

Assessment of Pathology Features in the Revised Bethesda Guidelines

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Amsterdam Criteria

To provide a standardized classification of HNPCC families presenting to high-risk clinics

Bethesda Guidelines

To identify CRC presenting in the population setting that should be tested for DNA MSI

Revised Bethesda Guidelines for MSI testing of CRC

- Less than 50 years of age at diagnosis
- Multiple CRC or HNPCC-related cancer
- MSI-H pathology and <60 years
- Relative with CRC or HNPCC-related cancer aged less than 50 yrs
- Two relatives with CRC or HNPCC-related cancer, any age

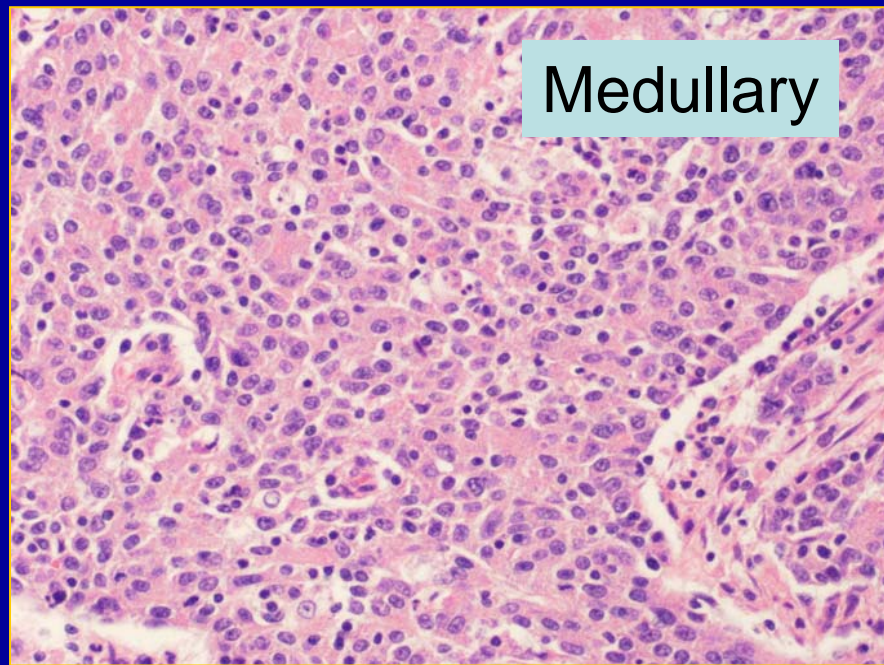
Pathology Features in Revised BG

- Medullary, Mucinous & Signet Ring Cell types
- Lymphocytic infiltration
 - Tumor infiltrating (TILs)
 - Crohn-like reaction (CLR)

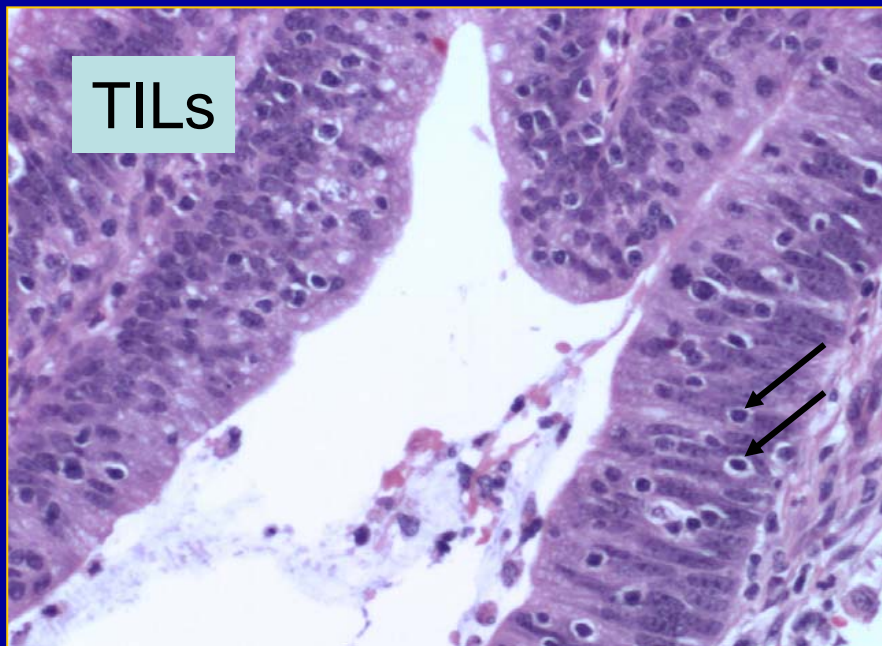
Mucinous



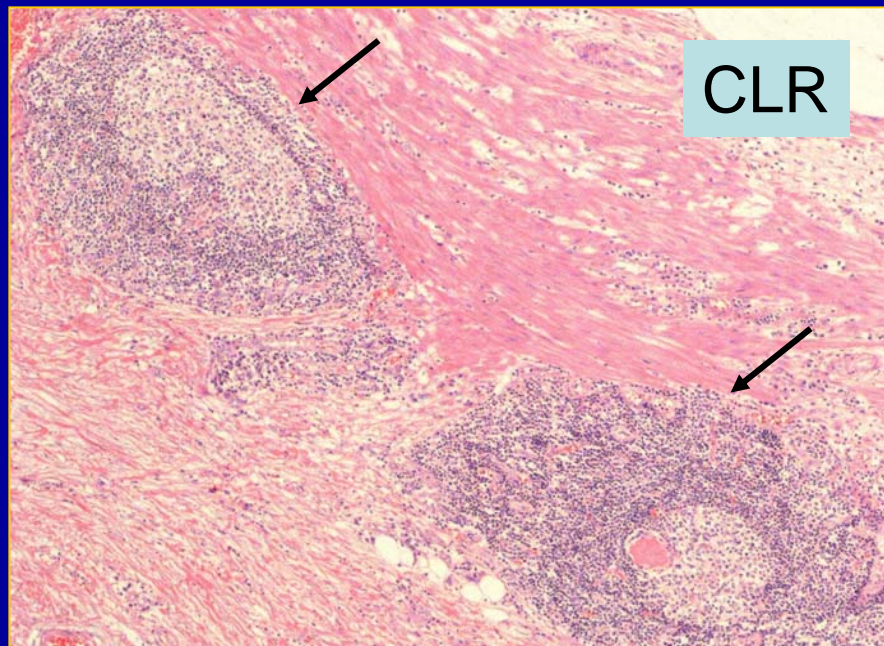
Medullary



TILs



CLR



Aim of study

- Identify pathology features that can predict MSI-H status in CRCs presenting in population-based subjects aged <60 years
- Predictive model based on independent features
- % of HNPCC identified by pathology that would otherwise have been missed

MSI-H testing

- **10 MS markers**
- **At least 4/10 evaluable**
- **Instability in 30% for MSI-H**
- **556 evaluable CRCs from Hawaii, Mayo & Australia**

Results

<i>MSI-H</i>	<i>MSI-L</i>	<i>MSS</i>	<i>Total</i>
72	66	418	556

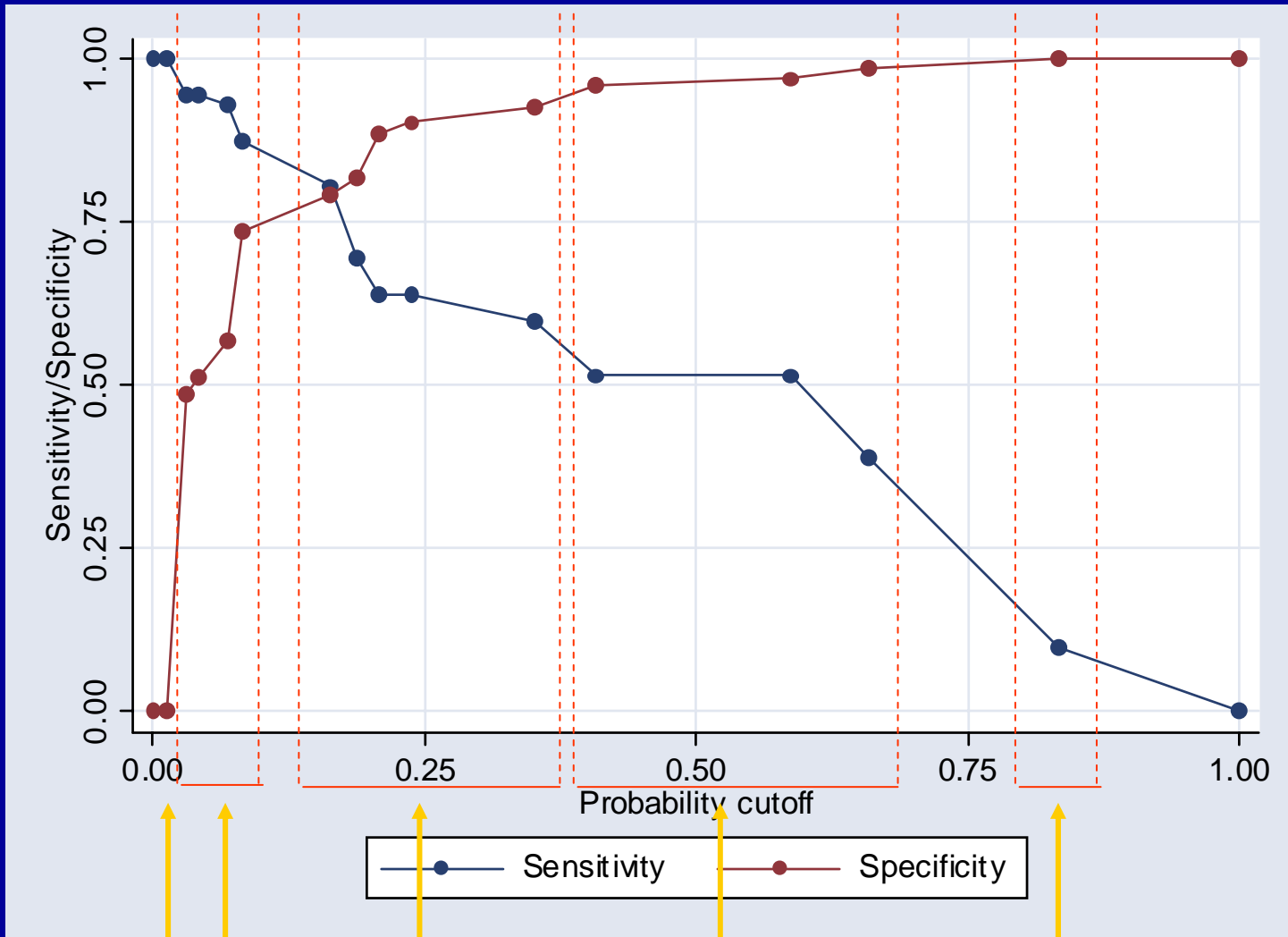
Predictors of MSI-H status: multivariate analysis

Feature	OR (95% CI)
TILs	7.3 (3.8-14.0)
Proximal	6.2 (3.2-11.7)
Crohn	3.5 (1.8-7.1)
Mucinous	2.6 (1.3-5.1)

MS-Path Score and increasing frequency of MSI-H status

Score	Proportion	MSI-H
0	43%	2%
1-2	29%	3-8%
2.3-3.8	18%	11-35%
4.1-5.1	9%	43-67%
6.1	1%	85%

Score is total for TILs (2.0), Proximal (1.8), Crohn (1.3), and Mucinous (1.0)



Minimum number of pathology features present

'MSI-H' cases 'missed' by pathology

Age	Markers	Monos	MMR
55	3/10	No	Normal
41	2/5	No	Normal
45	3/9	No	Normal
22	7/10	Yes	Abnormal*

**Loss of MLH1 and PMS2*

Distribution of MSI

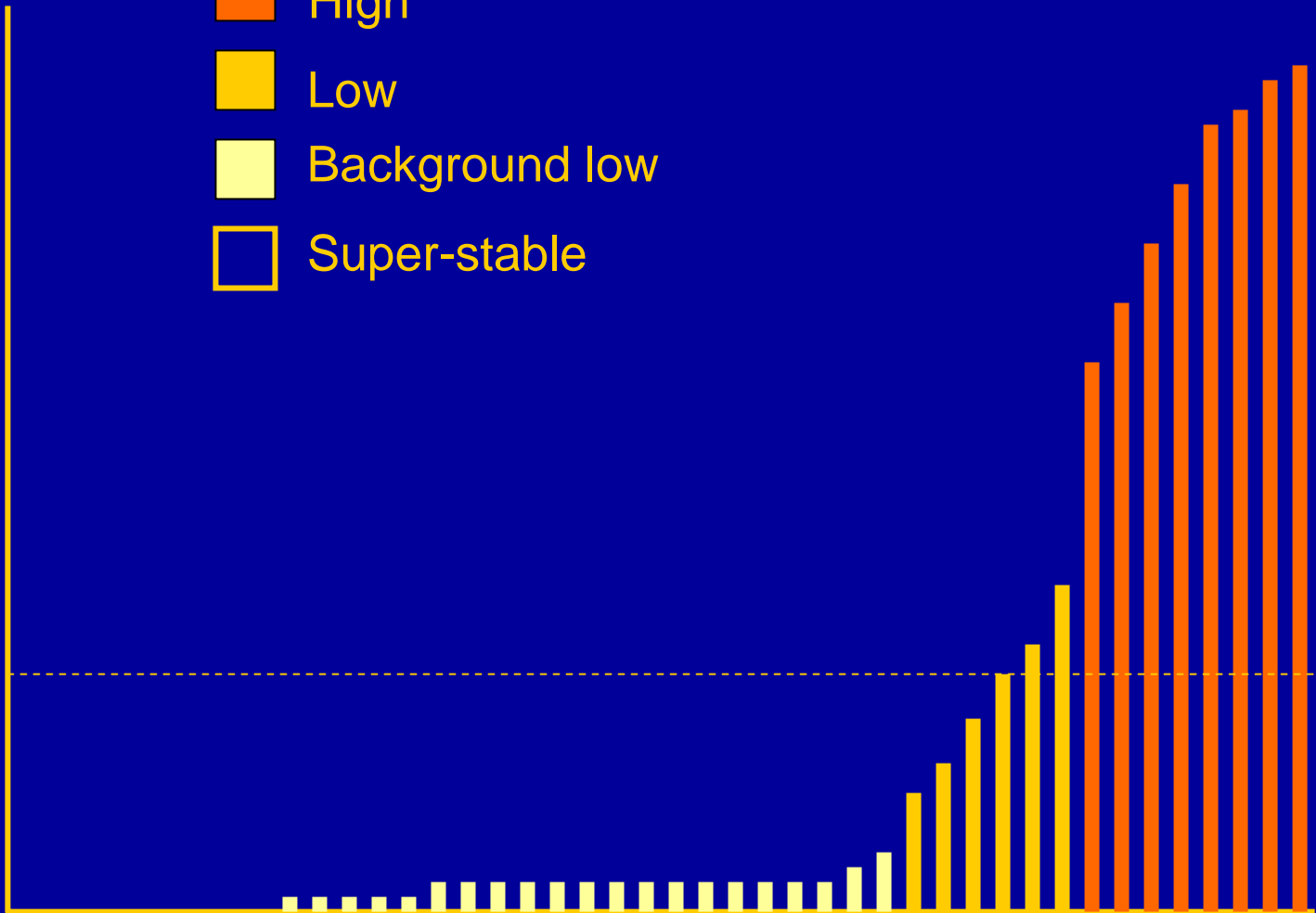
% of markers

100

30

- High
- Low
- Background low
- Super-stable

Cancers



**Evaluation of MS-Path score
for predicting MSI-H status
Zero versus One or More
(after re-assigning 3 cases)**

Sens	Spec	PPV	NPV
99%	49%	21%	99%

Conclusion

- Pathology is highly sensitive for MSI-H status (99%)
- No need to test CRCs (43%) that lack pathology features
- Pathology identifies MSI-H CRCs between age 50-59 that may be due to HNPCC

ROC Curve for Ms-Path Test

