Decreased Functional Biological Activity of Polyethylene Wear Debris From Revised HXLPE Liners

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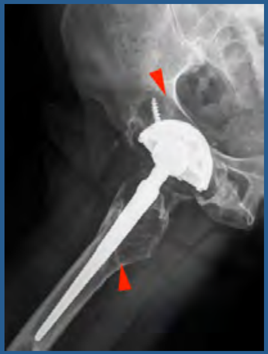
Rational of Study

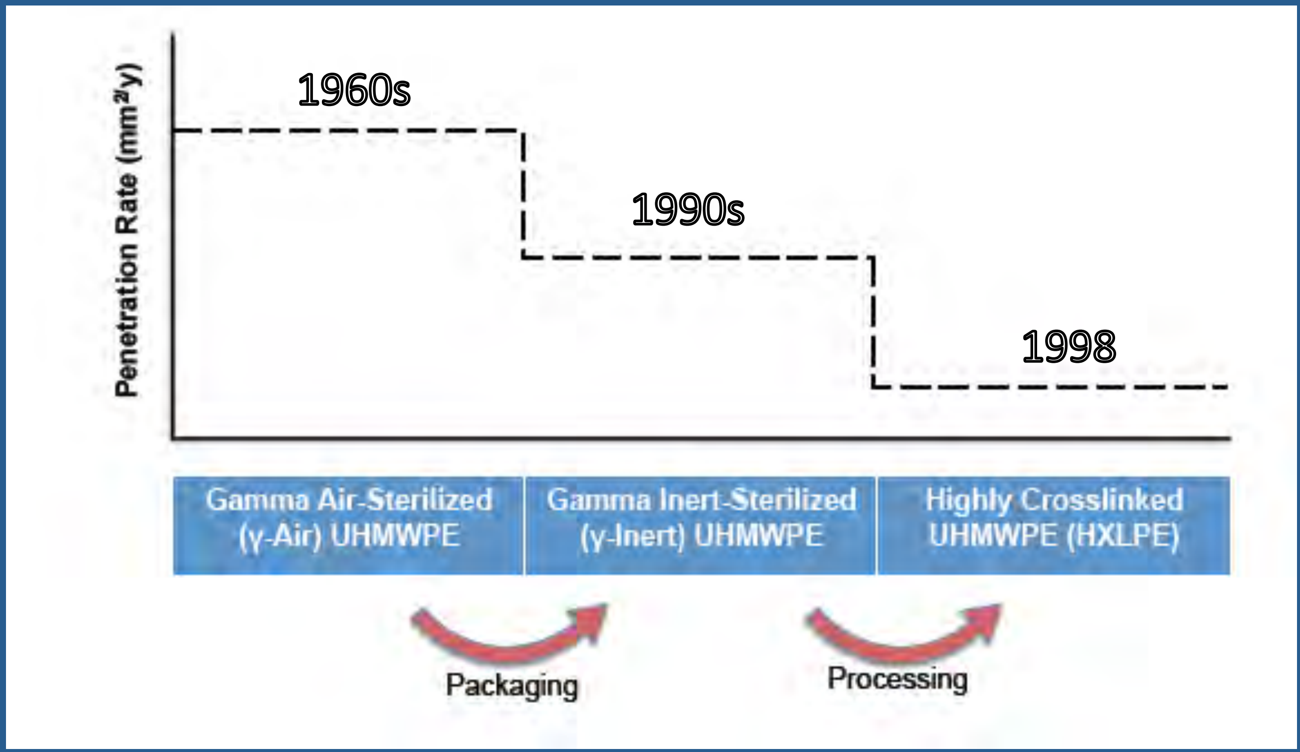


- Highly crosslinked UHMWPE (HXLPE) is known clinically to reduce osteolysis.
- *In vitro* cell culture studies, on the other hand, predict that submicron wear debris from these materials might show comparable osteolytic potential to conventional PE over time.

References:

1. Ingram, J.H., Stone, M., Fisher, J., Ingham, E., 2004. Biomaterials 25, 3511-3522.
2. Endo, M., Tipper, J.L., Barton, D.C., Stone, M.H., Ingham, E., Fisher, J., 2002. Proc Inst Mech Eng H 216, 111-122.
3. Fisher, J., Bell, J., Barbour, P.S., Tipper, J.L., Matthews, J.B., Besong, A.A., Stone, M.H., Ingham, E., 2001. Proc Inst Mech Eng H 215, 127-132.

Advances in Bearing Technology



Steven M. Kurtz PhD, Heather A. Gawel MS, Jasmine D. Patel PhD. History and Systematic Review of Wear and Osteolysis Outcomes for First-generation Highly Crosslinked Polyethylene. *Clin Orthop Relat Res* (2011) 469:2262–2277.

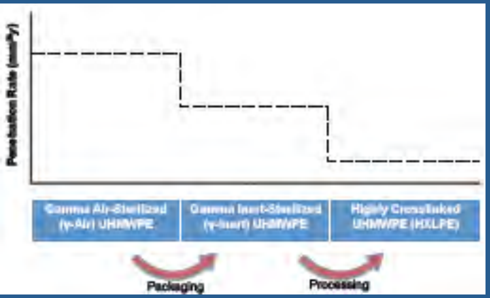
Highly Crosslinked Polyethylene

- Annealed HXLPE

  Electron beam or γ-Irradiation

  Thermally treated below crystalline melt transition

  Residual free radicals



- Remelted HXLPE

  Electron beam or γ-Irradiation

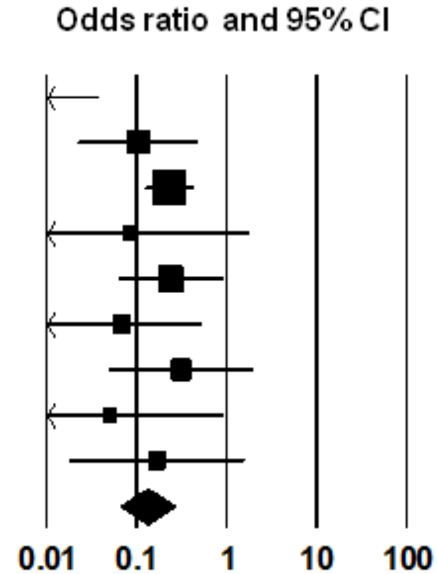
  Thermally treated above crystalline melt transition

  Decreased crystallinity and reduced mechanical properties

Frequency of Hip Osteolysis for Conventional and HXLPE Liners

Odds ratios of Osteolysis in Hips

Study name	Odds ratio	p-Value
Bitsch 2008	0.002	0.000
D'Antonio 2005	0.103	0.004
Engh 2006	0.230	0.000
Fukui 2010	0.081	0.111
Leung 2007	0.240	0.041
Mall 2011	0.067	0.011
Olyslaegers 2008	0.310	0.214
Rajadhyaksha 2009	0.050	0.044
Rohrl 2007	0.167	0.119
Total	0.131	0.000



Odds ratio for osteolysis of conventional vs HXLPE liners was 0.131 (nine studies).

Consensus that HXLPE reduces wear and osteolysis in total hip arthroplasty during the first 5-10 years after implantation.

Steven M. Kurtz PhD, Heather A. Gawel MS, Jasmine D. Patel PhD. History and Systematic Review of Wear and Osteolysis Outcomes for First-generation Highly Crosslinked Polyethylene. *Clin Orthop Relat Res* (2011) 469:2262–2277.

Aseptic Loosening & Osteolysis

Complex Etiology

- ✓ Poor initial fixation - loosening
- ✓ Stress shielding - loosening
- ✓ Intracapsular fluid pressure - loosening
- ✓ Endotoxin - loosening
- ✓ *Polyethylene wear debris* - osteolysis

Wear Particle Generation

- Level of polymer cross-linking
- Surface roughness
- Implant conformity
- Complexity of wear path
- Usage & Applied load

- *In vitro* simulator testing shows increased submicron wear debris generation due to multidirectional friction, PE oxidation, & increased PE cross-linking.

In Vivo Studies of HXLPE Wear Debris

- Previous *in vivo* studies have been limited to two single case reports of cemented HXLPE liners, and only one looked for submicron wear (>0.5μm).

- For first-generation HXLPE liners it remains unknown whether the decreased incidence of osteolysis can be attributed to a reduction in the biological activity (*size, shape and number*) of polyethylene wear particles generated *in vivo*.

In vivo References:

1. Bradford L, Kurland R, Sankaran M, Kim H, Pruitt LA, Ries MD. *J Bone Joint Surg Am.* 2004;86-A:1051-1056.
2. Minoda Y, Kobayashi A, Sakawa A, Aihara M, Tada K, Sugama R, Iwakiri K, Ohashi H, Takaoka K.. *J Biomed Mater Res B Appl Biomater.* 2008;86B:501-505.

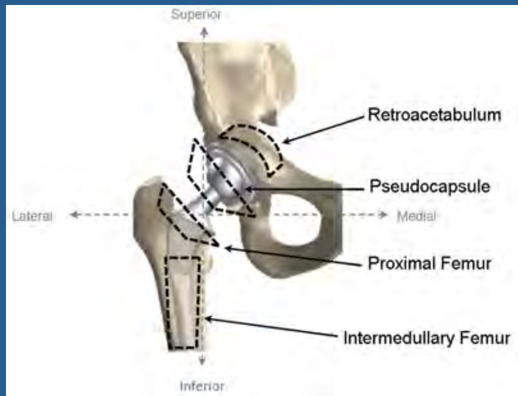
Objectives

- Determine the size, shape and number of polyethylene wear debris in tissues from primary THA revisions of CPE, remelted and annealed HXLPE liners.

- Assess how these differences affect the predicted biological, pro-inflammatory activity of particles that initiate osteolysis and implant loosening.

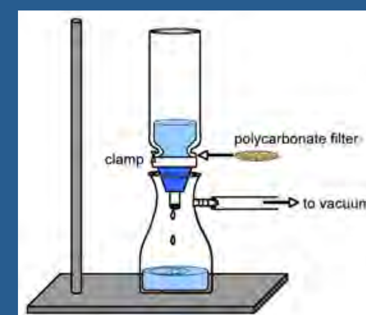
Tissue Cohorts

CPE cohort	Remelted Cohort	Annealed Cohort
N=4	N=5	N=5
revised after 6.4 yr (2.3-9.3yr)	revised after 3.3yr (1.7-6.6)	revised after 4.2 yr (2.0-5.2yr)
Howmedica Omnifit, Biomet Ringloc, Zimmer Trilogy	Zimmer Trilogy	Stryker Trident
wear, loosening & osteolysis (3 of 4)	loosening or malposition (1)	loosening or malposition (1)
female	4 female, 1 male	3 female, 2 male
68 ± 5 yr	61 ± 4 yr	61 ± 6 yr

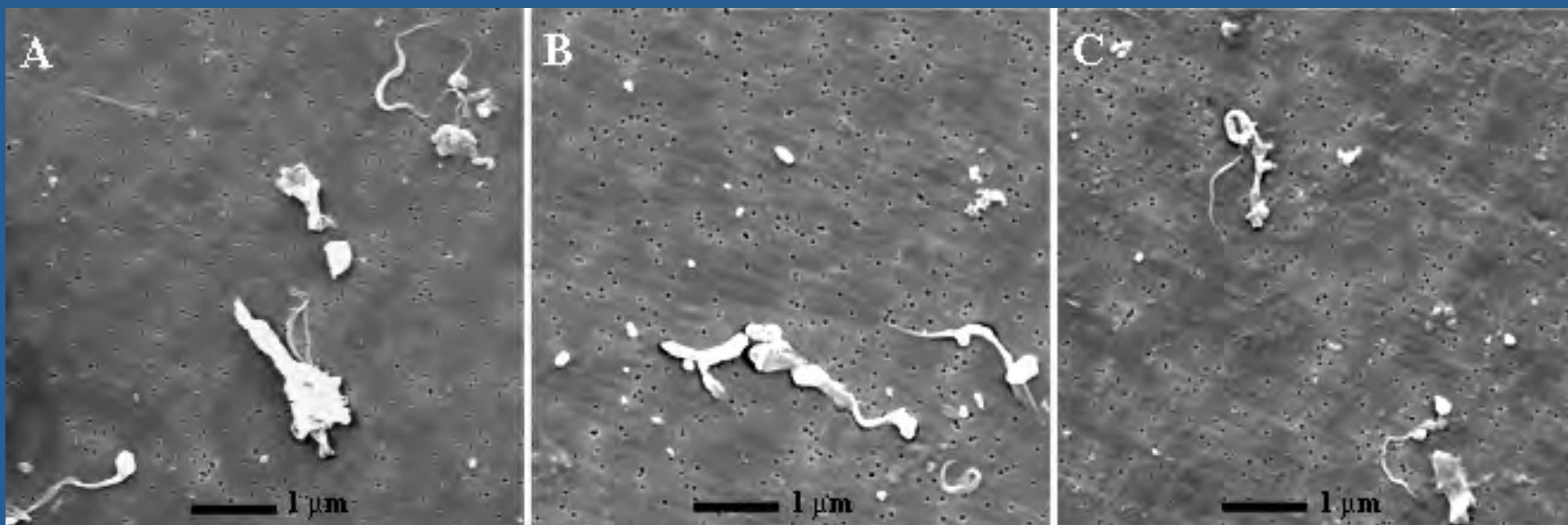


Approach

- Tissue (0.025g) digested with concentrated HNO_3
- Sequential filtration of digest through a 1.0μm & 0.05μm membrane
  - ~98% particle recovery
- Membranes are prepared for ESEM
- Imaged at 1,000, 5,000 & 12,000X
- Image Analysis of ≥1,000 particles per cohort using NIH ImageJ to determine particle area and dimension.



Representative Images of Polyethylene Wear Debris



CPE **Remelted HXLPE** **Annealed HXLPE**

>90% of particles were granular or ellipsoidal for all three groups, with the remainder being composed of fibrillar wear debris.

Particle Characteristics

- Equivalent Circular Diameter $ECD = \sqrt{\frac{4 \bullet A_P}{\pi}}$

  Size (circle diameter) particle area

- Aspect Ratio $AR = \frac{L_P}{W_P}$

  Ratio of particle length to breadth

- Roundness $R = \frac{4 \bullet A_P}{\pi \bullet (L_P)^2}$

  Measure of circularity based on particle length

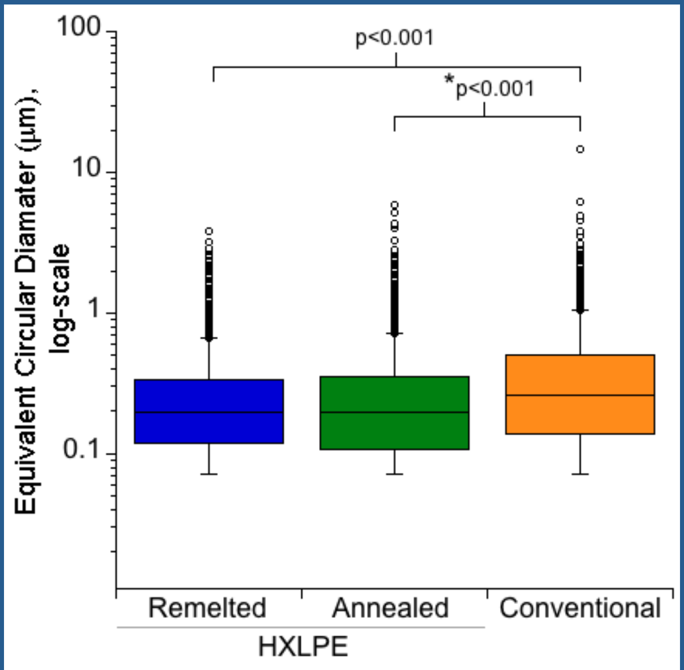
- Form Factor $FF = \frac{4 \bullet \pi \bullet A_P}{(\text{perimeter})^2}$

  Measure of circularity based on particle perimeter

- Number/gram wt. of tissue $N_P = N_I \bullet (A_F/A_I)/W_T$

Particle Size

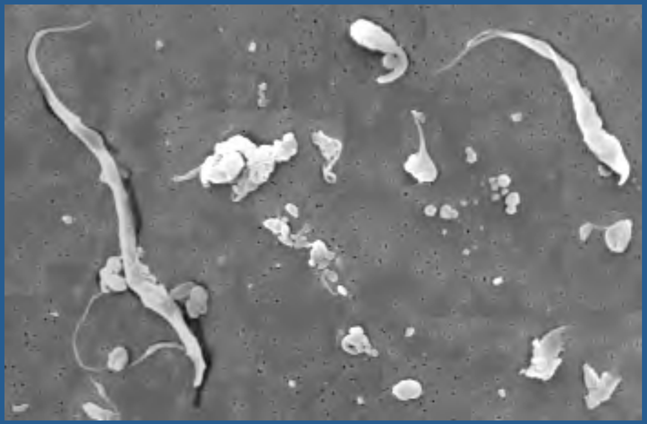
Non-parametric Wilcoxon Mann-Whitney. Boxed ranges of the 25th to 75th percentile & whiskers showing the 10th and 90th percentile.

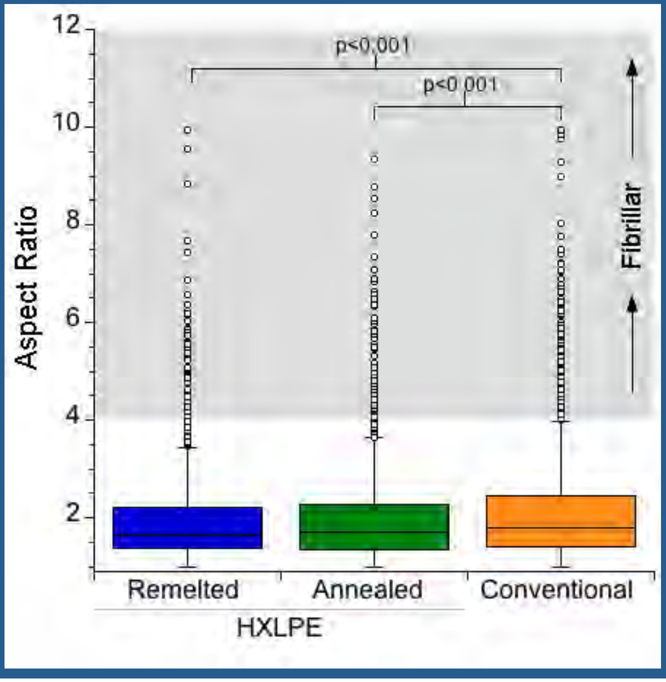


$$ECD = \sqrt{\frac{4 \bullet A_P}{\pi}}$$

	Remelted HXLPE	Annealed HXLPE	Conventional Polyethylene
Mean ± Std. Dev. (Median)	0.32 ± 0.37 µm (0.20)	0.31 ± 0.39 µm (0.20)	0.43 ± 0.53 µm (0.26)

Particle Morphology

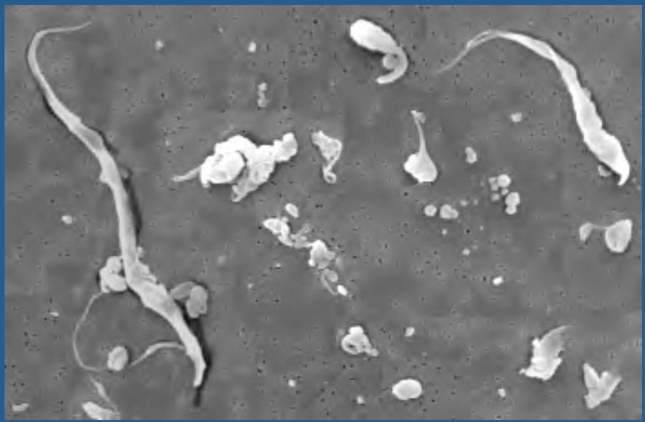


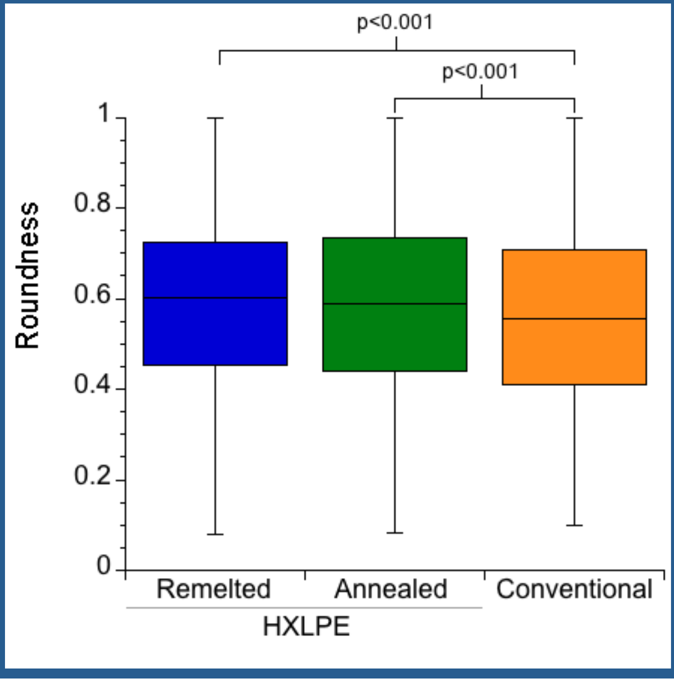


$$AR = \frac{L_P}{W_P}$$

	Remelted HXLPE	Annealed HXLPE	Conventional Polyethylene
Aspect Ratio	2.00 ± 1.06 (1.66)	2.01 ± 1.07 (1.70)	2.15 ± 1.13 (1.80)
Roundness	0.59 ± 0.19 (0.60)	0.58 ± 0.19 (0.59)	0.55 ± 0.19 (0.56)
Form Factor	0.63 ± 0.25 (0.66)	0.61 ± 0.24 (0.64)	0.52 ± 0.26 (0.53)

Particle Morphology





$$R = \frac{4 \bullet A_P}{\pi \bullet (L_P)^2}$$

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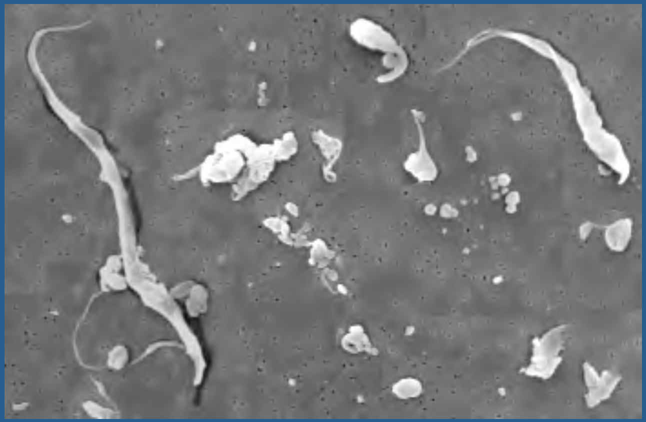

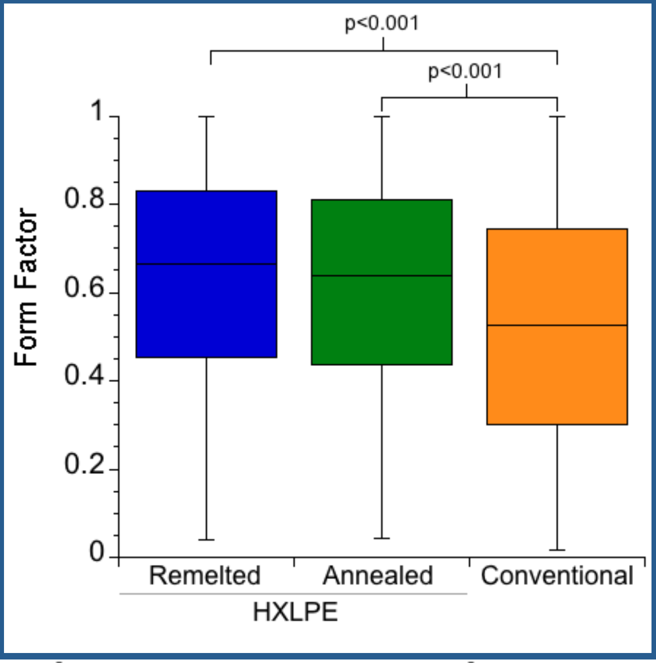

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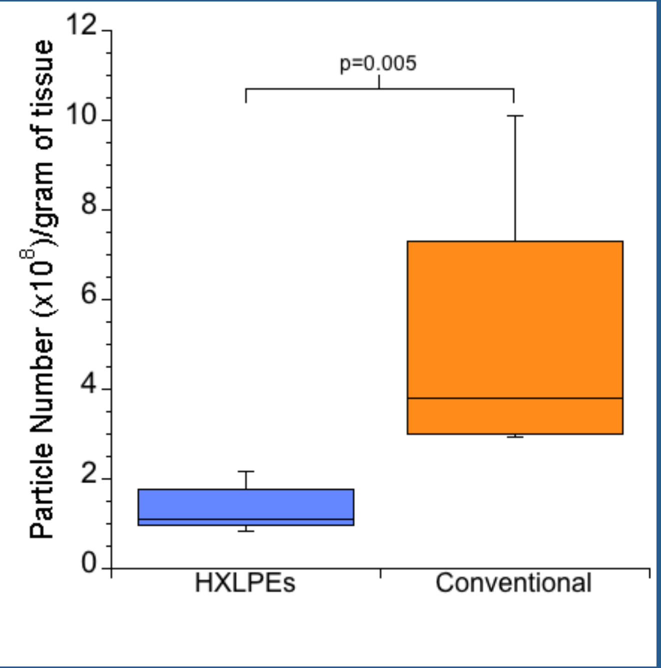
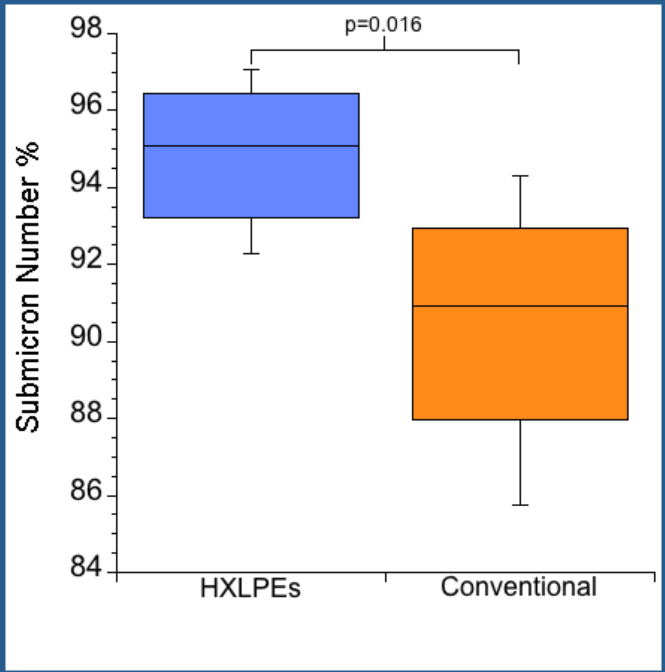
Particle Number



	HXLPEs	Conventional Polyethylene
Number ($x10^8$/gram of tissue)	1.34 ± 0.48 (1.11)	5.14 ± 3.37 (3.78)
Submicron Number %	94.83 ± 1.75 (95.08)	90.50 ± 3.60 (91.00)

Submicron Number Percentage



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Biological Pro-inflammatory & Osteolytic Activity

- Amount of TNF-α release from cultured monocytes
- Addition of particles based on size & volume

↑ Biological activity ↓ Particle size

Fisher, J., Bell, J., Barbour, P.S., Tipper, J.L., Matthews, J.B., Besong, A.A., Stone, M.H., Ingham, E., 2001. A novel method for the prediction of functional biological activity of polyethylene wear debris. Proc Inst Mech Eng H 215, 127-132.

Biological Activity

Original Model by Fisher et al. 2001

$$\mathrm{SBA} = \int_{0.1}^{100} C(r)B(r)\,\mathrm{d}r$$

Specific Biological Activity (SBA)
- relative biological activity per unit volume, where C(r) is the % volumetric concentration of wear debris as a function of particle size (r)

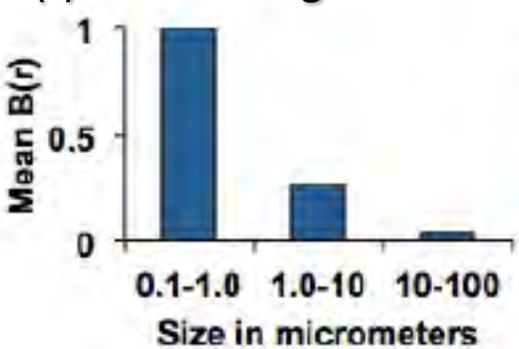
$$\mathrm{FBA} = V \times \mathrm{SBA}$$

The product of the volumetric wear rate ($mm^3/10^6$ cycles) X SBA

$$\mathrm{FBA} = \mathrm{SBA} \bullet \sum V_P$$

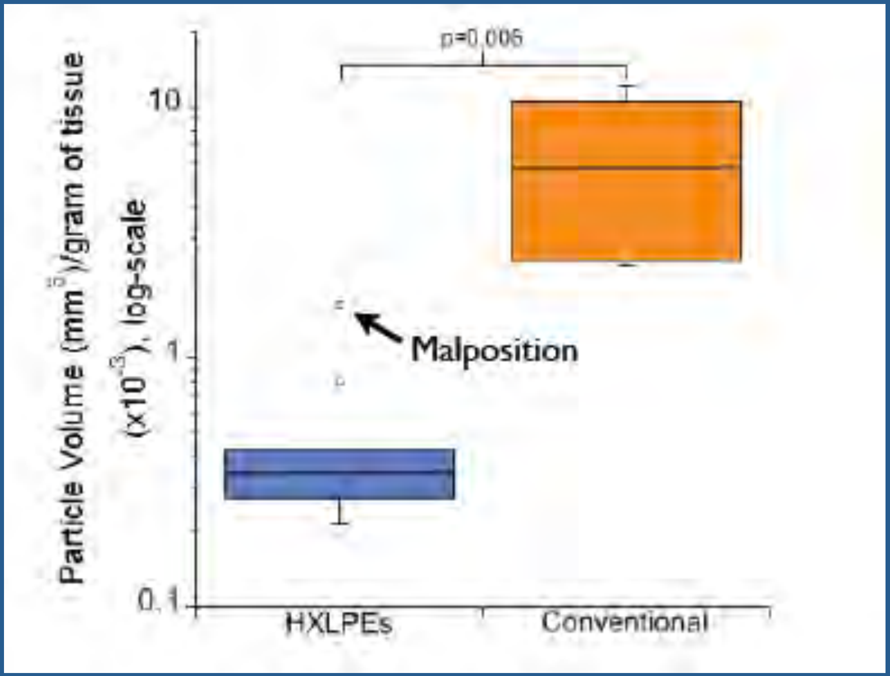
The product of the particle volume (mm^3)/gm of tissue X SBA

B(r) is the biological activity as a function of particle size



Scalar	Particle Size Range
1.00	ECD < 1 μm
0.20	1 μm < ECD < 10 μm
0.04	ECD > 10 μm

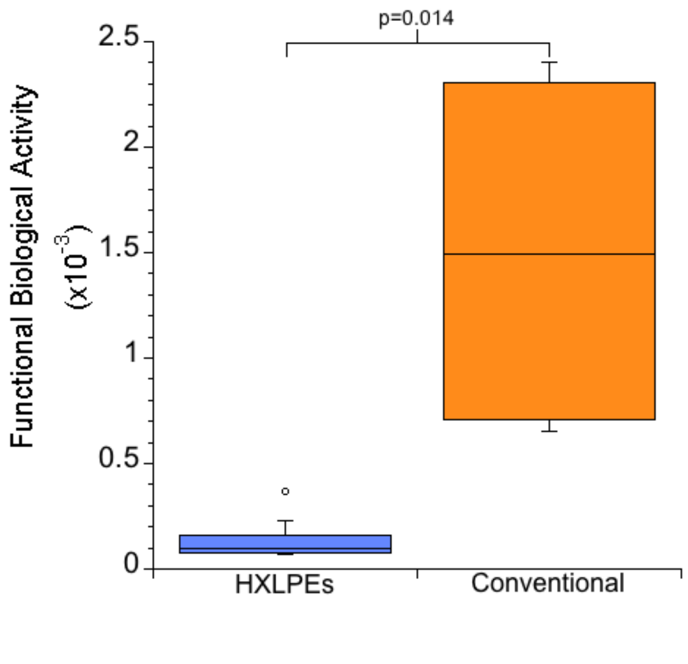
Cumulative Particle Volume



	HXLPEs	Conventional Polyethylene
Total Estimated volume (mm^3)/gram tissue ($x10^{-3}$)	0.36 ± 0.05 (0.35)	6.47 ± 4.83 (5.73)
Functional Biological Activity ($x10^{-3}$)	0.14 ± 0.09 (0.10)	1.51 ± 0.93 (1.49)

Functional Biological Activity

$$FBA = SBA \bullet \sum V_P$$



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Summary of Findings

- Submicron particle number is increased for HXLPE vs CPE liners
- Wear particle volume % is significantly decreased for HXLPE vs CPE liners
- Resulting in a wear particle FBA that is significantly less for HXLPE vs CPE

Conclusion

Based on the current findings the pro-inflammatory, osteolytic potential of HXLPE wear debris is out-weighted by a significant improvement in wear resistance and decrease in particle generation.

Funding

U.S. Department of Health and Human Services

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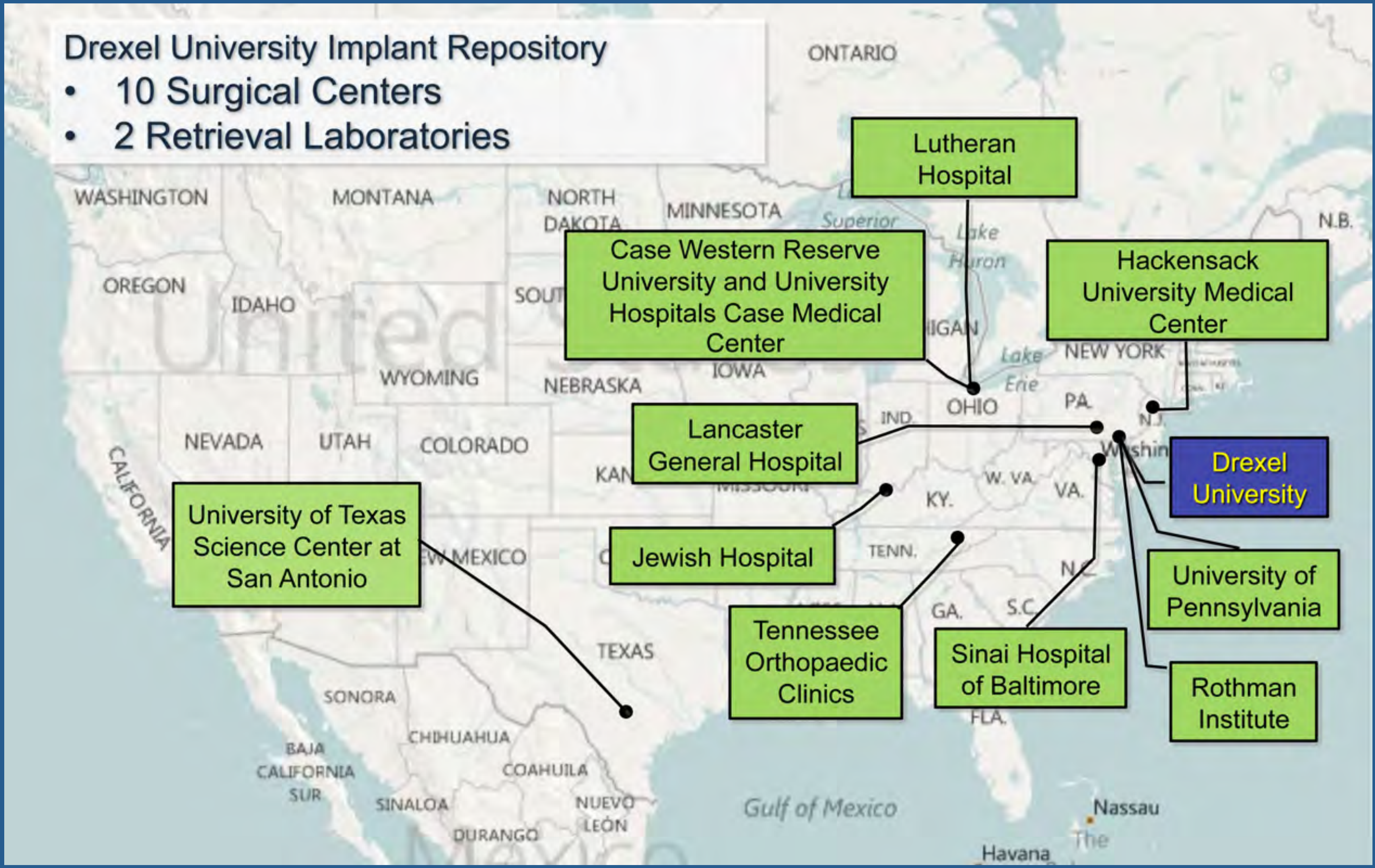
National Institutes of Health

NIAMS

National Institute of Arthritis and Musculoskeletal and Skin Diseases

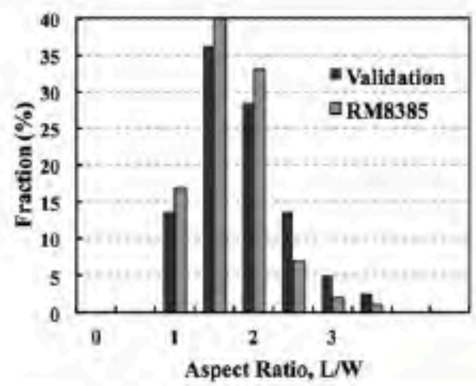
Questions?

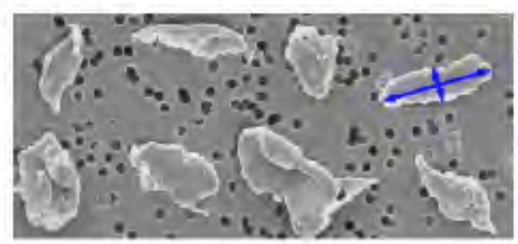

Drexel University Implant Repository
• 10 Surgical Centers
• 2 Retrieval Laboratories
Lutheran Hospital
Case Western Reserve University and University Hospitals Case Medical Center
Hackensack University Medical Center
Lancaster General Hospital
Drexel University
University of Texas Science Center at San Antonio
Jewish Hospital
University of Pennsylvania
Tennessee Orthopaedic Clinics
Sinai Hospital of Baltimore
Rothman Institute

Shape Validation

Validation: Shape

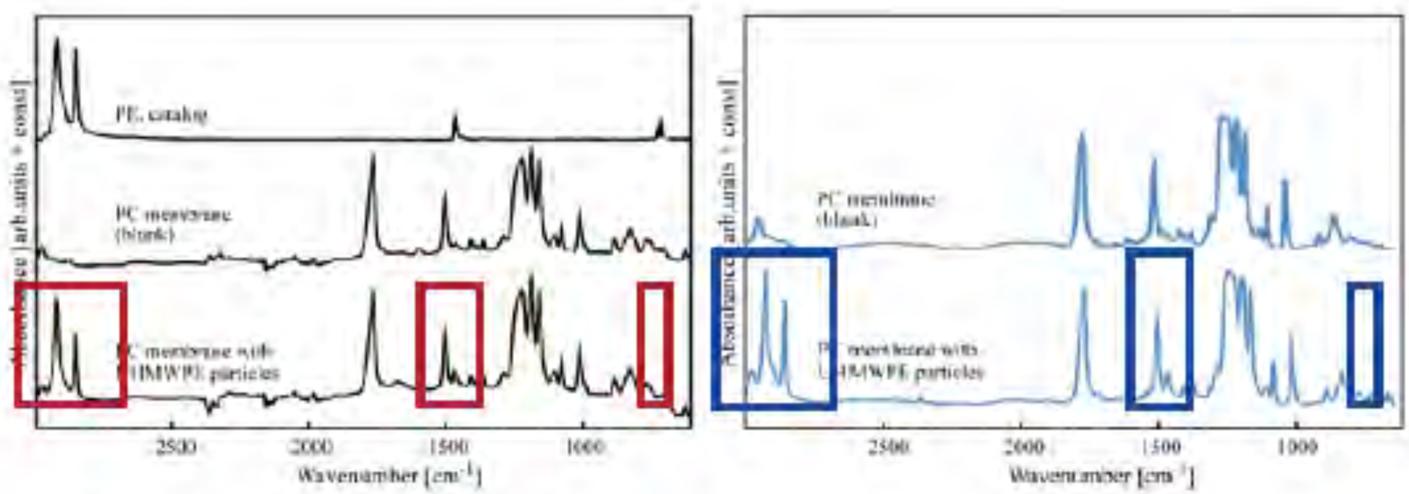
- NIST Traceable UHMWPE Wear Debris
  - R2 - Round
    - Diff: 1.3 ± 0.4 %
  - E1 - Elongated
    - Diff: 2.9 ± 0.8 %





Polyethylene Validation

- Fourier Transform Infrared (FTIR) Analysis

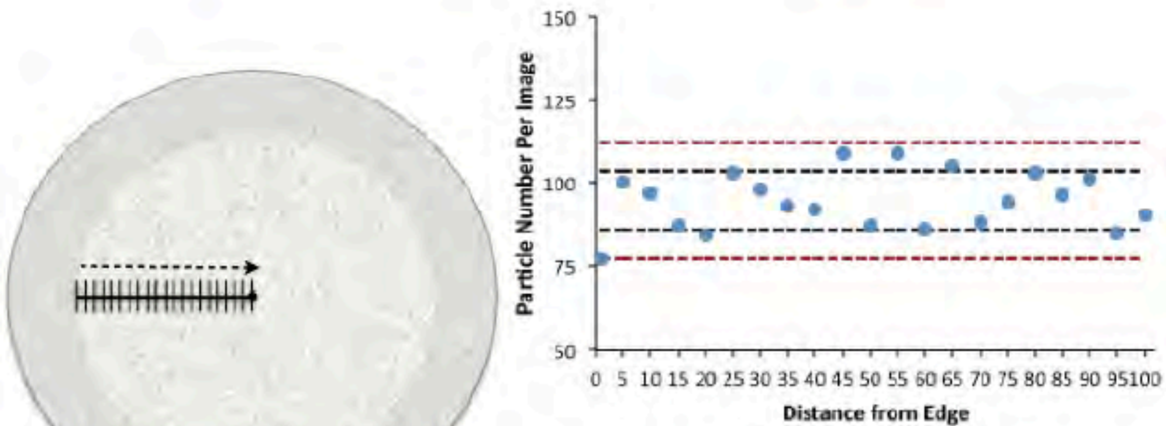


Lapcikova et al., (2009) Wear

Baxter et al., (2011)

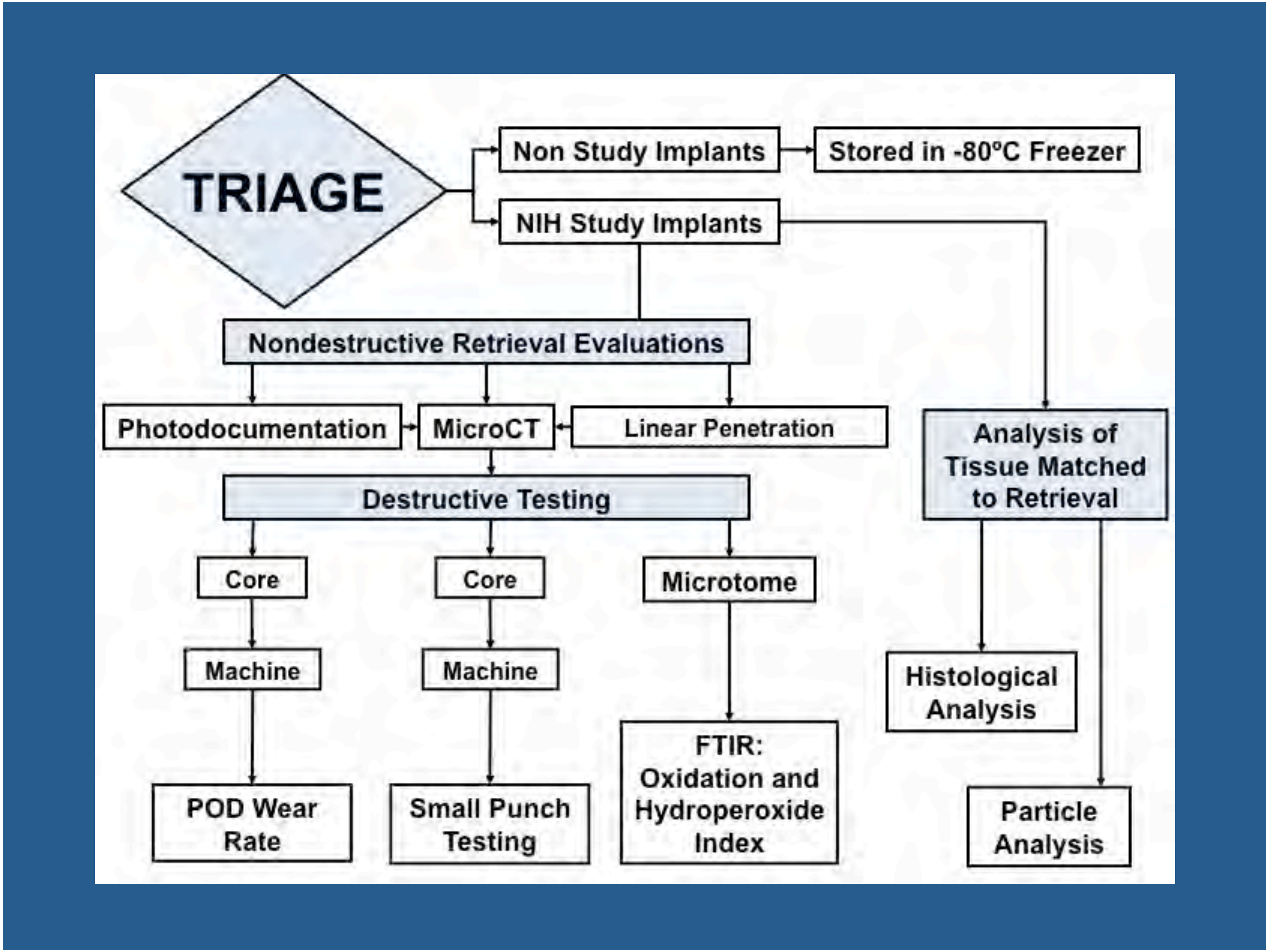
Homogeneity

Validation: Homogeneity



R^2=0.0167
Shapiro Wilk Goodness of Fit P<0.79

$$N_P = N_I \bullet (A_F/A_I)/W_T$$


TRIAGE
Non Study Implants
Stored in -80°C Freezer
NIH Study Implants
Nondestructive Retrieval Evaluations
Photodocumentation
MicroCT
Linear Penetration
Analysis of Tissue Matched to Retrieval
Destructive Testing
Core
Core
Microtome
Machine
Machine
Histological Analysis
POD Wear Rate
Small Punch Testing
FTIR: Oxidation and Hydroperoxide Index
Particle Analysis

References:

1. Ingram, J.H., Stone, M., Fisher, J., Ingham, E., 2004. The influence of molecular weight, crosslinking and counterface roughness on TNF-alpha production by macrophages in response to ultra high molecular weight polyethylene particles. Biomaterials 25, 3511-3522.
2. Endo, M., Tipper, J.L., Barton, D.C., Stone, M.H., Ingham, E., Fisher, J., 2002. Comparison of wear, wear debris and functional biological activity of moderately crosslinked and non-crosslinked polyethylenes in hip prostheses. Proc Inst Mech Eng H 216, 111-122.
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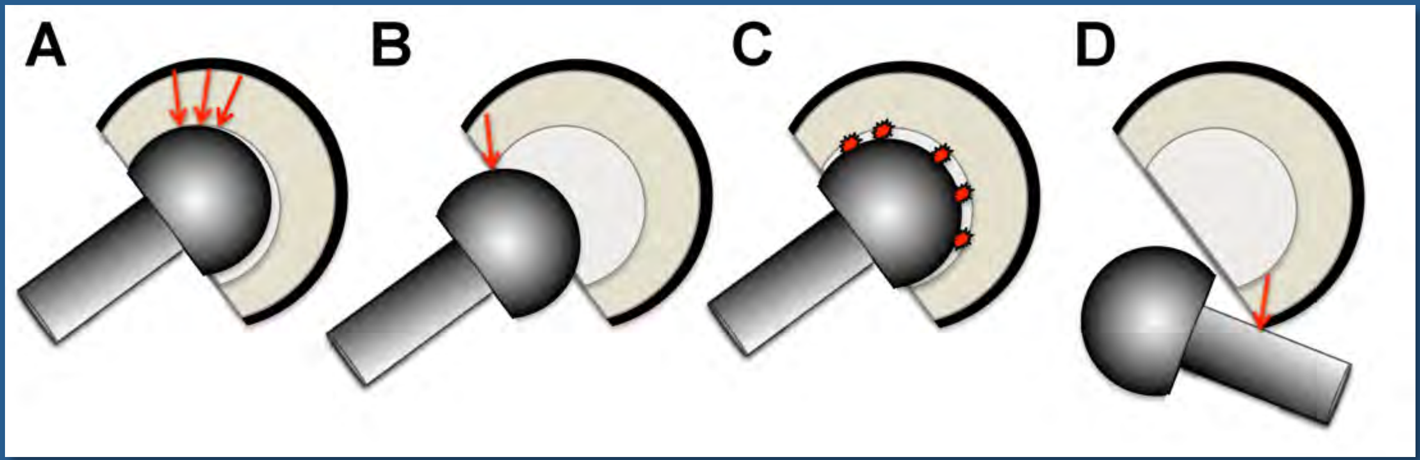
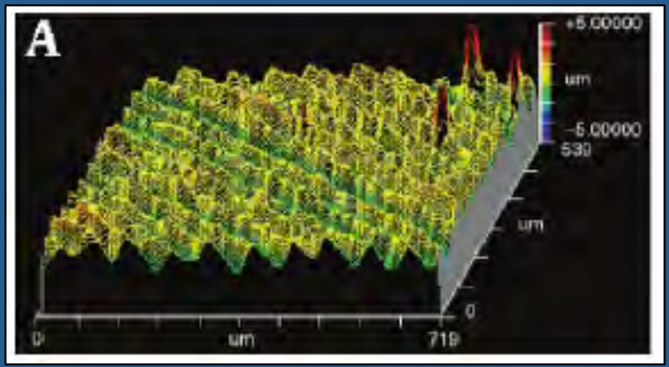
Modes of Wear & Wear Particle Generation

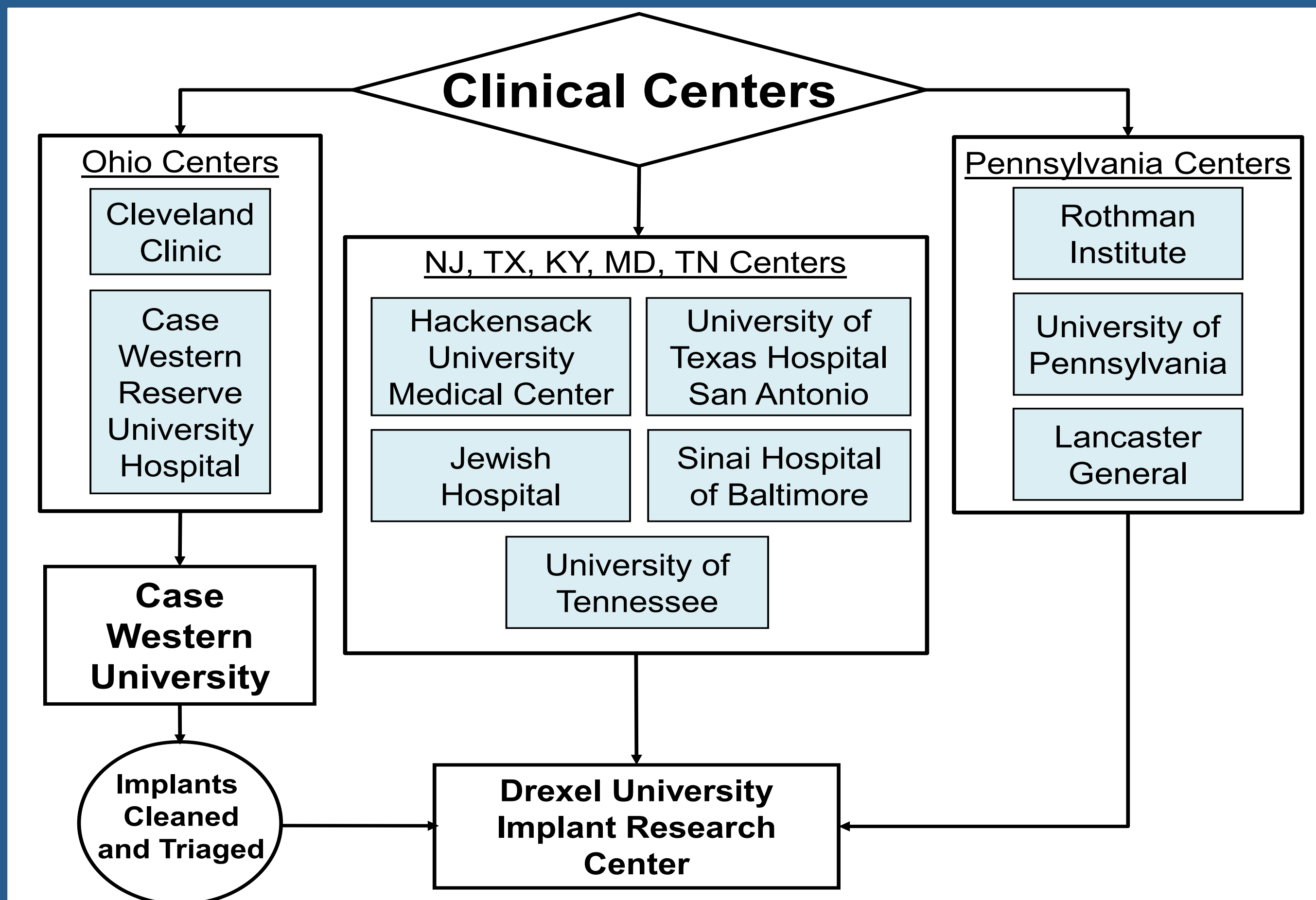


Intended Unintended Abrasive Impingement

- Usage
- Surface roughness
- Implant conformity
- Level of polymer cross-linking
- Complexity of wear path
- Applied load



Questions?


Clinical Centers
Ohio Centers
Cleveland Clinic
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NJ, TX, KY, MD, TN Centers
Hackensack University Medical Center
University of Texas Hospital San Antonio
Jewish Hospital
Sinai Hospital of Baltimore
University of Tennessee
Pennsylvania Centers
Rothman Institute
University of Pennsylvania
Lancaster General
Case Western University
Implants Cleaned and Triaged
Drexel University Implant Research Center