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Towards Molecular Classification of Uterine Sarcomas

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Pathology Grand Rounds University of Utah/ ARUP Laboratories December 15, 2022

Disclosures

• Paid consultant, AstraZeneca



Pathologists make discoveries through observation



Pathologists make discoveries through observation



Part 1: Morphologic correlation with next-generation sequencing (NGS) promotes explosion of new clinicopathologic entities



LGESS: low-grade endometrial stromal sarcoma

HGESS: high-grade endometrial stromal sarcoma

LMS: leiomyosarcoma

UTROSCT: uterine tumor resembling ovarian sex cord tumor



Private Information

2013: *ZC3H7B::BCOR* fusion is detected in ESS but its association with phenotype remains unknown

GENES, CHROMOSOMES & CANCER 52:610-618 (2013)

Fusion of the ZC3H7B and BCOR Genes in Endometrial Stromal Sarcomas Carrying an X;22-Translocation

Ioannis Panagopoulos,^{1,2*} Jim Thorsen,^{1,2} Ludmila Gorunova,^{1,2} Lisbeth Haugom,^{1,2} Bodil Bjerkehagen,³ Ben Davidson,^{3,4} Sverre Heim,^{1,2,4} and Francesca Micci^{1,2}





ZC3H7B::BCOR fusion suggests new HGESS subtype often mimicking myxoid LMS

ORIGINAL ARTICLE

Novel High-grade Endometrial Stromal Sarcoma

A Morphologic Mimicker of Myxoid Leiomyosarcoma

Lien N. Hoang, MD,* Amandeep Aneja, MD,* Niamh Conlon, MD,† Deborah F. Delair, MD,* Sumit Middha, PhD,* Ryma Benayed, PhD,* Martee L. Hensley, MD,‡ Kay J. Park, MD,* Travis J. Hollmann, MD,* Meera R. Hameed, MD,* Cristina R. Antonescu, MD,* Robert A. Soslow, MD,* and Sarah Chiang, MD*

	Case 1	Case 2	Case 3
CD10	Diffuse +	Diffuse +	Diffuse +
ER/ PR	Diffuse +	-	-
Desmin	-	Focal +	-
SMA	Focal +	-	Focal +
Initial diagnoses	ESS with LG and HG features Myxoid LMS	UUS with features of ESS and myxoid LMS	Myxoid LMS Melanoma
Fusion	<i>ZC₃H₇B::BCOR</i> MSK Solid Fusion (35 genes)	<i>ZC₃H₇B::BCOR</i> Foundation One (28 genes)	<i>ZC₃H₇B::BCOR</i> MSK Solid Fusion (35 genes)



1

2

3







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ZC3H7B::BCOR fusion confirms new subtype of HGESS with distinctive morphology

MODERN PATHOLOGY (2018) 31, 674-684 © 2018 USCAP, Inc All rights reserved 0893-3953/18 \$32.00

674

ZC3H7B-BCOR high-grade endometrial stromal sarcomas: a report of 17 cases of a newly defined entity

Natasha Lewis¹, Robert A Soslow¹, Deborah F Delair¹, Kay J Park¹, Rajmohan Murali¹, Travis J Hollmann¹, Ben Davidson^{2,3}, Francesca Micci⁴, Ioannis Panagopoulos⁴, Lien N Hoang⁵, Javier A Arias-Stella III¹, Esther Oliva^{6,7}, Robert H Young^{6,7}, Martee L Hensley⁸, Mario M Leitao Jr⁹, Meera Hameed¹, Ryma Benayed¹, Marc Ladanyi¹, Denise Frosina¹, Achim A Jungbluth¹, Cristina R Antonescu¹ and Sarah Chiang¹





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Bland spindle cells and myxoid matrix are common features of *ZC3H7B::BCOR* fusion HGESS







Vacuoles

Hyaline plaques

Entrapped glands



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ZC3H7B::BCOR fusion HGESS is often CD10/ cyclin D1 positive and desmin negative with variable ER/ PR expression



Private Information

Subset of ZC3H7B::BCOR fusion HGESS have BCOR overexpression and MDM2/CDK4 pathway alterations

Contents lists available at ScienceDirect Gynecologic Oncology journal homepage: www.elsevier.com/locate/ygyno

Genomic profiling of BCOR-rearranged uterine sarcomas reveals novel gene fusion partners, frequent CDK4 amplification and CDKN2A loss

Douglas I. Lin^{a,*}, Amanda Hemmerich^b, Claire Edgerly^b, Daniel Duncan^b, Eric A. Severson^b, Richard S.P. Huang^b, Shakti H. Ramkissoon^{b,c}, Yamicia D. Connor^d, Meghan Shea^e, Jonathan L. Hecht^f, Siraj M. Ali^a, Jo-Anne Vergilio^a, Jeffrey S. Ross^{a,g}, Julia A. Elvin^a

17.5%

BCOR is a robust diagnostic immunohistochemical marker of genetically diverse high-grade endometrial stromal sarcoma, including tumors exhibiting variant morphology

ERN PATHOLOGY (2017) 30, 1251-1261 USCAP, inc All rights reserved of on-nona / tr \$na.or

Sarah Chiang¹, Cheng-Han Lee^{2,3}, Colin JR Stewart⁴, Esther Oliva⁵, Lien N Hoang³, Rola H Ali⁶, Martee L Hensley⁷, Javier A Arias-Stella III¹, Denise Frosina¹, Achim A Jungbluth¹, Ryma Benayed¹, Marc Ladanyi¹, Meera Hameed¹, Lu Wang¹, Yu-Chien Kao^{1,8}, Cristina R Antonescu¹ and Robert A Soslow¹





BCOR clone C10 antibody coverage



	BCOR exon	ZC3H7B exon	BCOR expression (intensity, %)
(6	11	-
-	14	6	+ (strong, >95%)
7	7	11	+ (strong, >95%)
7	7	10	+ (strong, >95%)
7	7	10	+ (weak, >95%)

BCOR	100%	
ZC3H7B	78%	
MDM2	45%	
FRS2	40%	
CDK4	38%	
CDKN2A	28%	
CDKN2B	18%	
HMGA2	15%	
TP53	10%	
PDGFRA	8%	
NCOR2	8%	•1
KDR	5%	
ERBB3	5%	
FGF6	5%	
NF1	5%	•
CREBBP	5%	
PTCH1	5%	••
CCND2	2.5%	
кіт	2.5%	
NF2	2.5%	



BCOR positivity in fusion negative uterine sarcoma leads to discovery of *BCOR* ITD

BCOR is a robust diagnostic immunohistochemical marker of genetically diverse high-grade endometrial stromal sarcoma, including tumors exhibiting variant morphology

DERN PATHOLOGY (2017) 30, 1251-1261

Sarah Chiang¹, Cheng-Han Lee^{2,3}, Colin JR Stewart⁴, Esther Oliva⁵, Lien N Hoang³, Rola H Ali⁶, Martee L Hensley⁷, Javier A Arias-Stella III¹, Denise Frosina¹, Achim A Jungbluth¹, Ryma Benayed¹, Marc Ladanyi¹, Meera Hameed¹, Lu Wang¹, Yu-Chien Kao^{1,8}, Cristina R Antonescu¹ and Robert A Soslow¹









BCOR ITD HGESS shows overlapping features of YWHAE::NUTM2 and **ZC3H7B::BCOR** fusion HGESS





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BCOR ITD shows similar histology across primary sites with HGESS affecting pediatric and adult age groups

BCOR is a robust diagnostic immunohistochemical marker of genetically diverse high-grade endometrial stromal sarcoma, including tumors exhibiting variant morphology

Sarah Chiang¹, Cheng-Han Lee^{2,3}, Colin JR Stewart⁴, Esther Oliva⁵, Lien N Hoang³, Rola H Ali⁶, Martee L Hensley⁷, Javier A Arias-Stella III¹, Denise Frosina¹, Achim A Jungbluth¹, Ryma Benayed¹, Marc Ladanyi¹, Meera Hameed¹, Lu Wang¹, Yu-Chien Kao^{1,6}, Cristina R Antonescu¹ and Robert A Soslow¹

ORIGINAL ARTICLE

MODERN PATHOLOGY (2017) 30, 1251-1261

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BCOR Internal Tandem Duplication in High-grade Uterine Sarcomas

Adrián Mariño-Enriquez, MD, PhD,* Alexandra Lauria, BSc, RN,* Joanna Przybyl, PhD,† Tony L. Ng, MD, PhD,‡ Magdalena Kowalewska, PhD,§|| Maria Debiec-Rychter, MD, PhD,¶ Raji Ganesan, FRCPath,# Vaiyapuri Sumathi, FRCPath,** Suzanne George, MD,†↑ W. Glenn McCluggage, FRCPath,‡‡ Marisa R. Nucci, MD,* Cheng-Han Lee, MD, PhD,§§ and Jonathan A. Fletcher, MD*

Clinical Translational Research

Oncology

Oncology 2019;96:101–109 DOI: 10.1159/000493322 Received: August 27, 2018 Accepted: August 27, 2018 Published online: October 31, 2018

1251

A Pan-Cancer Landscape Analysis Reveals a Subset of Endometrial Stromal and Pediatric Tumors Defined by Internal Tandem Duplications of *BCOR*

Luke T. Juckett^a Doug I. Lin^b Russell Madison^a Jeffrey S. Ross^b Alexa B. Schrock^a Siraj Ali^a







HGESS with YWHAE and BCOR abnormalities form a distinct molecular group with NTRK3 mRNA upregulation

Modern Pathology (2021) 34:1008-1016 https://doi.org/10.1038/s41379-020-00705-6

ARTICLE

sarcoma

XUSCAP

Targeted RNA expression profiling identifies high-grade endometrial stromal sarcoma as a clinically relevant molecular subtype of uterine

Amir Momeni-Boroujeni 🖸 • Nissreen Mohammad² • Robert Wolber³ • Stephen Yip 📴 ²⁴ • Martin Köbel⁵ • Brendan C. Dickson 😳 • Martee L. Hensley⁷ • Mario M. Leitao Jr.⁸ • Cristina R. Antonescu 😳 • Ryma Benayed • • Marc Ladanyi • Cheng-Han Lee² • Sarah Chiang¹



Pan-Trk IHC cohort HGESS (n=35)

Pan-Trk IHC expression in >90% of HGESS



CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY



Pathologists make discoveries through observation



1980-2014: High grade transformation of LGESS is observed, but studies lack genotype data

GYNECOLOGIC ONCOLOGY 9, 108-113 (1980)

International Journal of Gynecological Pathology 29:374–377, Lippincott Williams & Wilkins, Baltimore © 2010 International Society of Gynecological Pathologists

CASE REPORT

Case Report

Dedifferentiation of Endolymphatic Stromal Myosis to Poorly Differentiated Uterine Stromal Sarcoma

MCCLURE L. SMITH, M.D.,¹ LOREN L. FAABORG, M.D.,² AND JAMES R. NEWLAND, M.D.³

Transition From Low-grade Endometrial Stromal Sarcoma to High-grade Endometrial Stromal Sarcoma

Yoshiki Ohta, Ph.D., Takao Suzuki, Ph.D., Mutsuko Omatsu, M.D., Shigeharu Hamatani, M.D., Akira Shiokawa, M.D., Miki Kushima, M.D., and Hidekazu Ota, M.D.

J Clin Pathol 1996;49:604-607

Mixed low grade and high grade endometrial stromal sarcoma of uterus: differences on immunohistochemistry and chromosome in situ hybridisation

ORIGINAL ARTICLE

Endometrial Stromal Sarcomas and Related High-grade Sarcomas: Immunohistochemical and Molecular Genetic Study of 31 Cases

Shuichi Kurihara, MD,* Yoshinao Oda, MD, PhD,* Yoshihiro Ohishi, MD, PhD,* Atsuko Iwasa, MD,* Tomonari Takahira, MD, PhD,* Eisuke Kaneki, MD, PhD,† Hiroaki Kobayashi, MD, PhD,† Norio Wake, MD, PhD,† and Masazumi Tsuneyoshi, MD, PhD*

A N-Y Cheung, W-F Ng, L-P Chung, U-S Khoo

Available online at www.sciencedirect.com

Gynecologic Oncology

Gynecologic Oncology 103 (2006) 1137-1140

www.elsevier.com/locate/vgvno

Case Report

Transition of endometrial stromal sarcoma into high-grade sarcoma

Frederic Amant^a,*, Heidi Woestenborghs^b, Vanessa Vandenbroucke^a, Patrick Berteloot^a, Patrick Neven^a, Philippe Moerman^b, Ignace Vergote^a

^a Division of Gynecological Oncology, Department of Obstetrics and Gynecology, UZ Gasthuisberg, Katholieke Universiteit Leuven, Herestraat 49, 3000 Leuven, Belgium
^b Department of Pathology, UZ Gasthuisberg, Katholieke Universiteit Leuven, Belgium

> Received 3 May 2006 Available online 21 August 2006

ORIGINAL ARTICLE

High-grade Endometrial Stromal Sarcomas

A Clinicopathologic Study of a Group of Tumors With Heterogenous Morphologic and Genetic Features

Andrew P. Sciallis, MD,* Patrick P. Bedroske, BSc,† John K. Schoolmeester, MD,* William R. Sukov, MD,*† Gary L. Keeney, MD,* Jennelle C. Hodge, PhD,† and Debra A. Bell, MD*

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Private Information

High grade histologic transformation may occur in ESS harboring LGESS-associated gene fusions

Similar to breast cancer, *ESR1* mutations may play role in endocrine therapy resistance in LGESS

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ESR1 mutations are associated with high grade transformation and endocrine treatment

ESR1 mutations are associated with high grade transformation and endocrine treatment

2002: Is uterine "PEComa" a single entity?

The American Journal of Surgical Pathology 26(1): 1-13, 2002

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Perivascular Epithelioid Cell Tumor ('PEComa') of the Uterus

A Subset of HMB-45-Positive Epithelioid Mesenchymal Neoplasms With an Uncertain Relationship to Pure Smooth Muscle Tumors

Russell Vang, M.D., and Richard L. Kempson, M.D.

Group B "PEComa"

Memorial Sloan Kettering Cancer Center

Group A "PEComa"

Uterine sarcomas may show ESS and "PEComa" histologic features and harbor *TSC2* mutations and *JAZF1::SUZ12* fusion

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www.nature.com/modpathol

ARTICLE

() Check for updates

TSC2-mutant uterine sarcomas with *JAZF1-SUZ12* fusions demonstrate hybrid features of endometrial stromal sarcoma and PEComa and are responsive to mTOR inhibition

Sarah Chiang¹⁸³, Varshini Vasudevaraja², Jonathan Serrano², Colin J. R. Stewart³, Esther Oliva⁴, Amir Momeni-Boroujeni ⁽¹⁾, Achim A. Jungbluth¹, Arnaud Da Cruz Paula⁵, Edaise M. da Silva ⁽¹⁾, Britta Weigelt ⁽¹⁾, Kay J. Park ⁽¹⁾, Robert A. Soslow ⁽¹⁾, Rajmohan Murali ⁽¹⁾, Lora H. Ellenson ⁽¹⁾, Ryma Benayed¹, Marc Ladanyi¹, Nadeem R. Abu-Rustum^{3,7}, Mark A. Dickson^{8,9} Seth Cohen¹⁰, Carol Aghajanian^{9,10}, Martee L. Hensley^{9,10}, Cheng-Han Lee ⁽¹⁾, Matija Snuderl² and Jason A. Konner^{4,10,25}

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Uterine sarcomas may show ESS and "PEComa" histologic features and harbor *TSC2* mutations and *JAZF1::SUZ12* fusion

Case	Age (y)	Initial Diagnosis	Morphology	Gene Fusion	Mutation
P1	46	LGESS	Epithelioid and spindled	JAZF1::SUZ12	TSC2Y429* TSC2L1575P
P2	61	LGESS	Spindled	JAZF1::SUZ12	<i>TSC2</i> 787* <i>TSC2</i> H1019Qfs*135
P3	55	LGESS	Epithelioid and spindled	JAZF1::SUZ12	TSC2 C646* TSC2 W1194*
Ρ4	50	HGESS	Epithelioid	Negative	<i>TSC</i> 2 W358* <i>TSC</i> 2 S1482fs
P5	65	PEComa	Epithelioid	JAZF1::SUZ12	TSC2 exon 11 splicing variant

TSC2-mutant uterine sarcomas cluster with LGESS by methylation and respond to mTOR inhibition

Baseline

Baseline

4od post mTORi

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2011: Unusual cervical sarcomas are described as endocervical fibroblastic malignant peripheral nerve sheath tumor ("MPNST")

Original Article

Endocervical Fibroblastic Malignant Peripheral Nerve Sheath Tumor (Neurofibrosarcoma): Report of a Novel Entity Possibly Related to Endocervical CD34 Fibrocytes

> Anne M. Mills, MD, Jason R. Karamchandani, MD, Hannes Vogel, MD, and Teri A. Longacre, MD

	Case 1	Case 2	Case 3
Age	32	60	25
Site	Cervix	Cervix	Cervix
CD34	+	+	+
S100	+	+	+
SOX10	-	-	-
Desmin	-	-	-
Keratins	-	-	-
ER/ PR	-	-	-

No endoneural or neural differentiation by electron microscopy

Cervical "MPNST" likely represents fibrosarcoma-like uterine sarcoma underpinned by *NTRK* fusions

ORIGINAL ARTICLE

NTRK Fusions Define a Novel Uterine Sarcoma Subtype With Features of Fibrosarcoma

Sarah Chiang, MD,* Paolo Cotzia, MD,* David M. Hyman, MD,† Alexander Drilon, MD,‡ William D. Tap, MD,§ Lei Zhang, MD,* Jaclyn F. Hechtman, MD,* Denise Frosina, BS,* Achim A. Jungbluth, MD, PhD,* Rajmohan Murali, MBBS, MD, FRCPA,* Kay J. Park, MD,* Robert A. Soslow, MD,* Esther Oliva, MD, ||¶ A. John Iafrate, MD, PhD, ||¶ Ryma Benayed, PhD,* Marc Ladanyi, MD,* and Cristina R. Antonescu, MD*

Modern Pathology (2019) 32:1008–1022 https://doi.org/10.1038/s41379-018-0184-6	
ARTICLE	

Uterine and vaginal sarcomas resembling fibrosarcoma: a clinicopathological and molecular analysis of 13 cases showing common *NTRK*-rearrangements and the description of a *COL1A1-PDGFB* fusion novel to uterine neoplasms

Sabrina Croce¹² · Isabelle Hostein¹ · Teri A. Longacre³ · Anne M. Mills ¹0⁴ · Gaëlle Pérot¹ · Mojgan Devouassoux-Shisheboran⁵ · Valérie Velasco¹ · Anne Floquet⁶ · Frédéric Guyon⁷ · Camille Chakiba⁶ · Denis Querleu⁷ · Emmanuel Khalifa¹ · Laetitia Mayeur¹ · Flora Rebier¹ · Sophie Leguellec⁸ · Isabelle Soubeyran¹ · W. Glenn McCluggage⁹

XUSCAP

NTRK fusion fibrosarcoma shows no line of differentiation but may have variable CD34 and S100 expression

Antibody	Staining pattern
Desmin	-
SMA	+ (focal)
ER	-
PR	-
CD34	+/-
S100	+ (varied extent)
SOX10	-
H3K27me3	+

S100

CD34

CD34 and S100 caveats

- Not always reproducible
- Not specific

NTRK fusion fibrosarcoma may respond to Trk inhibition

Uterine sarcoma fusions:

NTRK1: TPM3, LMNA, TPR
 NTRK3: RBPMS, EML4, SPECC1L

Histopathology 2020, 77, 100-111. DOI: 10.1111/his.14069

NTRK fusion cervical sarcoma: a report of three cases, emphasising morphological and immunohistochemical distinction from other uterine sarcomas, including adenosarcoma

Joseph T Rabban, ¹ W Patrick Devine, ¹ Ankur R Sangoi, ² Liina Poder, ³ Edwin Alvarez, ⁴ Jessica L Davis, ⁵ Erin Rudzinski, ⁶ Karuna Garg¹ & Gregory R Bean¹

¹Pathology Department, University of California, San Francisco, CA, ²Pathology Department, El Camino Hospital, Mountain View, CA, ³Radiology Department, University of California, San Francisco, CA, ⁶Gyuteologic Oncology Division, University of California, San Francisco, CA, ⁵Pathology Department, Oregon Health & Science University, Portland, OR, and ⁶Pathology Department, Seattle Children's Hospital, Seattle, WA, USA The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Larotrectinib in TRK Fusion– Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri,
 M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati,
 M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik,
 J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski,
 F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, LE. Raez, J.F. Hechtman, R. Benayed,
 M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox,
 D.S. Hawkins, D.S. Hong, and D.M. Hyman

One patient with *SPECC1L-NTRK3* fusion positive uterine sarcoma s/p polypectomy, doxorubicin/ifosfamide (5 cycles) and pelvic radiation, developed pleural metastasis and had complete radiographic response to larotrectinib

Genotype-phenotype correlation prompts changes in WHO uterine sarcoma classification

Pathologists make discoveries through observation

Clinical behavior of uterine smooth muscle tumors is difficult to predict by pathology criteria

ORIGINAL ARTICLE

Interobserver Variability in the Interpretation of Tumor Cell Necrosis in Uterine Leiomyosarcoma

Diana Lim, MBBS, FRCPath, FRCPA,* Teresa Alvarez, MD,† Marisa R. Nucci, MD,‡ Blake Gilks, MD,§ Teri Longacre, MD, Robert A. Soslow, MD,¶ and Esther Oliva, MD#

Histopathology

Histopathology 2018, 73, 284-298. DOI: 10.1111/his.13515

Predictors of adverse outcome in uterine smooth muscle tumours of uncertain malignant potential (STUMP): a clinicopathological analysis of 22 cases with a proposal for the inclusion of additional histological parameters

Mamta Gupta,^{1,2} Anna L Laury,³ Marisa R Nucci^{2,4} & Bradley J Quade^{2,4} ¹ Department of Pathology, Beth Isnel Duconess Medical Center, ² Harvard Medical School, Roston, MA, ³ Department of Pathology, Cedars-Sinai, Los Angeles, CA, and ⁴ Division of Women's and Perintual Pathology, Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA

Original Article

 (\mathbf{D})

A Nomogram to Predict Postresection 5-Year Overall Survival for Patients With Uterine Leiomvosarcoma

Oliver Zivanovic, MD¹; Lindsay M. Jacks, MS²; Alexia Iasonos, PhD²; Mario M. Leitao, Jr., MD¹; Robert A. Soslow, MD³; Emanuela Veras, MD², Dennis S. Chi, MD²; Nadeem R. Abu-Rustum, MD¹; Richard R. Barakat, MD¹; Murray F. Brennan, MD²; and Martee L. Hensley, MD⁶

Genomic landscape of uterine LMS by NGS identifies novel diagnostic markers

Uterine LMS profiled by MSK-IMPACT during 2014-2020 (n=167)

≥1 genomic landmark: 96% (n=160/167)
≥2 genomic landmarks: 80% (n=133/167)

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Uterine LMS genomic landmarks are detectable by immunohistochemistry (IHC)

IHC interpretation of surrogate markers correlates with NGS profiles and is reproducible

Molecular-based IHC is sensitive and specific in confirming LMS with ≥2 abnormal markers

	≥1 abnormal IHC	≥2 abnormal IHC
True positive (%)	100	92
False negative (%)	0	8
False positive (%)	18	0
True negative (%)	82	100
Sensitivity (%)	100	92
Specificity (%)	82	100

CASE 1 – patient seeking 2nd opinion at MSK

41 year old woman with fibroid uterus – outside slides reviewed at MSK

Outside pathology reports:

Myomectomy 2014

Cellular leiomyoma with bizarre nuclei and ischemic changes Note: Diffuse atypia, MI <3/10 HPF, infarct necrosis. Some pathologists may diagnose STUMP.

Total abdominal hysterectomy and bilateral salpingooophorectomy 2018

STUMP

Note: Diffuse atypia, MI <3/10 HPF, infarct necrosis, no LVI

Left 10th rib biopsy 2020

Low-grade spindle cell neoplasm similar to uterine primary

Molecular-based IHC on hysterectomy specimen

P53	Wildtype
ATRX	Loss
Rb	Loss
PTEN	Retained

Diagnosis: LMS

Hysterectomy specimen

Unpublished data

CASE 2 – MSK pathology consultation

46 year old woman with fibroid uterus – outside slides reviewed at MSK

Outside preliminary pathology report:

Supracervical hysterectomy and bilateral salpingo-oophorectomy

9 cm submucosal small round blue cell tumor, favor ESS

Mild atypia MI 7/10 HPF No necrosis

CD10	Negative	HMB ₄₅	Positive (rare)
ER	Positive (weak)	Melan A	Negative
PR	Positive (weak)	Cyclin D1	Negative
Desmin	Positive	OSCAR	Negative
SMA	Positive (weak)	AE1/AE3	Negative
Caldesmon	Positive	Inhibin	Negative
Myogenin	Negative	FLI1	Negative
CD34	Negative	CD99	Positive

Outside IHC

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CASE 3 – MSK pathology consultation

51 year old woman with fibroid uterus – outside slides reviewed at MSK

Outside pathology reports:

Total abdominal hysterectomy, bilateral salpingo-oophorectomy, sigmoidectomy, omentectomy, peritonectomy 2020 High grade poorly differentiated uterine sarcoma, 8 cm, transmurally invasive of the uterine and colonic walls with spread to left ovary and tube

CD10	Positive	Myogenin	Negative	LCA	Negative
ER	Positive	MyoD1	Negative	CD ₃₄	Negative
PR	Positive	S100	Negative	ERG	Negative
Desmin	Positive	SOX10	Negative	WT1	Negative
SMA	Positive	MDM2	Negative	E-cadherin	Negative
Caldesmon	Positive	CDK4	Negative	DOG1	Negative
Cyclin D1	Negative	AE1/AE3	Negative	cKIT	Negative

Outside IHC

Marked atypia MI 51/10 HPF Necrosis

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CASE 3 – MSK pathology consultation

51 year old woman with fibroid uterus – outside slides reviewed at MSK

Outside pathology reports:

Cervical polypectomy 2012

Most consistent with prolapsed submucosal uterine leiomyoma

Retrospective re-review: Was this 2012 "leiomyoma" related to the 2020 stage IV uterine sarcoma?

Outside IHC

Desmin	Positive
SMA	Positive
ER	Positive
PR	Positive
CD ₃₄	Negative
Caldesmon	Positive

Molecular-based IHC on hysterectomy specimen

	Polypectomy	Hysterectomy
P53	Null	Null
ATRX	Loss	Loss
Rb	Retained	Retained
PTEN	Loss	Loss

Diagnosis:

2020 specimens: LMS with epithelioid and myxoid features 2012 specimen: Atypical spindle cell neoplasm, likely incipient LMS

Private Information

Molecular-based IHC may be implemented in surgical pathology practice in lieu of NGS

+ - p53 is mutually exclusive with MDM2 and MTAP; if p53 is abnormal, MDM2 and MTAP should not be orderd.

- ATRX is mutually exclusive with DAXX; if ATRX is abnormal, DAXX should not be ordered.

In summary, pathologists make a huge impact on patient care by observing disease frozen in time

Gene fusions define novel uterine sarcoma subtypes with distinctive histologies

Next generation sequencing may uncover therapeutic targets and clinical biomarkers

Molecular-based IHC can aid evaluation of challenging uterine smooth muscle tumors

Memorial Sloan Kettering Cancer Center

Molecular Laboratory Marc Ladanyi Ryma Benayed

GYN Research Laboratory Britta Weigelt Pier Selenica Arnaud Da Cruz Paula

GYN Pathology

Robert Soslow Kay Park Rajmohan Murali Lora Ellenson Amir Momeni-Boroujeni M. Herman Chui

Pathology

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GYN Medical Oncology

Martee Hensley Jason Konner

GYN Surgery

Nadeem Abu-Rustum Mario Leitao, Jr. Kimberly Dessources Kathryn Miller Charles Ashley

Molecular Pathology Matija Snuderl Varshini Vasudevaraja Jonathan Serrano

Colin Stewart

King Edward Memorial Hospital

Women and Newborn Health Service

Esther Oliva Robert Young

Generative of alberta FACULTY OF MEDICINE & DENTISTRY

Cheng-Han Lee

In summary, pathologists make a huge impact on patient care by observing disease frozen in time

Gene fusions define novel uterine sarcoma subtypes with distinctive histologies

Next generation sequencing may uncover therapeutic targets and clinical biomarkers

Molecular-based IHC can aid evaluation of challenging uterine smooth muscle tumors

Thank you

