

# **NTRK and S100 staining to report *NTRK* fusion sarcoma of the cervix**

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# Disclosure of relevant financial relationships

No relevant financial relationships

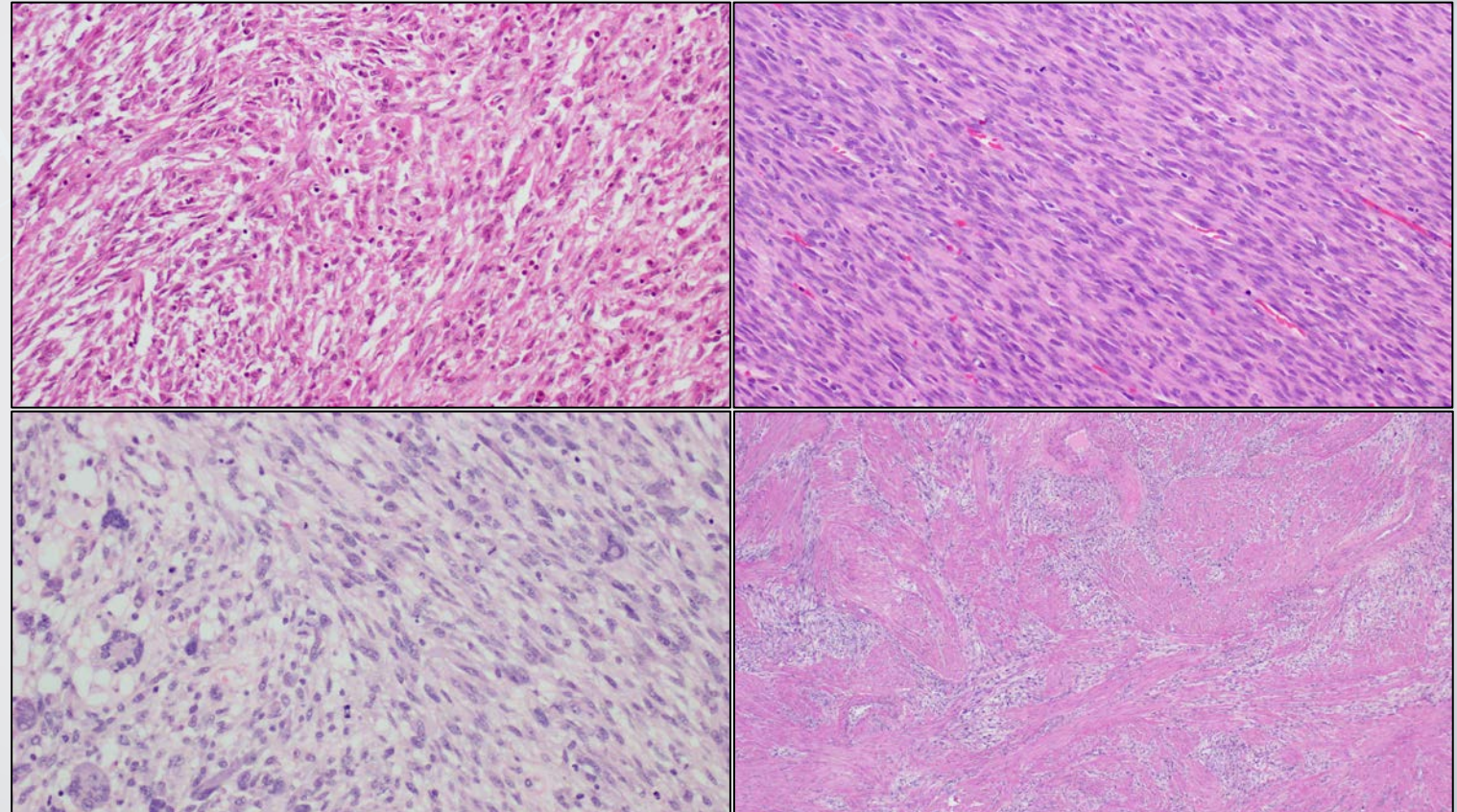


# *NTRK* fusion-positive uterine sarcoma is a distinct clinicopathologic entity

**Median age**  
32 y

**FIGO stage**  
IA: 7 (50%)  
IB: 6 (43%)  
IIB: 1 (7%)

**Cervix origin**  
93%



Chiang S, et al. Am J Surg Pathol 2018;42:791-8

Croce S, et al. Mod Pathol 2019;32:1008-22

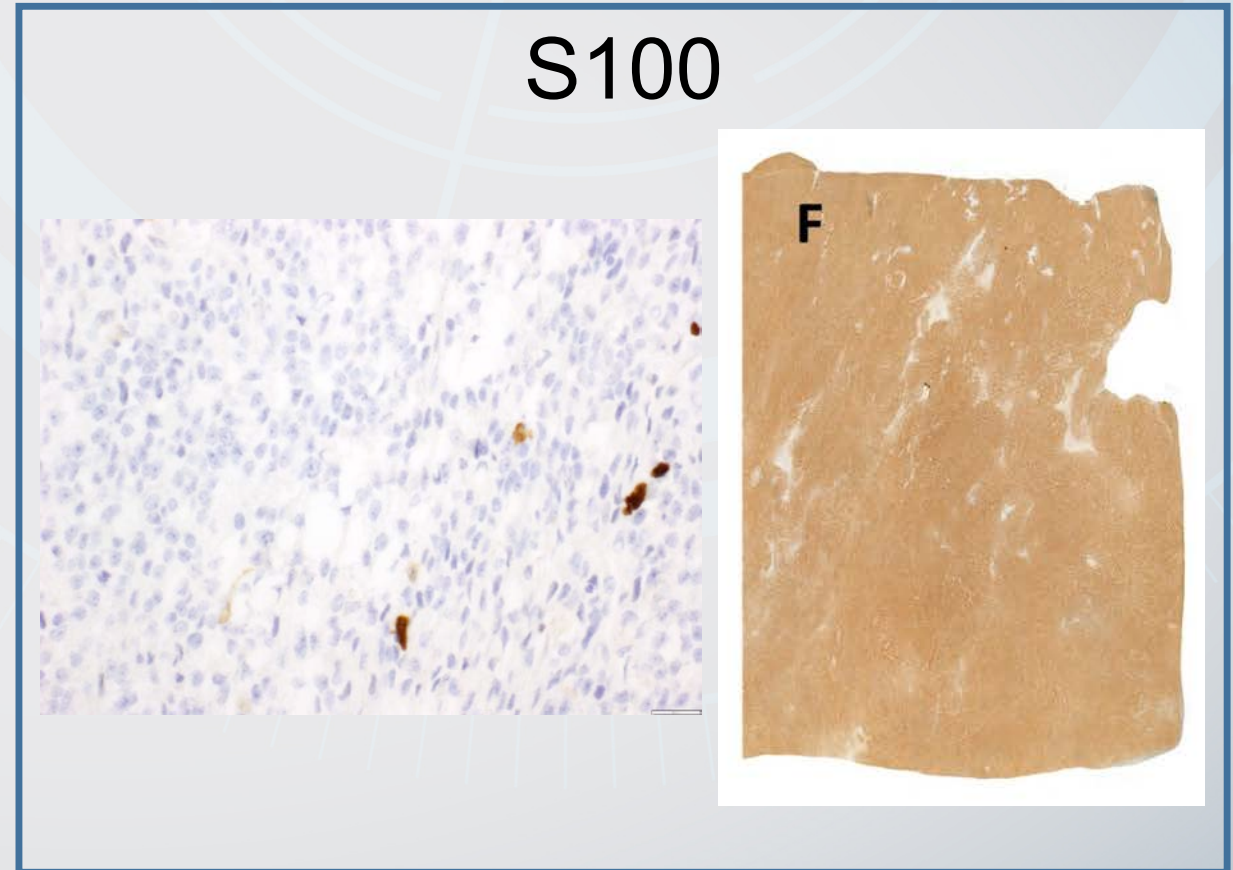
Hodgson A, et al. Int J Gynecol Pathol 2020;Epub ahead of print

Rabban JT, et al. Histopathol 2020;Epub ahead of print

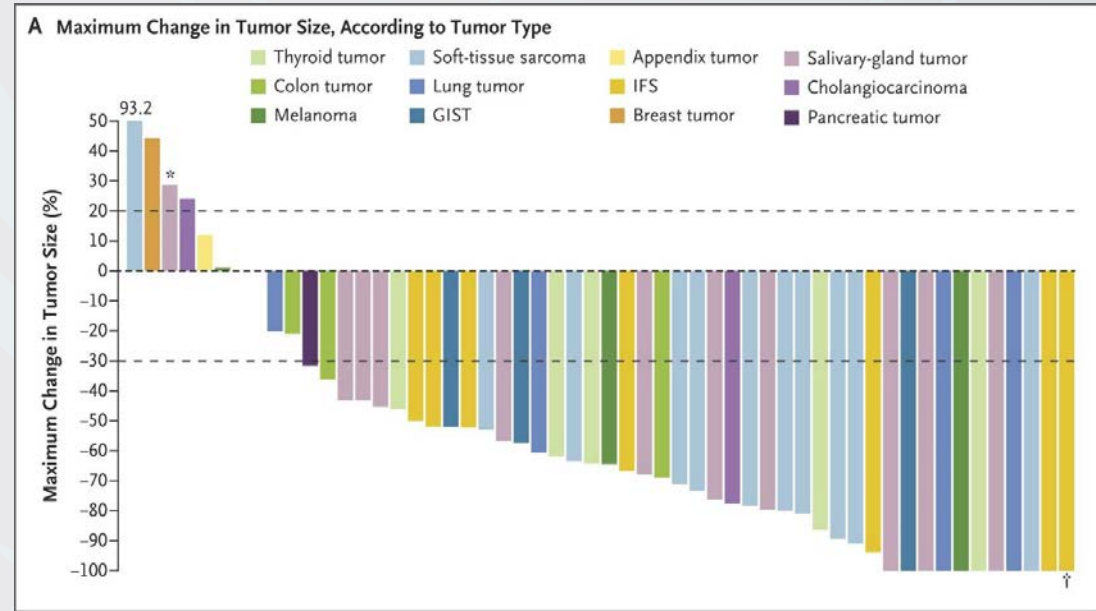
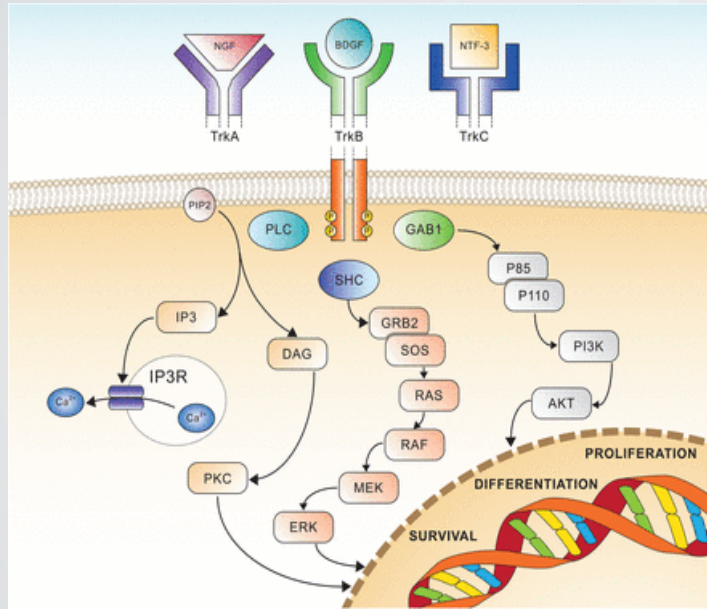


# *NTRK* fusion-positive uterine sarcomas lack evidence of cellular differentiation

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



# Uterine sarcoma subtype is defined by *NTRK* fusion and targetable by Trk inhibition



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

Chiang S, et al. Am J Surg Pathol 2018;42:791-8  
 Drilon A, et al. N Engl J Med. 2018;378:731-9  
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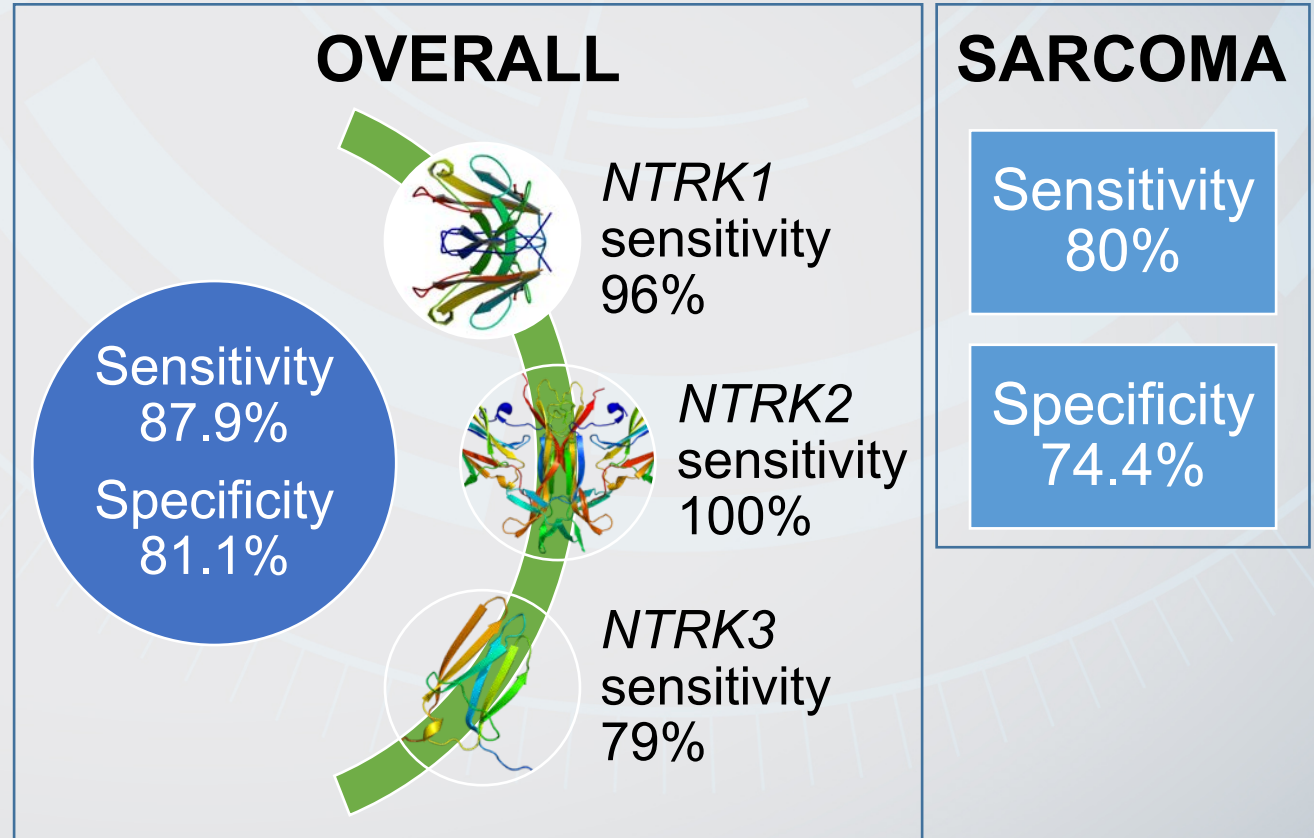
# Pan-Trk immunohistochemistry is a potential screen for *NTRK* fusion

Pan-Trk monoclonal antibody clone EPR 17341 (Abcam, Roche/Ventana)

Reactive to homologous region of TrkA, B and C near C terminus

Expressed in testis, neural tissue, smooth muscle

>1% of tumor cell staining = positive result



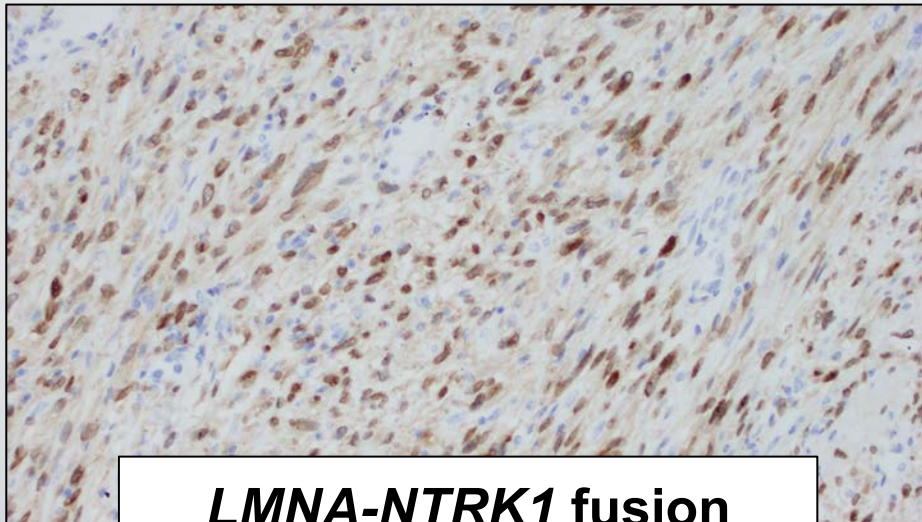


# Trk staining patterns vary due to different fusion partners

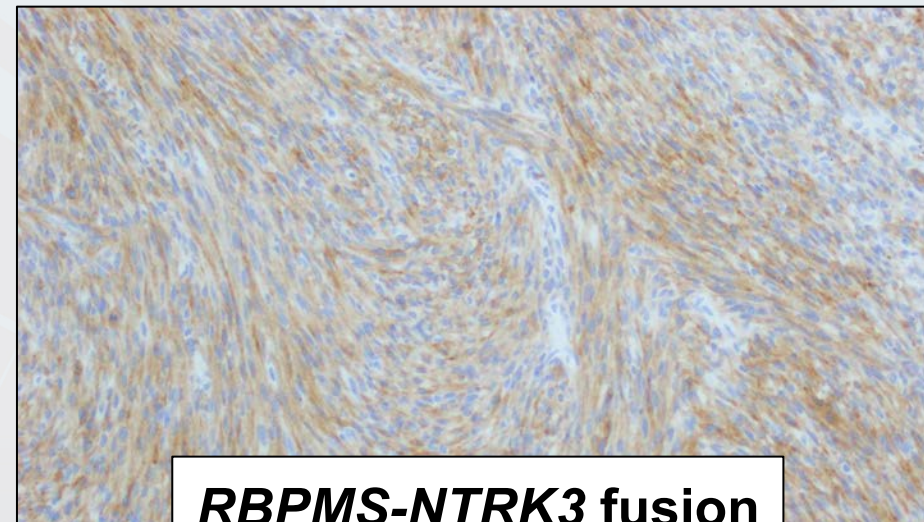
## Uterine sarcoma fusions:

*NTRK1: TPM3, LMNA, TPR, SPECC1L*

*NTRK3: RBPMS, EML4*

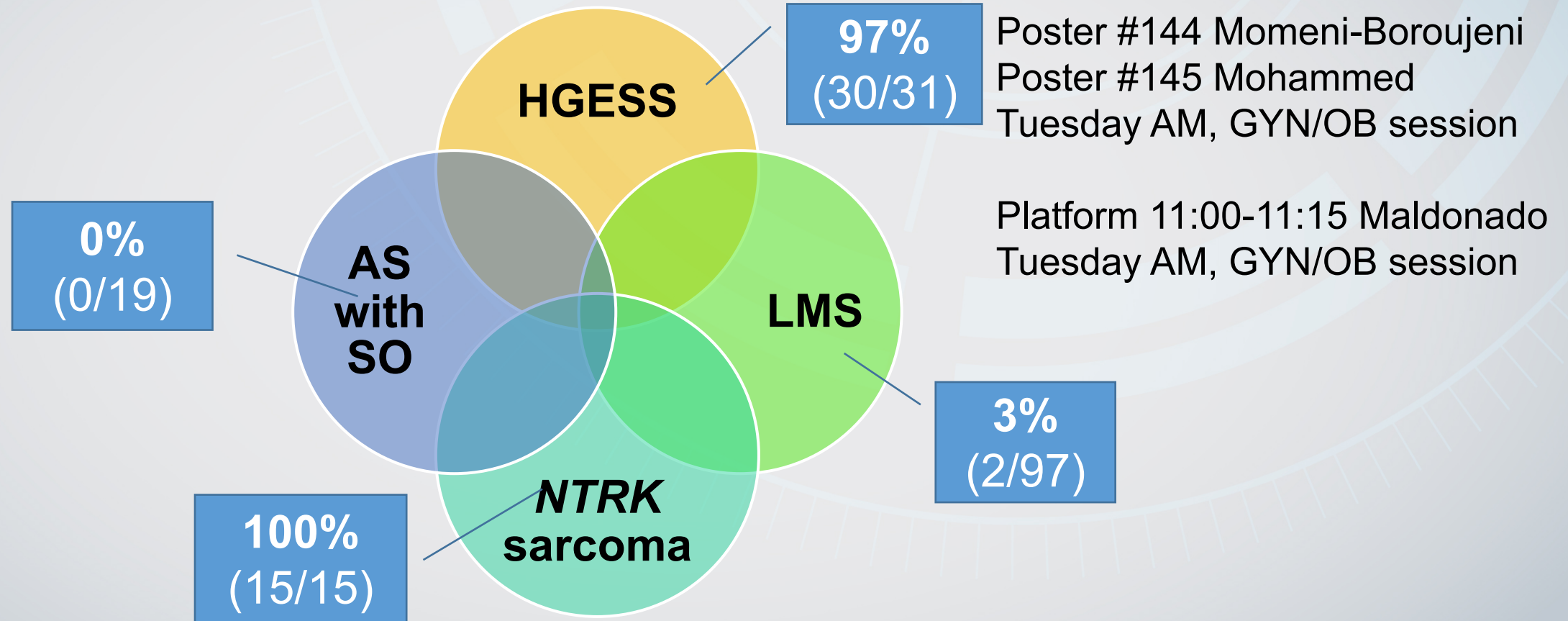


***LMNA-NTRK1* fusion**  
Cytoplasmic and perinuclear



***RBPMS-NTRK3* fusion**  
Cytoplasmic only

# Trk expression may be seen in morphologic mimickers



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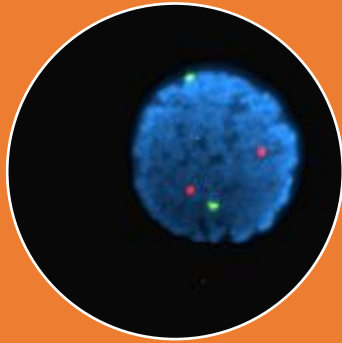
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# Trk expression requires confirmation of *NTRK* fusion by molecular methods



FISH



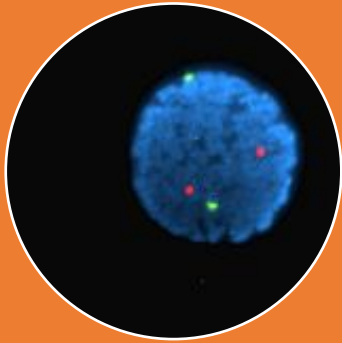
DNA-based  
NGS



RNA-based  
NGS



# Trk expression requires confirmation of *NTRK* fusion by molecular methods



FISH



## PRO

Commercially available probes  
Requires less material  
Short TAT

## CON

False-negatives with *NTRK1*



# Trk expression requires confirmation of *NTRK* fusion by molecular methods



DNA-  
based  
NGS



## PRO

Assessment of other genetic alterations  
Monitor for resistance mutations

## CON

Longer TAT  
Requires more material  
Requires intronic coverage  
Cannot determine functional expression  
Less sensitive than RNAseq

# Trk expression requires confirmation of *NTRK* fusion by molecular methods



RNA-  
based  
NGS



## PRO

- Intronic coverage not needed
- Detects functionally transcribed fusions
- Permits fusion discovery
- More sensitive than DNAseq

## CON

- Limited by RNA quality
- Longer TAT
- Requires more material



# Algorithm for *NTRK* fusion detection in uterine sarcoma depends on available test modalities

RNA sequencing is preferred

- Comprehensive fusion testing increasingly used as first-line test for sarcoma

Pan-Trk immunohistochemistry should be used with caution

- Lower specificity in sarcoma
- Trk expression observed in HGESS and uterine LMS

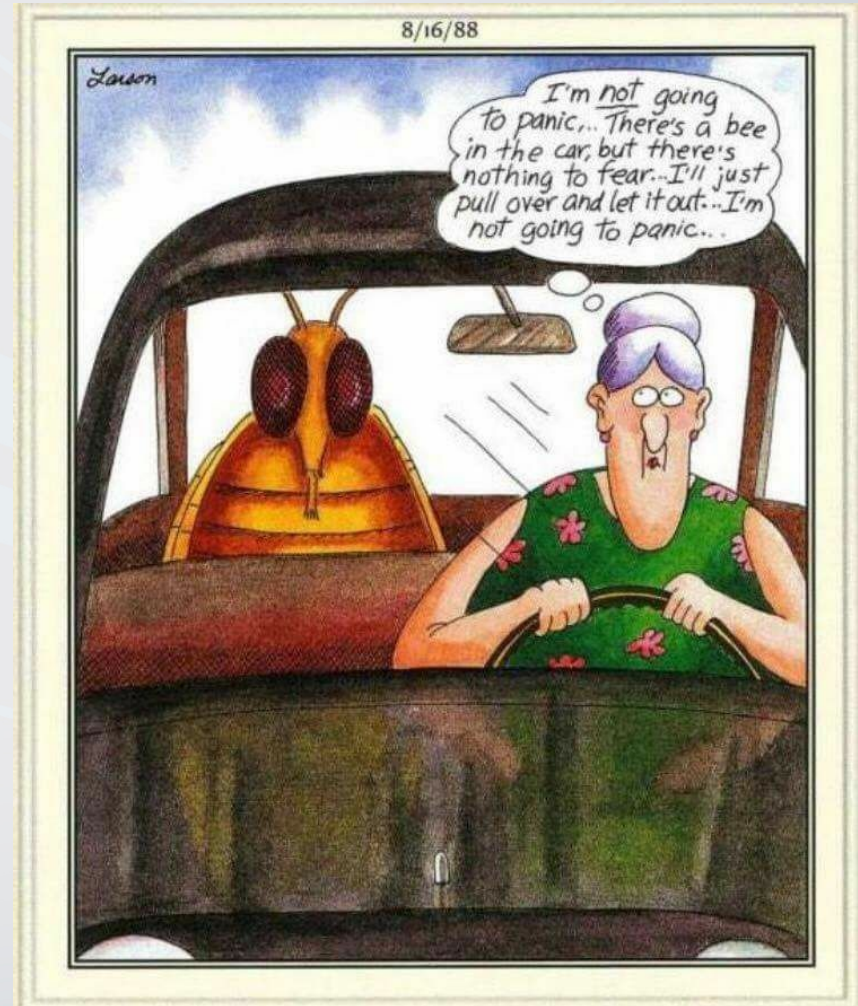
# Stakes are high in diagnosing *NTRK* fusion-positive uterine sarcomas

Rare disease

Morphologic heterogeneity

No quick and easy screening test

Treatment implications





# Join the uterine sarcoma profiling initiative!



***Goal: Integrated genetic, epigenetic and pathological diagnosis for uterine sarcoma***

- Network of gynecologic pathology departments sharing data and samples
- Collaborators can send clinical or research cases for profiling
  - MSK-IMPACT: matched tumor-normal DNA NGS of 468 genes
  - MSK Solid Fusion Assay: RNA NGS of 68 genes
  - Methylation MSK/NYU/Stanford: whole genome DNA methylation for molecular diagnosis and subclassification
- Share unclassifiable cases to establish new tumor entities

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