ADJUVANT SETTINGS OF COLON CANCER

RAS, BRAF: Microsatellite instability and other molecular markers – How useful are they? Pitfalls in diagnostic?

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No conflict of interest
AGENDA

- Precursor lesions of colorectal cancer and their association with molecular phenotype
- Microsatellite instability and Lynch Syndrome
- Analysis of relevant mutations (RAS, BRAF et al.) including diagnostic pitfalls
Tubular adenomas are the most common group of conventional adenomas detected during population screening. A small villous component (<25%) is acceptable in tubular adenomas.

Villous structures resembling small intestinal villi in >25% of the adenoma is required for the diagnosis of tubulovillous adenoma.

If >75% of the adenoma has a villous architecture, it is diagnosed as villous adenoma.
CONVENTIONAL ADENOMA

APC/β-catenin → KRAS → TP53, PIK3CA

Normal mucosa → Aberrant crypt focus → Early adenoma → Late adenoma → Invasive Carcinoma

Increasing chromosomal instability

SERRATED LESIONS AND POLYPS

Hyperplastic polyp (A): the microvesicular hyperplastic polyp (BRAF mut.) and the goblet cell-rich hyperplastic polyp (KRAS mut.) are the most common subtypes.

Sessile serrated lesion (B, SSL; formerly sessile serrated adenoma/polyp, SSA/P): the lesion is BRAF mut. and progresses via MSI (75%, methylation of MLH1) and MSS (25%) pathways.

Traditional serrated adenoma (TSA): presents typically as polypoid lesion within the distal colon.

Development occurs “de novo” (potentially from goblet cell-rich HP) with KRAS mutation as main driver or from a serrated precursor lesion (HP, SSL) with BRAF mutation as main driver.

Occurrence of “overt dysplasia” is the hallmark of tumour progression and may occur as consequence of secondary mutations (e.g. TP53).
SERRATED LESIONS AND POLYPS

SERRATED LESIONS AND POLYPS

SERRATED LESIONS AND POLYPS

Type 1 (7%)
Microsatellite instability [MSI]–high, CpG island methylator phenotype [CIMP] positive, positive for BRAF mutation, negative for KRAS mutation

Type 2 (4%)
Microsatellite stable [MSS] or MSI-low, CIMP-positive, positive for BRAF mutation, negative for KRAS mutation

Type 3 (26%)
MSS or MSI low, non-CIMP, negative for BRAF mutation, positive for KRAS mutation

Type 4 (47%)
MSS or MSI-low, non-CIMP, negative for mutations in BRAF and KRAS

Type 5 (4%)
MSI-high, non-CIMP, negative for mutations in BRAF and KRAS

Other (12%)

Phipps et al. Gastroenterology 2015
SERRATED LESIONS AND POLYPS

Fig. 11 Invasive carcinoma arising from serrated precursors. 

Table 4 Colorectal carcinomas associated with serrated precursors

<table>
<thead>
<tr>
<th>Type</th>
<th>CpG methylation</th>
<th>Prognosis</th>
<th>Precursor</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF mutated, mismatch repair deficient</td>
<td>++++</td>
<td>Good</td>
<td>Sessile serrated polyp</td>
<td>10–15%</td>
</tr>
<tr>
<td>KRAS mutated, mismatch repair proficient</td>
<td>+</td>
<td>Intermediate</td>
<td>Traditional serrated adenoma</td>
<td>Unknown</td>
</tr>
<tr>
<td>BRAF mutated, mismatch repair proficient</td>
<td>++++</td>
<td>Poor</td>
<td>Sessile serrated polyp or traditional serrated adenoma</td>
<td>5%</td>
</tr>
<tr>
<td>BRAF/KRAS wild-type, mismatch repair deficient</td>
<td>++++</td>
<td>Good</td>
<td>Sessile serrated polyp</td>
<td>5–0%</td>
</tr>
</tbody>
</table>
MOLECULAR PATHOLOGY OF COLORECTAL CANCER

Bettington et al. Histopathology 2013
MOLECULAR PATHOLOGY OF COLORECTAL CANCER

Bettington et al. Histopathology 2013
MOLECULAR PATHOLOGY OF COLORECTAL CANCER

Bettington et al. Histopathology 2013
SPECIAL ISSUES IN MOLECULAR PATHOLOGY

- Microsatellite instability (MSI)
  - Familial setting: Lynch syndrome
  - Sporadic setting: CpG island methylator phenotype (CIMP) with widespread genome hypermethylation, resulting in epigenetic inactivation of tumour suppressor genes, e.g. hypermethylation of the MLH1 gene promoter ("serrated route" to cancer)

- Further relevant genes
  - KRAS / NRAS
  - BRAF
  - Other relevant genes

- Consensus molecular subtypes (CMS 1-4)
**MICROSATELLITE INSTABILITY (MSI)**

- Microsatellites are short repetitive sequences (e.g. tandem repeats) of DNA distributed throughout the genome that are commonly shortened (and display length variation, microsatellite instability, MSI) in the setting of deficient mismatch repair (dMMR) protein activity.
- The most commonly altered DNA MMR genes are MLH1, MSH2, MSH6 and PMS2, with >90% having alterations in MLH1 and MSH2.
- Secondary to dMMR status these tumours develop 100 to 1000s of mutations (→ enhanced neoantigen load) leading to the potential for enhanced immune recognition (→ candidates for immunotherapy)

Lynch Syndrome is a hereditary disorder caused by a *germline mutation in a MMR gene* in which affected individuals have a higher than normal chance of developing colorectal cancer, endometrial cancer, and various other types of cancers, often at a young age.
TWO EVENTS ARE NECESSARY TO INACTIVATE A MMR ENZYME

Steinke. Dtsch Arztebl Int 2013

<table>
<thead>
<tr>
<th>Lynch Syndrome: Tumour Spectrum</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>34-73%</td>
<td>32-59%</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>-</td>
<td>39-50%</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>-</td>
<td>7-8%</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>1-6%</td>
<td></td>
</tr>
<tr>
<td>Cancer of renal pelvis / ureter</td>
<td>2-8%</td>
<td></td>
</tr>
<tr>
<td>Cancer of the bile ducts</td>
<td>1-4%</td>
<td></td>
</tr>
<tr>
<td>Cancer of the small bowel</td>
<td>1-4%</td>
<td></td>
</tr>
<tr>
<td>CNS tumours</td>
<td></td>
<td>approximately 2%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td></td>
<td>approximately 4%</td>
</tr>
<tr>
<td>Tumours of the sebaceous glands (Muir-Torre)</td>
<td></td>
<td>depends on affected gene</td>
</tr>
</tbody>
</table>
FEATURES THAT RAISE SUSPICION OF AN MSI TUMOUR

- **Clinical features**
  - Age < 60
  - Right-sided location
  - Multiple (synchronous or metachronous) CRCs

- **MSI-H histology**
  - Type: medullary, mucinous (“any mucin”), signet ring cell (“any signet ring cell”)
  - Inflammation: tumour-infiltrating lymphocytes (TILs), peritumoural lymphocytes, lymph follicles (“Crohn-like reaction”)
  - Histology: poor differentiation, expansive growth (“pushing border”), heterogeneity, no necrosis
MICROSATELLITE INSTABILITY TESTING

Colorectal cancer surgical specimen

- (MSI testing)¹

  - MSI-high

  - IHC testing

  - Normal

  - No further testing

  - Loss of MHL1 & PMS2

  - Loss of other MMR proteins

  - BRAF testing (and/or promoter hypermethylation testing)

  - Presence of BRAF mutation (and/or presence of MLH1 promoter hypermethylation)

  - Refer to genetic counseling for consideration for germline testing (guided by IHC testing results)

  - Absent BRAF mutation (and/or MLH1 promoter hypermethylation)

¹ MSI (microsatellite instability testing) is an alternative to immunohistochemistry testing
### Table VI. Mismatch repair (MMR) function testing in colorectal cancer (modified after Bellizzi [108])

<table>
<thead>
<tr>
<th>Immunohistochemistry</th>
<th>Frequency</th>
<th>Interpretation</th>
<th>Action(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All four proteins intact</td>
<td>80 to 85%</td>
<td>Normal MMR function (Lynch syndrome unlikely)</td>
<td>Consider additional MSI testing in cases with high clinical suspicion for the presence of Lynch syndrome</td>
</tr>
<tr>
<td>MLH1/PMS2 lost and MSH2/MSH6 intact</td>
<td>15%</td>
<td>Abnormal MMR function</td>
<td>BRAF V600E and/or MLH1 promoter methylation testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Likely sporadic MMR deficiency due to MLH1 promoter methylation</td>
<td>If the above are normal, refer to genetic counseling for MLH1 germline testing (followed by PMS2 if needed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less likely Lynch syndrome due to MLH1 (usually) or PMS2 (rarely) germline mutation</td>
<td></td>
</tr>
<tr>
<td>MSH2/MSH6 lost and MLH1/PMS2 intact</td>
<td>1 to 2%</td>
<td>Abnormal MMR function</td>
<td>Refer to genetic counseling for MSH2 germline testing (followed by MSH6 if needed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Likely Lynch syndrome due to MSH2 (usually) or MSH6 (rarely) germline mutation</td>
<td></td>
</tr>
<tr>
<td>MSH6 lost and MLH1/PMS2/MSH2 intact</td>
<td>Up to 0.5%</td>
<td>Abnormal MMR function</td>
<td>Refer to genetic counseling for MSH6 germline testing (followed by MSH2 if needed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Likely Lynch syndrome due to MSH6 (usually) or MSH2 (rarely) germline mutation</td>
<td></td>
</tr>
<tr>
<td>PMS2 lost and MLH1/MSH2/MSH6 intact</td>
<td>Up to 0.5%</td>
<td>Abnormal MMR function</td>
<td>Refer to genetic counseling for PMS2 germline testing (followed by MLH1 if needed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Likely Lynch syndrome due to PMS2 (usually) or MLH1 (rarely) germline mutation</td>
<td></td>
</tr>
</tbody>
</table>
MICROSATELLITE INSTABILITY AND IMMUNOTHERAPY

- MSI testing can assist clinicians in genetic counselling.
- MSI-H/dMMR patients have a proven better prognosis in stage II and III than low frequency MSI (MSI-L) or microsatellite stable (MSS) patients.
- MSI testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC (tumor mutational burden)
GENOMIC LANDSCAPE OF COLORECTAL CANCER

Genes mutated in colorectal cancer

Wood et al. Science 2006
GENOMIC LANDSCAPE OF COLORECTAL CANCER

Wood et al. Science 2006
Molecular testing in colorectal cancer: standard of care

- RAS mutational status (KRAS, NRAS) is a predictive biomarker for therapeutic choices involving EGFR antibody therapies in the metastatic setting (mandatory before initiating therapy)
- Primary tumors as well as metastatic sites (liver > lymph node) can be used for testing
- Mutations of BRAF, KRAS, and NRAS are mutually exclusive, whereas mutations of the PI3K pathway may overlap with mutations in BRAF, KRAS, and NRAS
THE RAS (KRAS, NRAS) FAMILY

Distribution of somatic mutations in KRAS

Courtesy to Prof. Gerald Höfler, MU Graz, Austria
THE RAS (KRAS, NRAS) FAMILY

Ion AmpliSeq™ Colon and Lung Cancer Research Panel v2

KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBX7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2

Courtesy to Prof. Gerald Höfler, MU Graz, Austria
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Courtesy to Prof. Gerald Höfler, MU Graz, Austria
THE RAS (KRAS, NRAS) FAMILY

Distribution of mutations in KRAS / NRAS genes in patients with colorectal cancer analysed at the Institute of Pathology, MU Graz (6/2013 – 9/2014)
352 tests

Overall, the following mutation frequencies may be expected
KRAS 45%
NRAS 5-10%

Courtesey to Prof. Gerald Höfler, MU Graz, Austria
BRAF (V600E)

- BRAF is a serine/threonine kinase downstream of RAS in the RAS/RAF/MEK/ERK pathway.
- Mutations are found in about 10% of CRC patients with the majority V600E which leads to constitutive activation of BRAF and the downstream signaling pathway.
- Two thirds of BRAF mutant primary cancers are found on the right side (home of SSL).
- BRAF mutation – indicator of poor prognosis?
  - Significant negative prognosticator in stage IV, but has principally to be related to MSS/MSI status (negative predictor in MSS cancers) → need for aggressive/additional therapy? BRAF inhibitors unsatisfactory (unlike malignant melanoma).
  - Data on response to anti-EGFR therapy inconsistent.
  - Non-V600E mutations may indicate good prognosis (some mutations inactivate BRAF).
- No BRAF mutation in Lynch Syndrome-associated cancers (association with MLH1 promoter methylation).
ADDENDAL PERSPECTIVES

- **PIK3CA** is the gene that encodes for p100α catalytic subunit of PI3K, a phosphoinositide kinase important in the PI3K/mTOR signalling pathway
  - Activation of this pathway leads to enhanced protein synthesis, cell cycle progression, cell growth and survival
  - Mutations in **PIK3CA** are found in about 20% of colorectal cancers (gene analysis included in most NGS panel investigations), with 48% of those occurring in the kinase domain and 43% occurring in the helical domain

- **HER2** amplification
  - Activation of human epidermal growth factor receptor 2 (HER2) is a rare event in colorectal cancers (3-5% of cases), leading to upregulation of RAS/RAF/MEK/ERK and PI3K/mTOR signaling pathways
  - Diagnostic: immunohistochemistry (as in gastric cancer), FISH
- The tropomyosin receptor kinase family comprise three transmembrane proteins referred to as TrkA, B and C receptors that are encoded by the NTRK1, NTRK2 and NTRK3 genes.

- Gene fusions (intra- / interchromosomal rearrangement) involving NTRK genes lead to transcription of chimeric Trk proteins with constitutively activated or overexpressed kinas function conferring oncogenic potential.

- These genetic abnormalities have recently emerged as targets for cancer therapy (entrectinib, larotrectinib).
NTRK gene fusions occur in a tumor-agnostic manner, with inconsistent break points and fusion partners.

The optimal detection method should not require knowledge of fusion break points and/or fusion partners.
NTRK FUSIONS AND COLORECTAL CANCER

- Expected frequency in colorectal cancer 0.23 – 0.31%
- Positive correlation with MSI status (TILs, PDL1 expression), negative correlation with other oncogenic drivers (RAS, BRAF, PIK3CA)
- Various diagnostic assays exist at the DNA, RNA and protein level
  - Immunohistochemistry has overall sensitivity of 87.9% and specificity of 81.1% (low for NTRK3 fusions)

Key points

- NTRK fusions, encoding TRK fusion proteins, are oncogenic drivers of a wide variety of adult and paediatric tumours, supporting a basket trial approach to drug development.
- These alterations are found at high frequencies (up to or greater than 90%) in rare cancer types (secretory breast carcinoma, mammary analogue secretory carcinoma, cellular or mixed congenital mesoblastic nephroma and infantile fibrosarcoma) and at lower frequencies (commonly <1%) in a range of other tumour types.
- NTRK fusions are clinically actionable: first-generation TRK tyrosine kinase inhibitors (larotrectinib or entrectinib) result in histology-agnostic responses in both adult and paediatric patients with NTRK fusion-positive cancers.
- Resistance to TRK inhibition can be mediated by the acquisition of NTRK kinase domain mutations, including solvent-front and gatekeeper mutations; second-generation TRK inhibitors have been developed to overcome these mechanisms of resistance.
- First-generation TRK inhibitors are generally well-tolerated and, with consideration of the biological roles of TRK receptors in normal development and adulthood, the occasional on-target adverse effects are predictable.
TISSUE BASED MOLECULAR ANALYSIS: A STEP BY STEP APPROACH

- Clinical question (e.g. RAS mutation analysis for targeted anti-EGFR monoclonal antibody treatment)
- Pre-analytics: 10% neutral buffered formalin (4% formaldehyde), optimal fixation time (>6 and <48 hours)
- Selection of appropriate sample by the pathologist
- Mark area on HE slide (consider: size of area, percentage of tumor cells, necrotic areas) for macro-dissection (→ enrichment of neoplastic cells)
- Minimum of neoplastic cells should be twice the limit of detection (LOD) of the assay used (in case the percentage of neoplastic cells is lower than twice the LOD and no mutation is detected, state the limitation of the analysis in your report)
- Relate molecular findings with pathohistological diagnosis (ideally by primary pathologist)
PROBLEM: LOW PERCENTAGE OF TUMOR CELLS

95% probability that a mutation with an allele frequency of >5% is detected (tumour cell content 5-10%. RAS wt)

Courtesy to Prof. Gerald Höfler, MU Graz, Austria
PROBLEM: LOW PERCENTAGE OF TUMOR CELLS

23% of all samples have 20% or less tumor cells
The significance of these four subtypes as such is still largely unclear though the underlying genetic changes (mutations, epigenetic modifications; e.g. MSI, mutations in BRAF and KRAS genes) and their consequences (e.g. enhanced neoantigen load and immune cell infiltration in MSI tumours) are already today of clinical relevance or about to become relevant in the future.
# RIGHT VERSUS LEFT CANCER BIOLOGY

## Table 1. Molecular Features of Preneoplastic Lesions and CRC by Site

<table>
<thead>
<tr>
<th></th>
<th>CIMP-High</th>
<th>MSI-High</th>
<th>MLH1 Methylation</th>
<th>BRAF Mutation</th>
<th>CIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preneoplastic lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sessile serrated adenoma (right-sided)</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Conventional adenoma (right and left-sided)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Colorectal cancers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-sided CRC</td>
<td>High prevalence</td>
<td>High prevalence</td>
<td>High prevalence</td>
<td>High prevalence</td>
<td>Low prevalence</td>
</tr>
<tr>
<td>Left-sided CRC</td>
<td>Low prevalence</td>
<td>Low prevalence</td>
<td>Low prevalence</td>
<td>Low prevalence</td>
<td>High prevalence</td>
</tr>
</tbody>
</table>

## Table 2. Rates of Mutations in Key Oncogenes and Tumor Suppressors by Primary Site in The Cancer Genome Atlas Dataset

<table>
<thead>
<tr>
<th>Gene</th>
<th>Total (n=276)</th>
<th>Right (n=92)</th>
<th>Left (n=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>75.0%</td>
<td>63.6%</td>
<td>81.9%</td>
</tr>
<tr>
<td>TP53</td>
<td>54.0%</td>
<td>34.8%</td>
<td>64.6%</td>
</tr>
<tr>
<td>KRAS</td>
<td>42.0%</td>
<td>45.5%</td>
<td>40.3%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>20.1%</td>
<td>27.3%</td>
<td>14.6%</td>
</tr>
<tr>
<td>FBXW7</td>
<td>16.5%</td>
<td>22.7%</td>
<td>12.5%</td>
</tr>
<tr>
<td>SMAD4</td>
<td>11.6%</td>
<td>15.2%</td>
<td>9.7%</td>
</tr>
<tr>
<td>TGFBRI</td>
<td>10.3%</td>
<td>27.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>BRAF</td>
<td>9.4%</td>
<td>24.2%</td>
<td>2.1%</td>
</tr>
<tr>
<td>NRAS</td>
<td>8.9%</td>
<td>7.6%</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

Lee et al. J Natl Compr Canc Netw 2017
RIGHT VERSUS LEFT CANCER BIOLOGY

RIGHT

LEFT

CMS1  CMS2  CMS3  CMS4

Lee et al. J Natl Compr Canc Netw 2017
### Table 3. Key Features of the 4 Consensus Molecular Subtypes

<table>
<thead>
<tr>
<th>Feature</th>
<th>CMS1 MSI/Immune</th>
<th>CMS2 Canonical</th>
<th>CMS3 Metabolic</th>
<th>CMS4 Mesenchymal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of total samples</td>
<td>14%</td>
<td>37%</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>% right-sided (vs left-sided)</td>
<td>77%</td>
<td>23%</td>
<td>51%</td>
<td>35%</td>
</tr>
<tr>
<td>Grade 3 (vs 1–2)</td>
<td>45%</td>
<td>5%</td>
<td>12%</td>
<td>19%</td>
</tr>
<tr>
<td>MSI-high</td>
<td>76%</td>
<td>1%</td>
<td>16%</td>
<td>8%</td>
</tr>
<tr>
<td>CIMP-high</td>
<td>67%</td>
<td>3%</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>Hypermutated (≥180 events)</td>
<td>94%</td>
<td>6%</td>
<td>28%</td>
<td>9%</td>
</tr>
<tr>
<td>Somatic copy number alteration–high</td>
<td>20%</td>
<td>92%</td>
<td>54%</td>
<td>84%</td>
</tr>
<tr>
<td>KRAS mutated</td>
<td>23%</td>
<td>28%</td>
<td>68%</td>
<td>38%</td>
</tr>
<tr>
<td>NRAS mutated</td>
<td>4%</td>
<td>7%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>BRAF mutated</td>
<td>42%</td>
<td>1%</td>
<td>7%</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Gene set enrichment analysis**

- Immune infiltration
- Cytotoxic T cell infiltration
- T<sub>reg</sub>1 infiltration
- PD-1 activation
- Natural killer cell infiltration
- Epithelial signature
- MYC activation
- WNT activation
- SRC activation
- Epithelial signature
- Sugar/amino acid/nucleotide metabolism
- Fructose/mannose metabolism
- Glutamine metabolism
- Epithelial mesenchymal transition
- Matrix remodeling
- Stromal infiltration
- TGF-β activation
- VEGF-VEGFR activation
RIGHT VERSUS LEFT CANCER BIOLOGY

RIGHT-SIDED CRC
- Lower outcomes
- Poorer prognosis
- Sessile serrated polyps
- CMS1 and CMS2
- CIMP-high
- Midgut
- BRAF mutant
- MSI-high
- Bile acid exposure
- Invasive bacteria biofilms

LEFT-SIDED CRC
- Superior outcomes with cetuximab
- Better prognosis
- Tubular adenoma
- CMS2 and CMS4
- Higher EREG/AREG expression
- Hindgut

Lee et al. J Natl Compr Canc Netw 2017
TAKE HOME MESSAGES

- Conventional adenomas are the prototypic precursors of left-sided sporadic MSS colorectal cancers as well as cancers in hereditary settings (Lynch, FAP)
- Sessile serrated lesions (SSL) are the prototypic precursors of right-sided sporadic MSI colorectal cancers (75%)
- Traditional serrated adenomas progress via KRAS / BRAF-dependant pathways and are the precursors of BRAF mutant MSS colorectal cancers (also MMR proficient SSL, 25%)
- Testing for microsatellite instability (immunohistochemistry, molecular) can help to identify colorectal cancers within Lynch Syndrome, but does also provide prognostic and predictive (immunotherapy) information
- Analysis of other relevant genetic abnormalities (RAS, BRAF) provides additional prognostic / predictive information (mandatory before anti-EGFR therapy)
- Future perspectives include PIK3CA, HER2 amplification and NTRK fusions
THANK YOU VERY MUCH FOR YOUR KIND ATTENTION!

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