, Christensen)



TUNEL assay
(Henkel *et al*., 2004)



Halo assay
(Sperm Chromatin Dispersion test)
(Fernandez *et al*., 2003)

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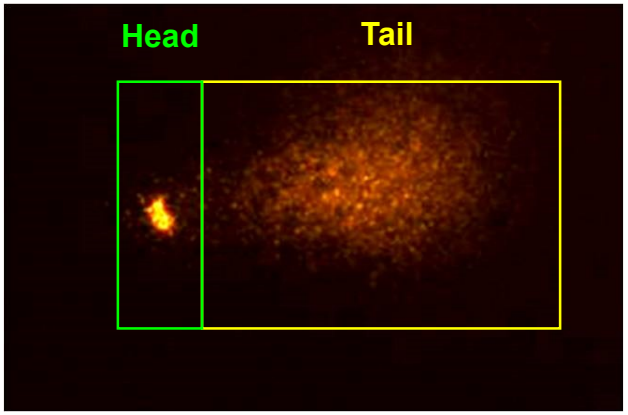
BENEFITS OF SPERM COMET

- Second generation test
- Detects damage in 70 v 15% of sperm
- Quantifies damage per individual sperm
- Strong diagnostic tool
- Strong predictive value for ART
- Ongoing Research Program
- Utilisation with severe OATS
- Utilisation with testicular samples

Sperm with little DNA damage

Sperm with high DNA damage



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BACKGROUND

- Lister has been using the SpermComet test since 2011
- Initial clinical thresholds seen as a limitation of the test:
  - 0-25% No significant DNA damage
  - 25-50% Consider IVF
  - >50% ICSI recommended
- Majority of clinic results fall in the 25-50% range
- Tighter thresholds would be more clinically useful in guiding treatment selection.

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OBJECTIVES

- Determine and compare novel **Comet Plot** parameters to identify which has the highest ability to predict a live birth following IVF and also ICSI.
- Analyze the relationship between treatment pathway, live birth and sperm DNA damage for clinic patients who have had the SpermComet test.
- Define clinic specific thresholds to better guide the selection of treatment pathway.

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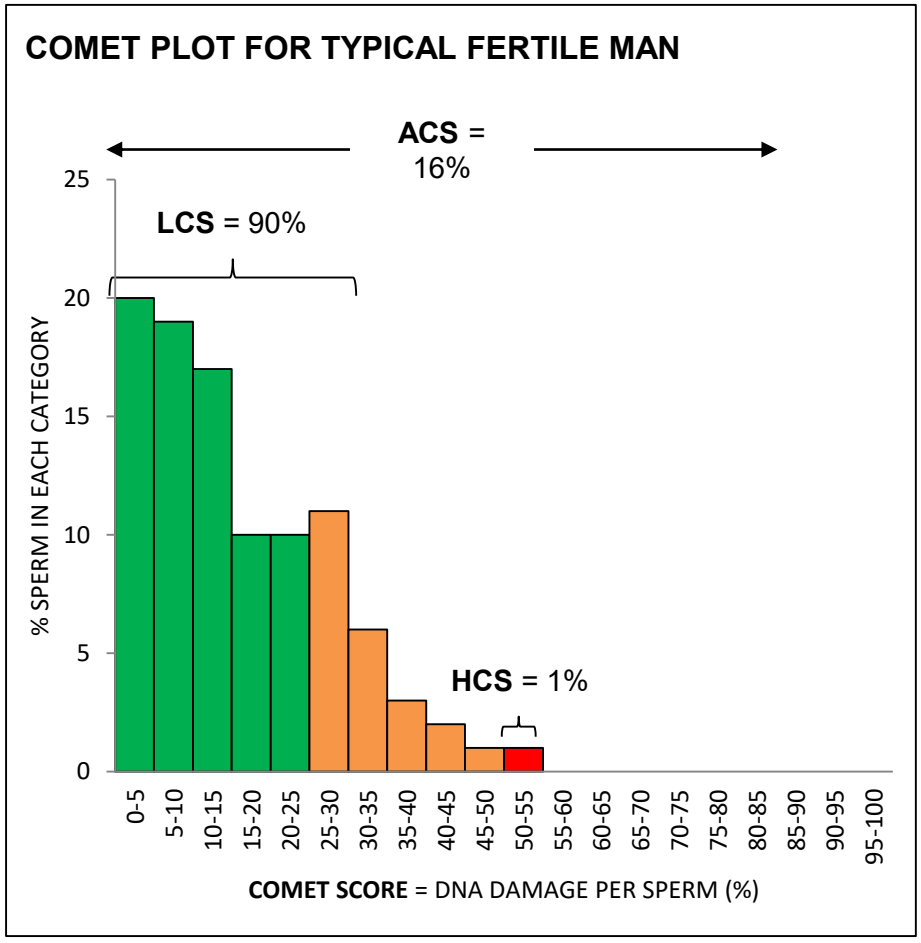
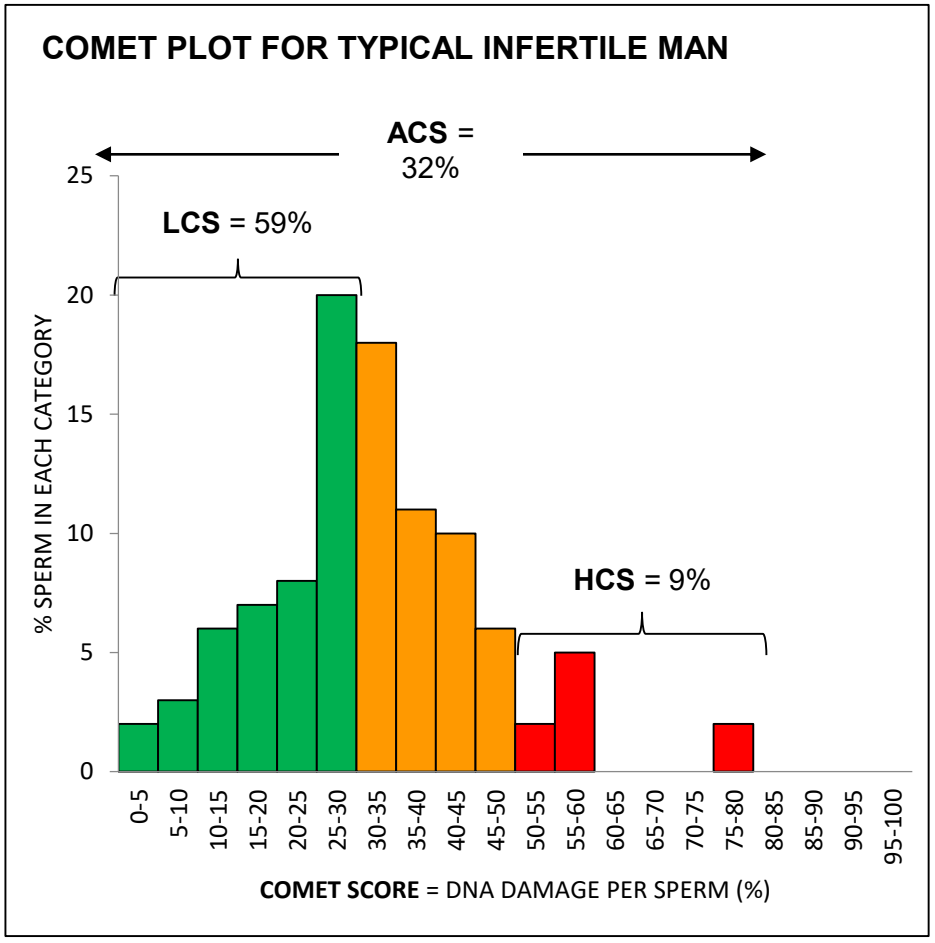
IDENTIFICATION OF NOVEL COMET MARKERS

ACS = Average **Comet Score** (mean of all comets scored)
LCS = Low **Comet Score**
HCS = High **Comet Score**





Source: SpermComet fertile donor database (N= 76); SpermComet Unexplained database (N= 166) .

METHODS

- 3 COMET markers
  - % Average COMET score
  - % Low COMET score (LCS)
  - % High COMET score (HCS)
- Receiver Operator Curve Analysis (ROC) for potential to diagnose male infertility
  - 76 fertile donors / 166 men from couples with idiopathic subfertility
- Receiver Operator Curve Analysis (ROC) for effect on ART outcome
  - 381 male partners of subfertile couples undergoing ART

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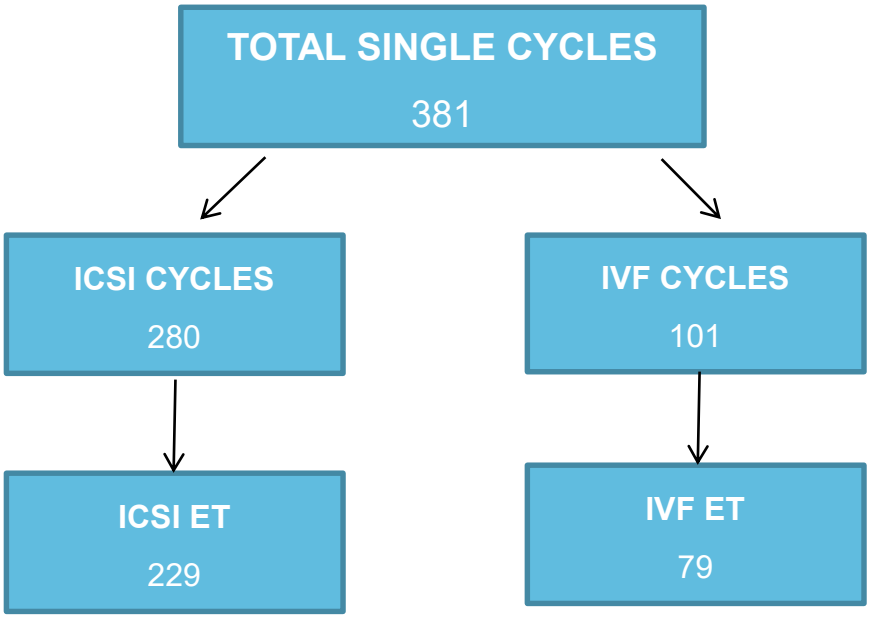
METHODS



- Split IVF/ICSI, abandoned and converted to IUI excluded.
- Single cycle selected for each couple based on treatment cycle closest to SpermComet test.
- Only cycles resulting in embryo transfer included.
- 'Ongoing' outcome classification assumed to be live birth as majority >40 weeks.

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RESULTS

DIAGNOSIS OF MALE INFERTILITY

Result parameter	Threshold value	ROC curve (95% CI)	*P* value	Sensitivity	Specificity	PPV	NPV	Odds ratio	Relative risk
ACS	>=26%	**0.925** (0.893-0.956)	<0.0001	0.735	1.000	1.000	0.632	N/A	2.7
LCS	<=74%	**0.936** (0.908-0.964)	<0.0001	0.783	0.934	0.963	0.664	51.2	2.7
HCS	>=4%	**0.909** (0.872-0.942)	<0.0001	0.843	0.803	0.903	0.701	21.9	3.0

Source: SpermComet fertile donor database (N= 76); SpermComet Unexplained database (N= 166) .

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CONCLUSIONS

All COMET markers highly predictive of male subfertility confirming role for testing in unexplained infertility

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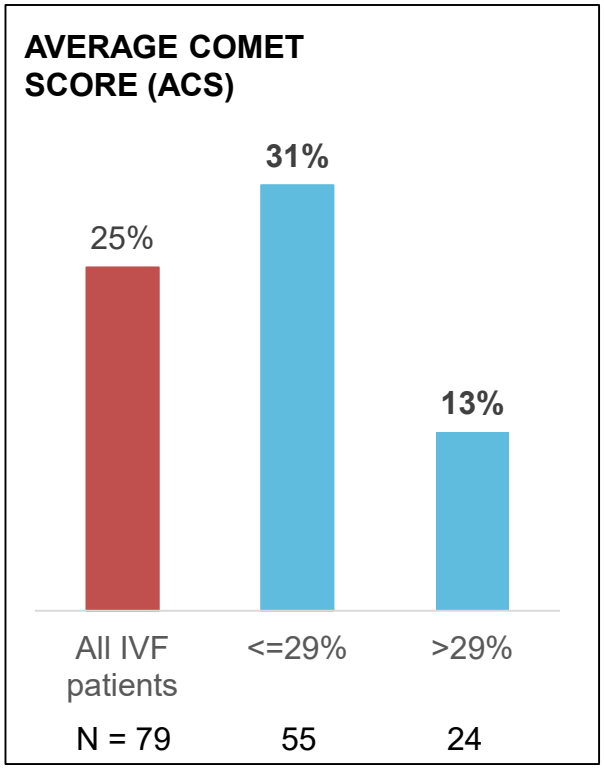
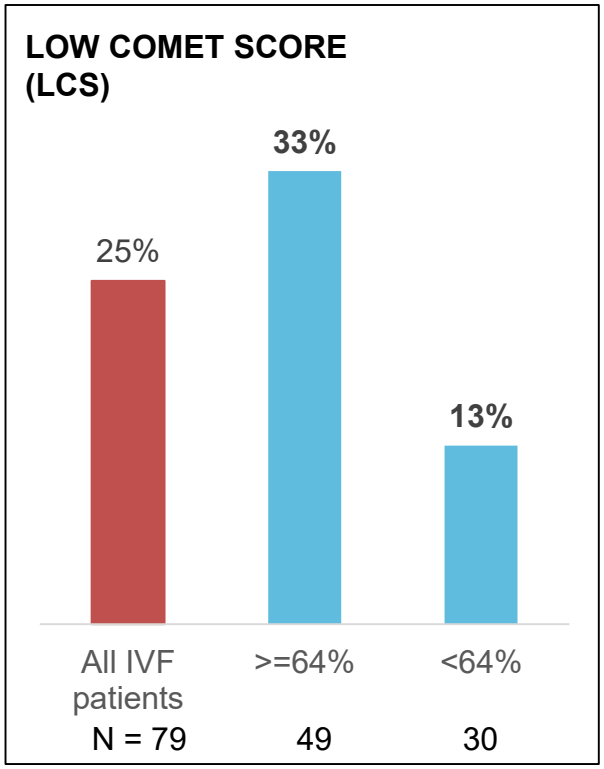
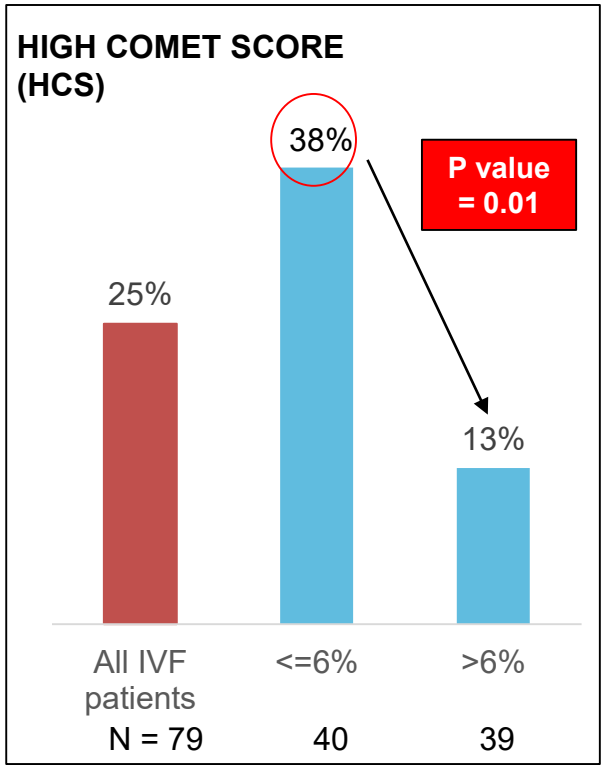
IMPACT ON IVF OUTCOME







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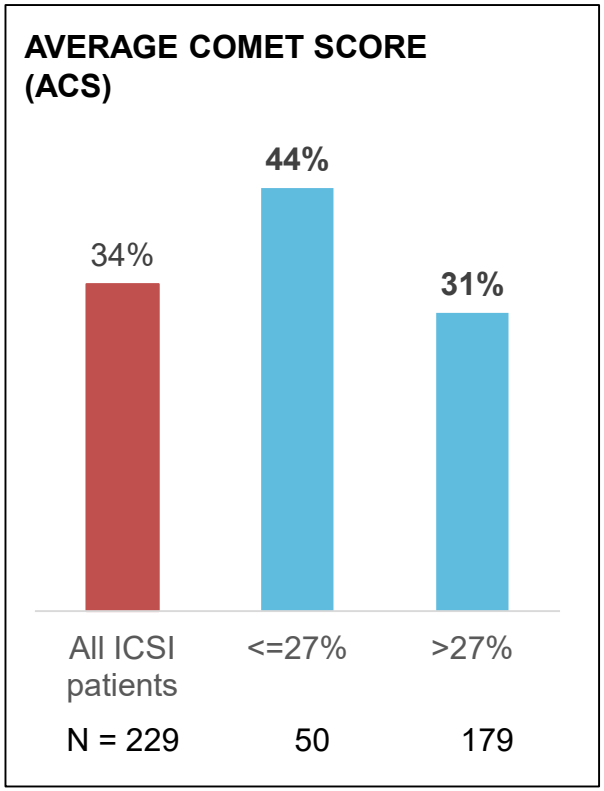
Source: Lister IVF dataset (N= 79) . P value calculated using Chi square.

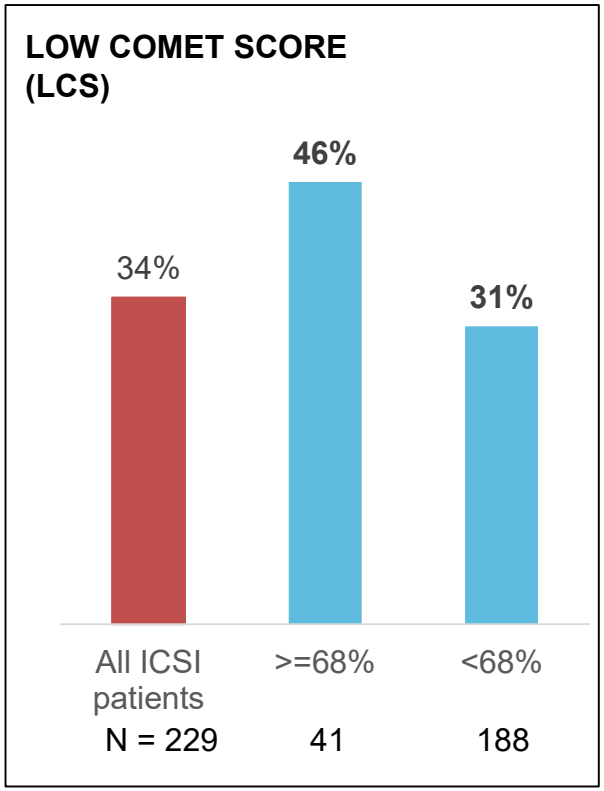
CONCLUSIONS

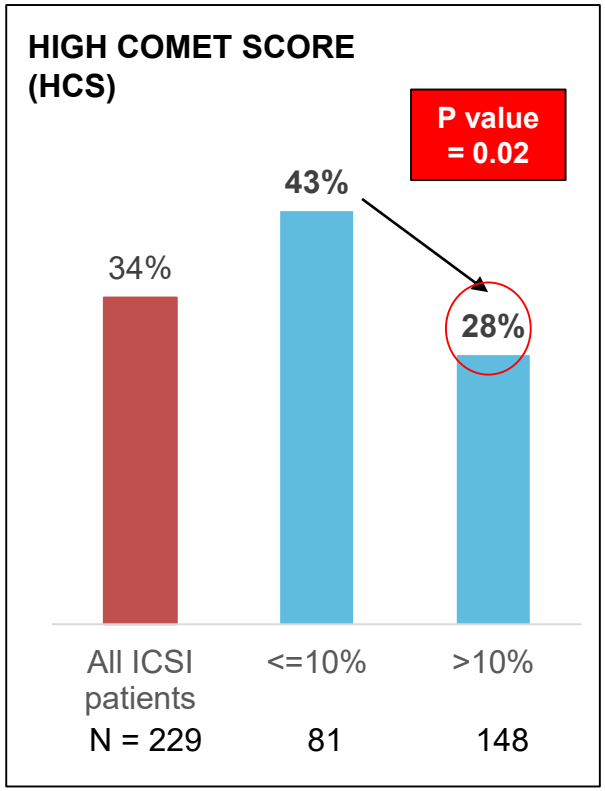
All COMET markers highly predictive of male subfertility confirming role for testing in unexplained infertility

IVF Livebirth rate declined sharply once sperm DNA damage exceeded all ROC threshold levels identified with HCS > 6% the most predictive (38% vs 13%)

IMPACT ON ICSI OUTCOME







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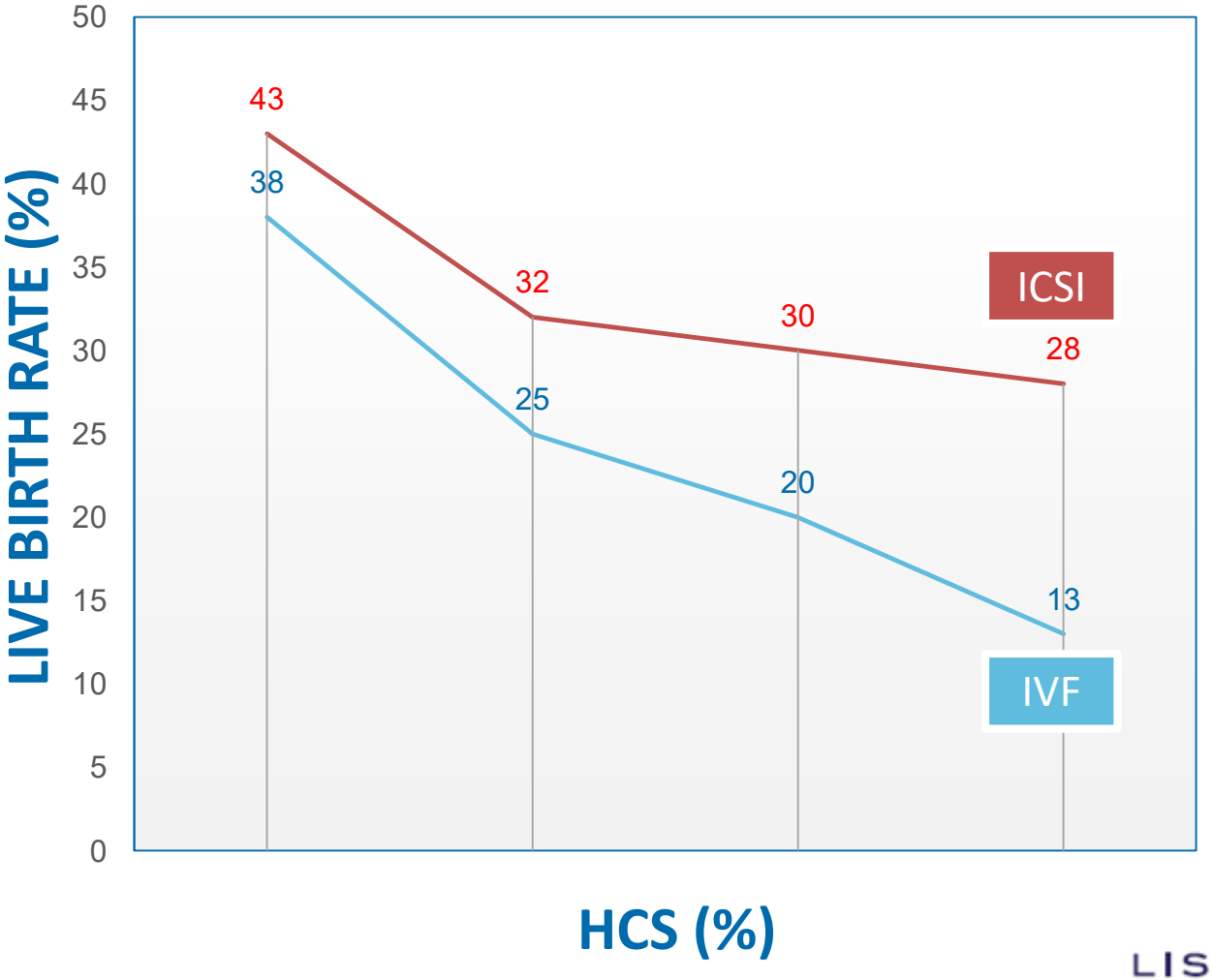
Source: Lister ICSI dataset (N= 229) . P value calculated using Chi square.

Trends in IVF compared to ISCI



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CONCLUSIONS

All COMET markers highly predictive of male subfertility confirming role for testing in unexplained infertility

IVF Livebirth rate declined sharply once sperm DNA damage exceeded all ROC threshold levels identified with HCS > 6% the most predictive (38% vs 13%)

ICSI Livebirth rate moderately declined once sperm DNA damage exceeded all ROC threshold levels identified with HCS > 10% the most predictive (43% vs 28%)

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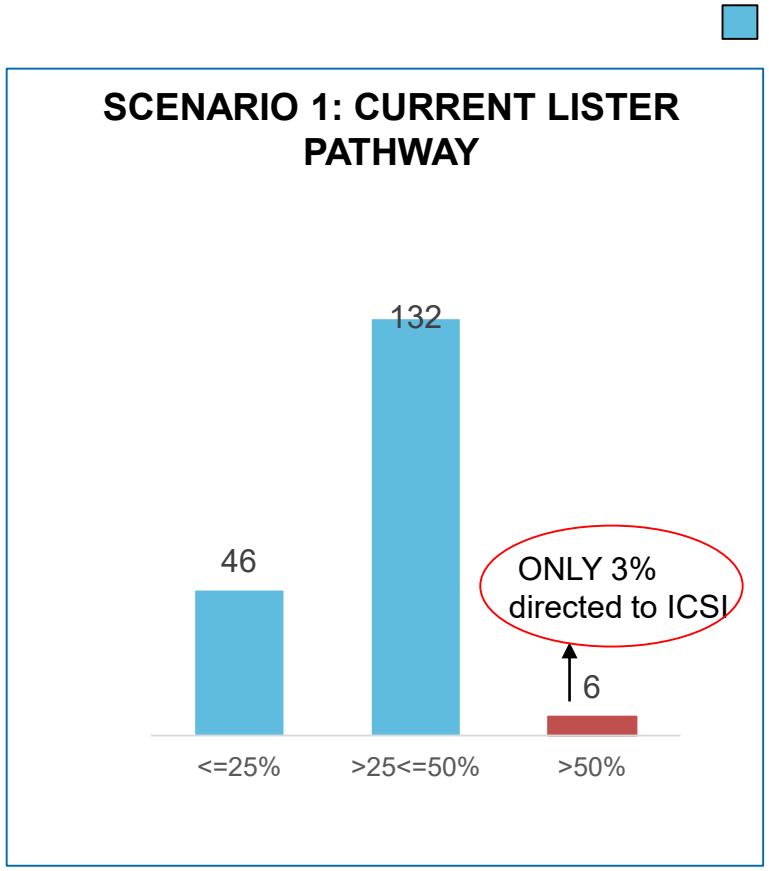
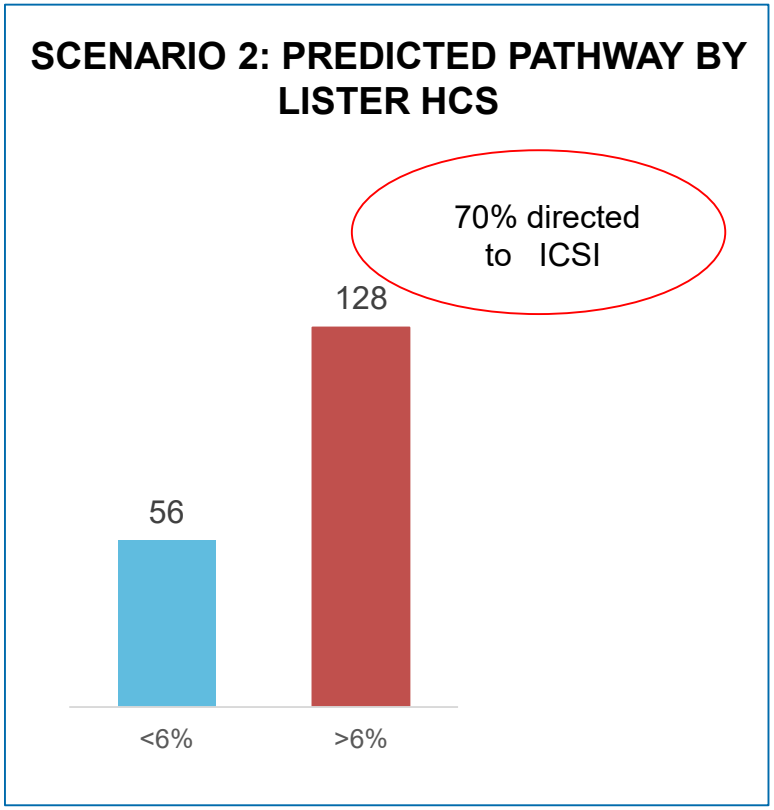
IMPACT ON TREATMENT CLINIC CYCLES

NORMOZOOSPERMIC PATIENTS SPLIT BY SPERM DNA DAMAGE THRESHOLDS

N = 184





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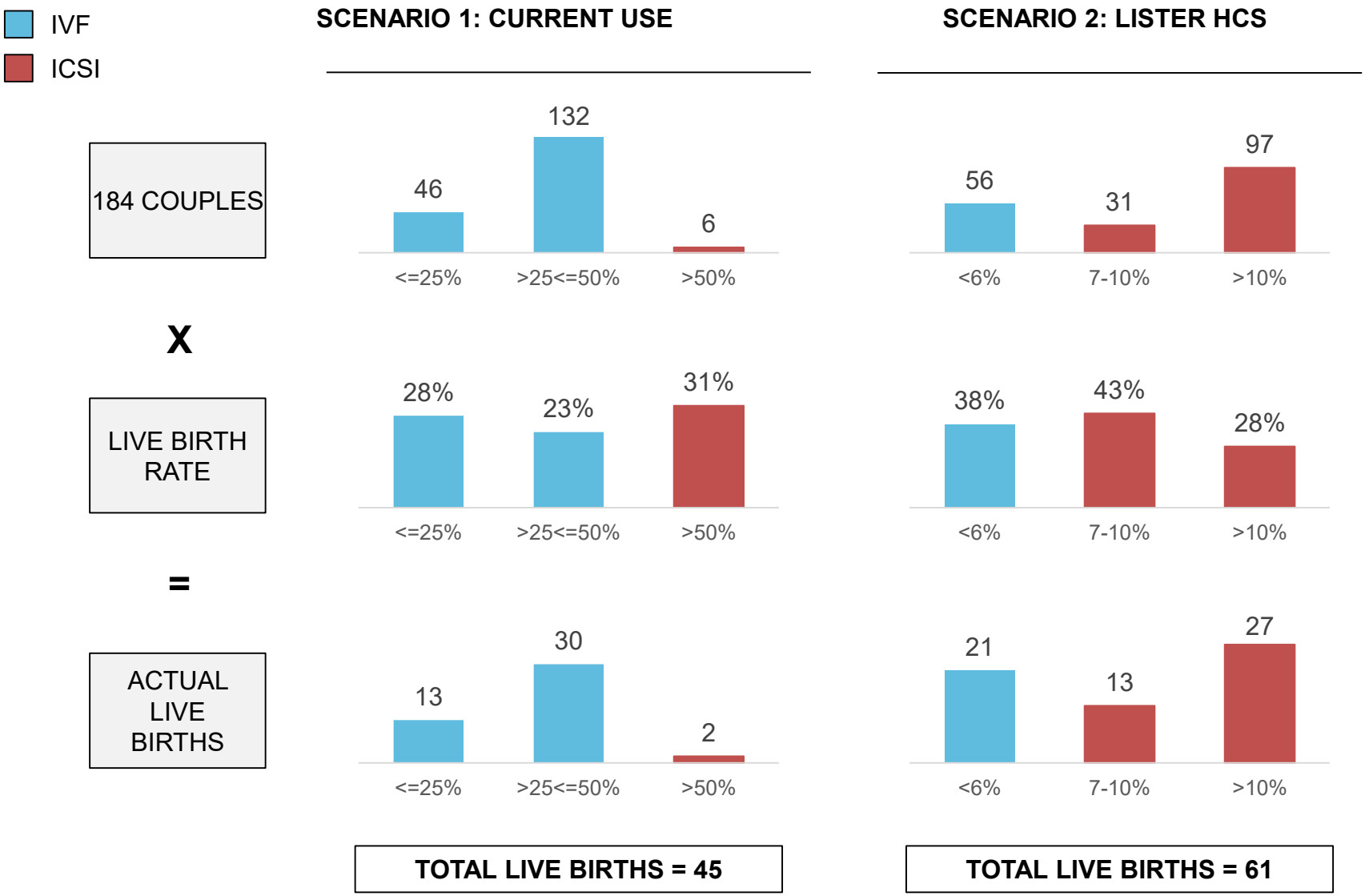
Source: Lister Outcome Database.

IMPACT ON POTENTIAL LIVEBIRTH OUTCOME



SUMMARY

- We have identified clinic-specific thresholds for ACS and novel SpermComet parameters
- Role for testing in Unexplained Subfertility
- Role for prediction of ART outcome / improved treatment pathway
  - HCS parameter is most predictive of IVF and ICSI Livebirth
  - Recommend IVF over ICSI even with normal semen parameters with COMET scores above identified thresholds
  - ICSI livebirth also impacted by COMET scores suggesting role for urological intervention to reduce damage before treatment
  - ?Role for testicular retrieval with very high levels / recurrent cycle failures

THANKS

- Multidisciplinary team at the Lister caring for this group of patients
- Professor Lewis and her SpermComet team for testing and data analysis
- Peter Larsen (Cryos) for control group samples
- Urological input in ongoing management of these patients
  - Mr Suks Minhas
  - Mr Jonathan Ramsay

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