RACENT LABORATORY TESTS IN CANCER COLON MANAGEMENT

By : Dr. Eman Elkoumy

EPIDEMIOLOGY

- colorectal cancer is the second leading cause of cancer related death worldwide ,it is also the fourth most frequently diagnosed cancer.

- The majority of patients with sporadic cancer are >50 years of age.

- Invasive colorectal cancer is a preventable disease. Early detection through widely applied screening programs is the most important factor in the recent decline of colorectal cancer in developed countries.

Northern America
Incidence
m: 30.1, f: 22.7
Mortality
m: 11.3, f: 7.8

Western Europe
Incidence
m: 39.1, f: 24.9
Mortality
m: 13.3, f: 8.3

Northern Europe
Incidence
m: 36.5, f: 25.3
Mortality
m: 13.4, f: 9.2

Central and Eastern Europe
Incidence
m: 34.5, f: 21.7
Mortality
m: 20.3, f: 11.7

Western Asia
Incidence
m: 17.6, f: 12.4
Mortality
m: 10.0, f: 7.1

South-central Asia
Incidence
m: 7.0, f: 5.2
Mortality
m: 5.1, f: 3.8

Eastern Asia
Incidence
m: 22.4, f: 14.6
Mortality
m: 10.2, f: 6.8

Southern Europe
Incidence
m: 39.5, f: 24.1
Mortality
m: 15.4, f: 8.7

South-eastern Asia
Incidence
m: 15.2, f: 10.2
Mortality
m: 9.7, f: 6.4

Caribbean
Incidence
m: 16.3, f: 16.6
Mortality
m: 9.1, f: 9.1

Central America
Incidence
m: 8.8, f: 7.1
Mortality
m: 4.9, f: 3.8

Western Africa
Incidence
m: 4.5, f: 3.8
Mortality
m: 3.5, f: 3.0

Northern Africa
Incidence
m: 8.5, f: 6.9
Mortality
m: 5.6, f: 4.5

Micronesia
Incidence
m: 24.8, f: 16.6
Mortality
m: 10.5, f: 6.4

South America
Incidence
m: 17.1, f: 14.6
Mortality
m: 9.4, f: 7.7

Central Africa
Incidence
m: 4.7, f: 4.8
Mortality
m: 3.8, f: 3.9

Southern Africa
Incidence
m: 14.2, f: 8.7
Mortality
m: 10.0, f: 5.8

Eastern Africa
Incidence
m: 7.1, f: 6.1
Mortality
m: 5.5, f: 4.6

Australia and New Zealand
Incidence
m: 44.8, f: 32.2
Mortality
m: 11.6, f: 8.5

Melanesia
Incidence
m: 11.1, f: 6.9
Mortality
m: 7.7, f: 4.9

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incidence and mortality rates in men (m) and women (f) (per 100.000 people) across geographic zones.

Highest rates occur in Australia and New Zealand, Europe and North America.

RISK FACTORS

- Both genetic and environmental factors play an important part in the etiology of colorectal cancer.

- positive family history has a role in approximately 15-20% of patients with colorectal cancer.

- Although much about colorectal cancer genetics remains unknown, current research indicates that genetic factors have the greatest correlation to colorectal cancer.

- Hereditary mutation of the adenomatous polyposis coli (*APC)* gene is the cause of familial adenomatous polyposis (FAP), in which affected individuals carry an almost 100% risk of developing colon cancer by age 40 years. Familial adenomatous polyposis is an autosomal dominant disorder with an incidence of about 1 in 8000 to 15,000 characterized by hundreds to thousands of adenomatous polyps both in the colon and rectum. FAP accounts for 1% of CRC cases .

- Hereditary nonpolyposis colon cancer syndrome (HNPCC), or Lynch syndrome, poses about 50% to 70% lifetime risk of developing colorectal cancer; individuals with this syndrome are also at increased risk for urothelial cancer, endometrial cancer, and other, less common cancers. Lynch syndrome is characterized by deficient mismatch repair (dMMR) due to inherited mutation in one of the DNA mismatch repair genes, HNPCC is a cause of about 3% to 5% of all colon cancers.
- This disorder has an incidence of about 1 in 500 .

- Impaired mismatch repair during replication gives rise to accumulation of DNA mutations, which occur, in particular, in microsatellite DNA fragments with repetitive nucleotide sequence. This microsatellite instability (MSI) can be identified by means of polymerase chain reaction (PCR) testing, which compares normal and tumour DNA of the same patient.

- Chronic colitis due to inflammatory bowel disease (IBD) is also associated with increased risk of colorectal cancer.

- A range of environmental — largely modifiable — lifestyle factors influence the risk of developing colorectal cancer :
- smoking,
- alcohol intake
- increased body weight. With each unit increase of the body mass index, the risk for colorectal cancer increases by 2–3%
- patients with type 2 diabetes mellitus also have an increased risk for colorectal cancer.
- Intake of red meat and processed meat increases colorectal cancer risk by an estimated 1.16-fold per 100 g increase of daily intake.

- By contrast, consumption of milk, whole grains, fresh fruits and vegetables, as well as intake of calcium, fibre, multivitamins and vitamin D, decrease risk. The decrease of risk is estimated to approximate 10% per daily intake of every 10 g fiber, 300 mg calcium or 200 ml milk . Daily physical activity for 30 minutes has a similar magnitude of effect . Low-dose aspirin has also been associated with decreased risk of colorectal cancer.

Epidemiology of Colorectal Cancer
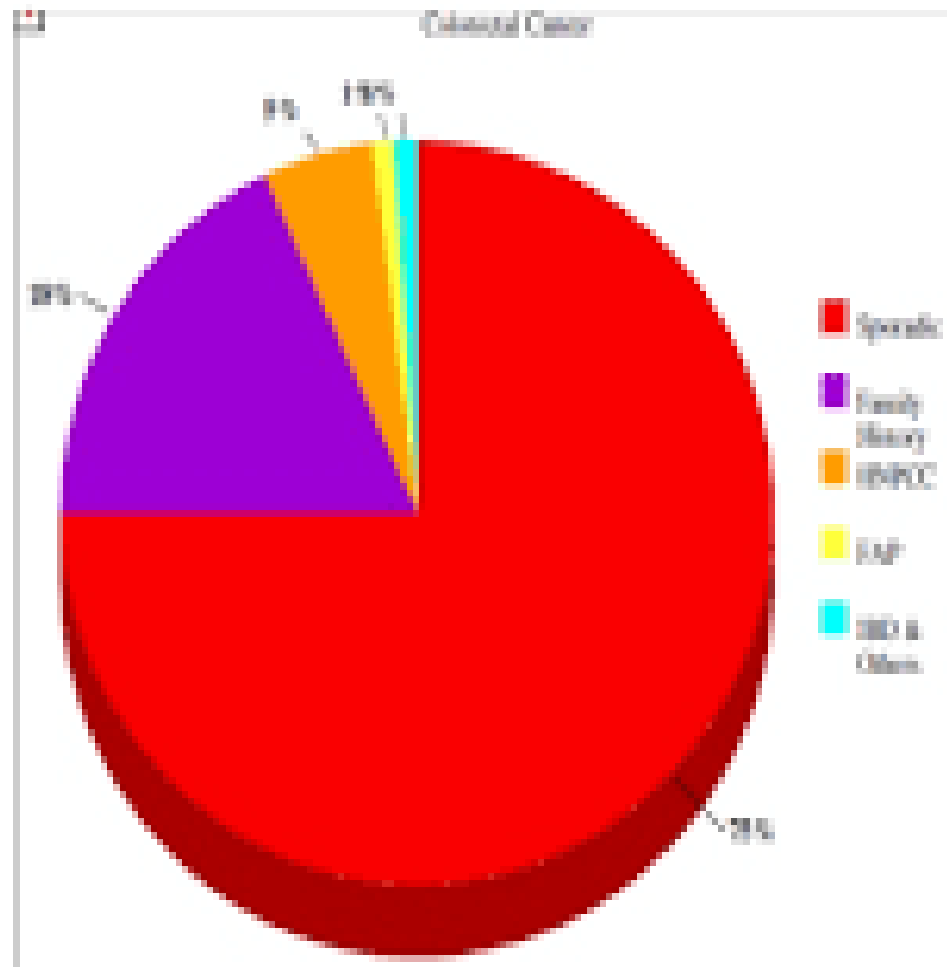
- **Sporadic** : 70-80%
- **Family** h/o CRC : 15-20%
- **HNPCC** : 4-7%
- **FAP** : 1%
- **IBD & others** : 1%

PATHOPHYSIOLOGY

- The environmental and genetic factors that cause colorectal cancer activate oncogenes and inactivate tumour suppressor genes.

- In the 'classic' colorectal cancer formation model, the vast majority of cancers arise from a polyp beginning with an aberrant crypt, which then evolves into an early adenoma (<1 cm in size, with tubular or tubulovillous histology). The adenoma then progresses to an advanced adenoma (>1cm in size, and/or with villous histology) before finally becoming a colorectal cancer. This process takes 10–15 years to occur but can progress more rapidly in certain settings (for example, in patients with Lynch syndrome)
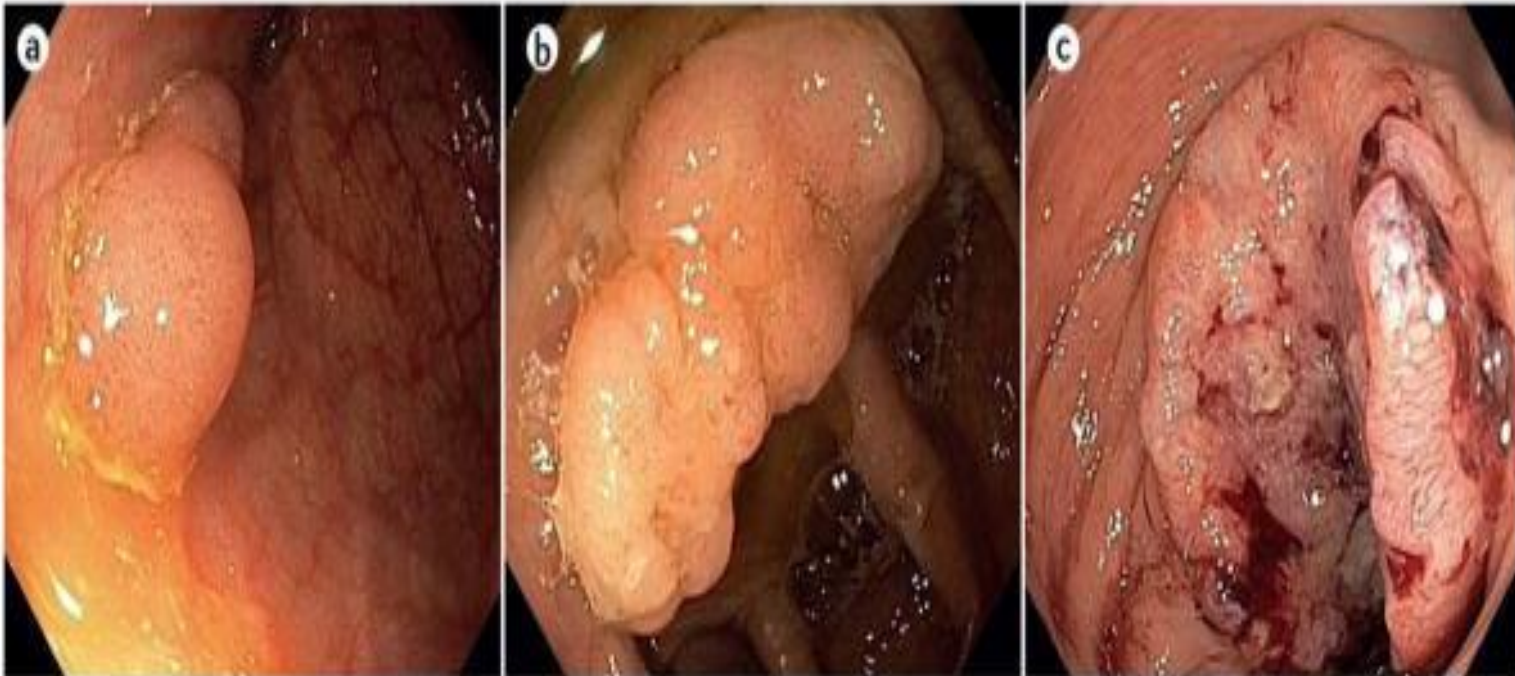
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Colorectal neoplasia at different stages
(a) A small sessile adenoma.
(b) An advanced, larger sessile adenoma.
(c) A large, dish-shaped, ulcerating sigmoid carcinoma.

DIAGNOSIS

- A diagnosis of colorectal cancer either results from an assessment of a patient presenting with symptoms, or as a result of screening.

- Symptoms include blood in stools, change in bowel habits and abdominal pain. Other symptoms include fatigue, anaemia-related symptoms such as pale appearance and shortness of breath, and weight loss.

- Right-sided tumors are more likely to bleed and cause diarrhea, whereas left-sided tumors are usually detected later and may appear as bowel obstruction.

DIAGNOSIS

- Colonoscopy is the gold standard for diagnosis of colorectal cancer. It has a high diagnostic accuracy and can assess the location of the tumor.

SCREENING AND PREVENTION

- Colorectal cancer is more suitable for population screening than any other malignancy owing to a combination of factors[1].

- Firstly, the incidence of the disease is high also has a long preclinical stage. the progression from adenoma to cancer takes at least 5–10 years. The long preclinical stage of disease offers a large window of opportunity for screening.

- Second, adenomas and early cancers are detectable and treatable entities.
- Last, both endoscopic removal of adenomas as well as treatment of early stage cancer have a profound impact on colorectal cancer mortality.

- colonoscopy has the highest accuracy and is generally considered the gold standard for screening.
- limitations in endoscopy capacity preclude the use of colonoscopy for primary screening. For these reasons, many countries prefer a two-step approach in population screening.
- first using noninvasive screening test to select a subgroup of screenees who are at high risk of cancer for subsequent colonoscopy.

- Typically, faecal occult blood test is this primary screen[1], either using :
- (1) guaiac fecal occult blood (gFOBTs) which detect the pseudo-peroxidase activity of hemoglobin or
- (2) fecal immunochemical test (FITs) which detect the globin component of hemoglobin. FITs have a number of advantages over guaiac tests. FITs are easier to use and can be automated, they can provide quantitative rather than qualitative results with adjustable cutoff points, they are less vulnerable to interference (eg, due to diet or drugs), they have greater analytical specificity and better clinical sensitivity for cancers and advanced adenomas, and they are cost-effective.

Guaiac reaction for occult blood in stool

$H_2O_2 + Hb \longrightarrow O_2$

Peroxidase activity

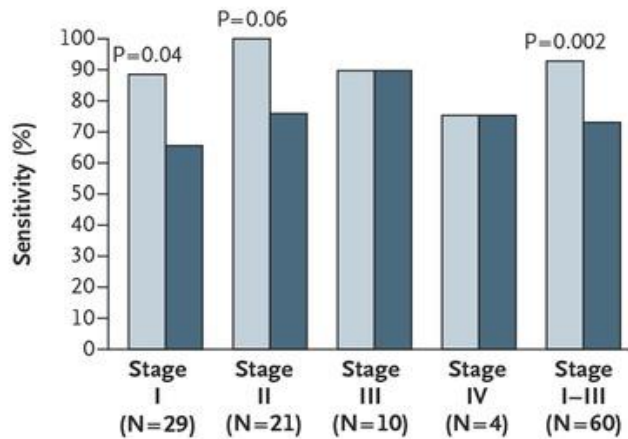Guaiac reagent + O_2 ──Oxidized──▶ Oxidized Guaiac + $2H_2O$
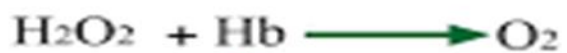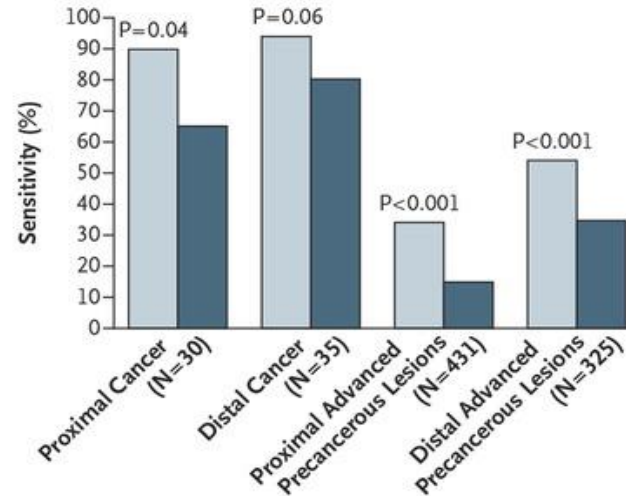
Colorless

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- gFOBT screening routinely makes use of a 1–2-year interval, the higher accuracy of FIT can allow for extension of the screening interval to 3 years··

- (3) the multi-target fecal DNA Stool DNA test targets molecular debris in stool including abnormal DNA present in malignancies such as mutant KRA, actin, FIT, aberrantly methylated BMP3, and NDRG4 promoter regions.

- Analysis of genetic and/or epigenetic markers in fecal material forms the basis of an automated DNA screening test for colorectal cancer that has been approved by the FDA. The sensitivity of the test was superior to FIT for detection of both colorectal cancer and advanced precancerous lesions, but FIT was more specific, resulting in fewer false-positive results.
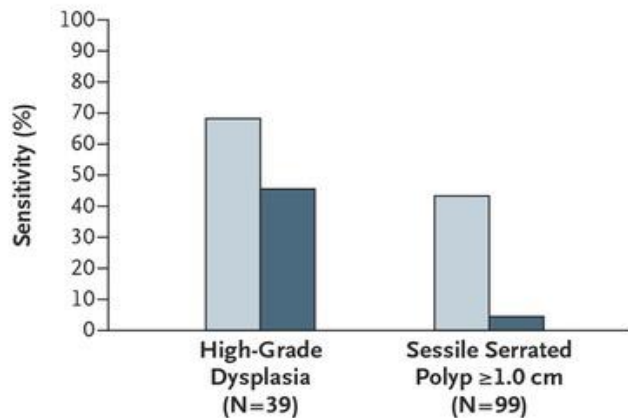
Legend: ☐ Multitarget DNA test ■ FIT
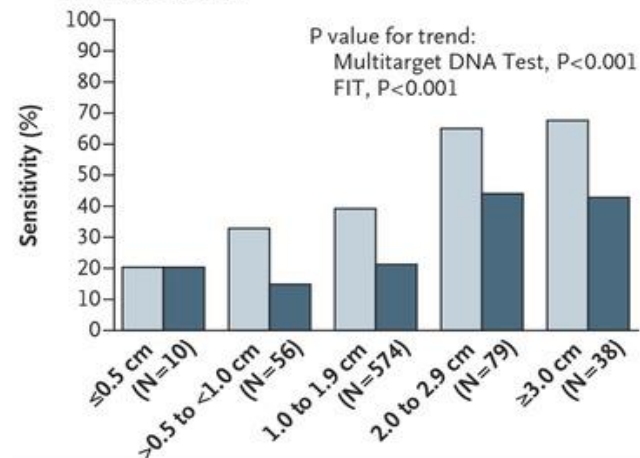
A Colorectal Cancer According to Stage

Sensitivity (%) vs Stage I (N=29) [P=0.04], Stage II (N=21) [P=0.06], Stage III (N=10), Stage IV (N=4), Stage I–III (N=60) [P=0.002]

B Cancer and Advanced Precancerous Lesions According to Location

Sensitivity (%) vs Proximal Cancer (N=30) [P=0.04], Distal Cancer (N=35) [P=0.06], Proximal Advanced Precancerous Lesions (N=431) [P<0.001], Distal Advanced Precancerous Lesions (N=325) [P<0.001]

C Higher-Risk Types among Advanced Precancerous Lesions

Sensitivity (%) vs High-Grade Dysplasia (N=39), Sessile Serrated Polyp ≥1.0 cm (N=99)

D Advanced Precancerous Lesions According to Size of Largest Lesion

P value for trend:
Multitarget DNA Test, P<0.001
FIT, P<0.001

Sensitivity (%) vs ≤0.5 cm (N=10), >0.5 to <1.0 cm (N=56), 1.0 to 1.9 cm (N=574), 2.0 to 2.9 cm (N=79), ≥3.0 cm (N=38)

- Methylated SEPT9
- Septins are a group of scaffolding proteins that provide structural support during cell division. Epi proColon (also referred to as the mSEPT9 assay) became FDA approved for CRC screening in April 2016, it is the first blood test used for this goal. The mSEPT9 assay relies on qualitative detection by Real-Time PCR of the methylated Septin 9 gene that is present in increased levels in patients with colon cancer.
- relative to multi-target fecal DNA , the SEPT9

test appears to be less sensitive for both CRC and advanced adenomas in actual practice, but with a higher specificity for cancer.

- Several randomized controlled trials have shown that population-based screening using fecal occult blood testing (FOBT) can reduce mortality from colorectal neoplasia, with an average reduction in mortality of at least 16%.

Guaiac reaction for occult blood in stool

$H_2O_2 + Hb \longrightarrow O_2$

Peroxidase activity

Guaiac reagent $+ O_2$ $\xrightarrow{\text{Oxidized}}$ Oxidized Guaiac$+2H_2O$

Colorless

Blue color

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Guaiac Test
- detects the presence of fecal occult blood.
Positive guaiac test shown on right, as would be seen for this patient. Negative result (on left) included for comparison.

multi-target fecal DNA

Methylated SEPT9

- According to a guidance statement from the **American College of Physicians** ACP released in November 2019, clinicians should screen for colorectal cancer in average-risk adults aged 50-75 years. Other guidelines, such as those from the American Cancer Society (ACS), now recommend screening begin in average-risk adults at age 45 years.

- The ACP suggests these screening tests and intervals:

- Fecal immunochemical testing or high-sensitivity guaiac-based fecal occult blood testing: every 2 years

- Colonoscopy: every 10 years (depending on findings)

- Flexible sigmoidoscopy: every 10 years, plus fecal immunochemical testing every 2 years

- Blood-based markers such as carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9, are for monitoring response to treatment as they have a low sensitivity and specificity making them unsuitable as screening or diagnostic markers

- The ACP recommends discontinuing screening for colorectal cancer in average-risk adults older than 75 years or in adults with a life expectancy of 10 years or less. However, the ACS recommends that screening for average-risk adults aged 76-85 years should be tailored to individual preference, life expectancy, overall health, and prior screening history. The ACS guidelines suggest that colorectal cancer screening should be discontinued in adults older than 85 years.

MANAGEMENT

- Surgery is the mainstay curative treatment for patients with non-metastasized colorectal cancer.

- carcinoembryonic antigen CEA is preferably obtained before colorectal cancer surgery to provide a baseline value for postoperative surveillance.

SURVEILLANCE AFTER RESECTION

- Patients who have adenomatous polyps or colorectal cancer continue to be at risk for new neoplastic lesions after these have initially been removed

- In addition to endoscopic surveillance after cancer resection, follow-up surveillance by measuring carcinoembryonic antigen (CEA) levels in the plasma and/or CT imaging might detect curatively treatable metastatic recurrence. CEA testing is likely to be more cost-effective than CT.

- It is now generally agreed that CEA testing should be performed every 3 to 6 months for 5 years following curative surgery for colorectal cancer. CEA results within the reference interval do not exclude recurrence.

- Measurement of CEA is also recommended during chemotherapy for metastatic disease, although care in interpretation is required because CEA concentrations may be affected by factors other than tumor progression (eg, liver damage). Confirmed increases during treatment can inform decisions to change treatment or withdraw ineffective treatment. CEA-defined responses agree well with radiologic responses (the "gold standard") in over 90% of cases, enabling the conclusion that use of CEA is as accurate as CT imaging for assessing the response of colorectal cancer liver metastases to chemotherapy.

COLORECTAL CANCER AND MOLECULAR TESTING

- Approximately 80% of all colorectal cancers express or overexpress **epidermal growth factor** receptor EGFR; overexpression correlates with reduced survival and increased risk of metastases. The EGFR tyrosine kinase can be blocked by monocloncal antibodies specific to the extracellular domain of the receptor such as cetuximab, which is a recombinant monoclonal IgG1 antibody, and panitumumab, which is a human EGFR-specific antibody.

- These antibodies show efficacy in chemotherapy-naive patients as well as in patients whose tumours are refractory to chemotherapy by improving the overall response rate of the tumours. These strategies also improve overall survival in patients with metastatic colorectal cancer. However, a prerequisite for the efficacy of these agents is that the tumours do not harbour activating mutations in *KRAS* and *NRAS* .

- *RAS* is mutated in about half of all colorectal cancers, with codons 12 and 13 being most commonly affected; codons 61 and 146 of *KRAS* and codons 12, 13 and 61 of *NRAS* are affected to a lesser extent.

- The mutations render the RAS GTPase constitutively active; active Ras induces a plethora of tumorigenic intracellular signalling pathways. Thus, the Ras status of the tumour must be examined before treatment with EGFR-specific antibodies.

- Cetuximab and panitumumab have a favorable survival impact in patients with *KRAS* wild-type CRC; both agents should be initiated only in patients with *KRAS* wild-type CRC. however, mutated *BRAF* was associated with a poor prognosis.

- In a *RAS* wild-type population data suggest that the mutated *BRAF* gene, which is present in 5-10% of tumors, can affect response to (EGFR) antibody therapy.

- It is unclear to what extent the lack of response in *KRAS* wild-type Colorectal Cancer is due to *BRAF* mutations, but data suggest that mutated *BRAF* confers resistance to anti-EGFR therapy given beyond first-line treatment.
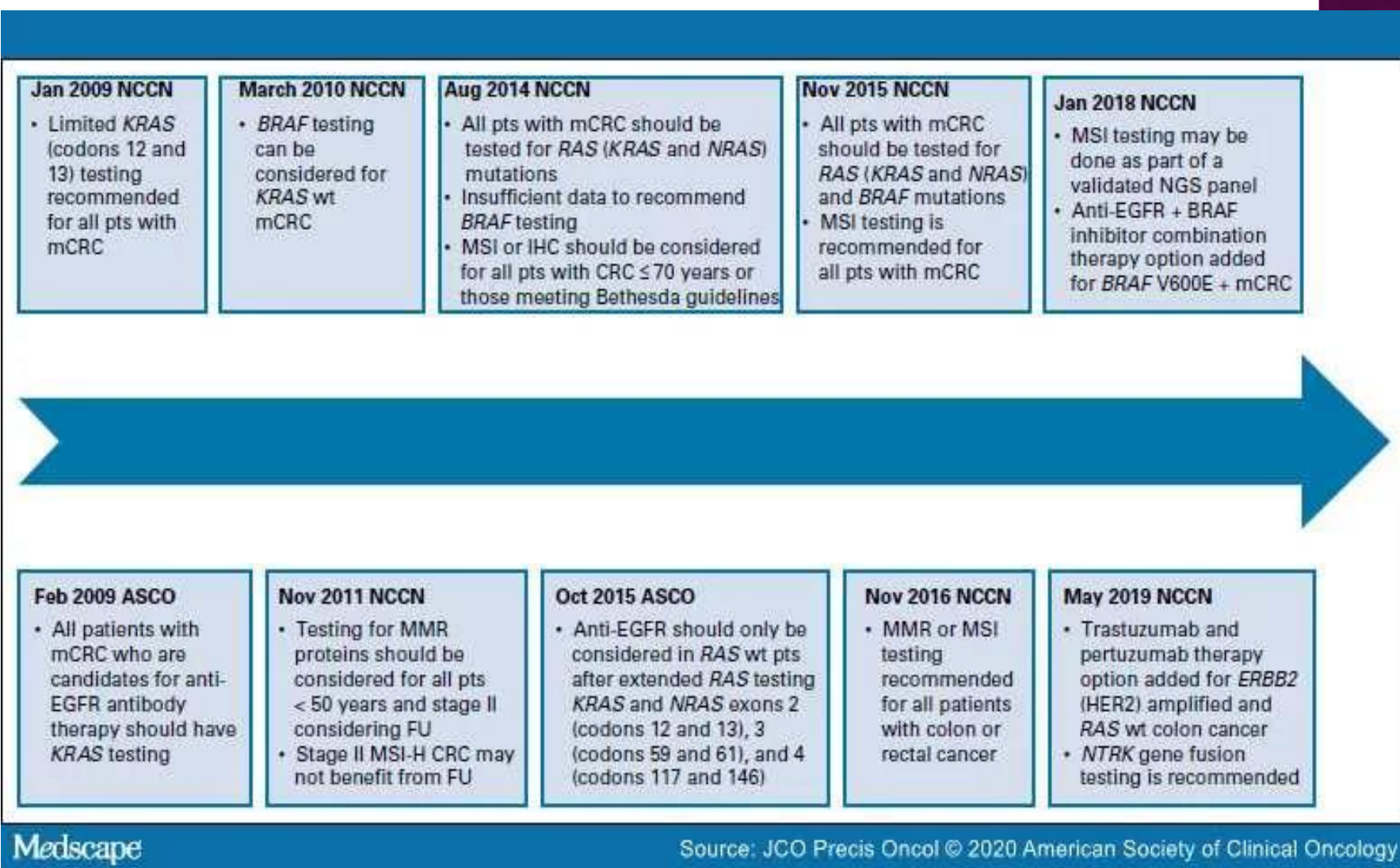
- Additionally, testing for microsatellite instability and mismatch repair lends information for the option to use pembrolizumab, which gained approval from the FDA in May 2017 for unresectable or metastatic colon cancer that has tested positive for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR)
.

- The European Society for Medical Oncology (ESMO) Consensus Guidelines for the Management of Patients with Metastatic Colorectal Cancer which are endorsed by American Society of Clinical Oncology(ASCO) recommend that patients with metastatic CRC receive *RAS* mutational testing, because the presence of *RAS* mutations is a negative predictive biomarker for response to epidermal growth factor receptor antibody therapy. The ESMO guidelines also provide recommendations for other biomarker testing, including *BRAF* mutational analysis.

- Treatment of metastatic colorectal cancer is increasingly guided by molecular testing of the tumor. The ASCP, CAP, AMP, and the ASCO have issued evidence-based guidelines on colorectal cancer molecular testing. Recommendations include:

- *RAS* mutational testing of colorectal carcinoma tissue should be performed for patients who are being considered for anti-*EGFR* therapy; this analysis must include *KRAS* and *NRAS* codons 12 and 13 of exon 2, 59 and 61 of exon 3;, and 117 and 146 of exon 4 ("expanded" or "extended" *RAS*).

- *BRAF* V600 mutational analysis should be performed in conjunction with dMMR/MSI testing for prognostic stratification.

- dMMR/MSI testing must be performed in all patients with colorectal cancer for prognostic stratification and identification of patients with Lynch syndrome. *BRAF* mutation testing for Lynch syndrome is not needed if there is no high MSI with loss of *MLH1*.

- Molecular marker testing (*KRAS*, extended *RAS*, *BRAF*, and dMMR/MSI) of the primary colorectal carcinoma tissue is acceptable; if metastatic tissue is available, that is also acceptable and is preferable in patients with metastatic disease.

- Formalin-fixed, paraffin-embedded tissue is an acceptable specimen; use of other specimens will require additional adequate validation, as would any changes in tissue-processing protocols.

- Targeting NTRK, Larotrectinib is now included as a second-line treatment option for patients with metastatic CRC who have NTRK gene fusions (occurring in ~1% of patients), regardless of tumor type.

Jan 2009 NCCN
- Limited *KRAS* (codons 12 and 13) testing recommended for all pts with mCRC

March 2010 NCCN
- *BRAF* testing can be considered for *KRAS* wt mCRC

Aug 2014 NCCN
- All pts with mCRC should be tested for *RAS* (*KRAS* and *NRAS*) mutations
- Insufficient data to recommend *BRAF* testing
- MSI or IHC should be considered for all pts with CRC ≤ 70 years or those meeting Bethesda guidelines

Nov 2015 NCCN
- All pts with mCRC should be tested for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations
- MSI testing is recommended for all pts with mCRC

Jan 2018 NCCN
- MSI testing may be done as part of a validated NGS panel
- Anti-EGFR + BRAF inhibitor combination therapy option added for *BRAF* V600E + mCRC

Feb 2009 ASCO
- All patients with mCRC who are candidates for anti-EGFR antibody therapy should have *KRAS* testing

Nov 2011 NCCN
- Testing for MMR proteins should be considered for all pts < 50 years and stage II considering FU
- Stage II MSI-H CRC may not benefit from FU

Oct 2015 ASCO
- Anti-EGFR should only be considered in *RAS* wt pts after extended *RAS* testing *KRAS* and *NRAS* exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146)

Nov 2016 NCCN
- MMR or MSI testing recommended for all patients with colon or rectal cancer

May 2019 NCCN
- Trastuzumab and pertuzumab therapy option added for *ERBB2* (HER2) amplified and *RAS* wt colon cancer
- *NTRK* gene fusion testing is recommended

Medscape

Source: JCO Precis Oncol © 2020 American Society of Clinical Oncology

Evolution of guidelines for molecular testing in metastatic colorectal cancer (mCRC). FU, fluorouracil; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability high; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; pts, patients; wt, wild type.

LABORATORY TESTING FOR KRAS/BRAF

- Lab tests include the following:
- The rascreen KRAS RGQ (Rotor-Gene Q) PCR (polymerase chain reaction) Kit. Tests for mutations in codons 12 or 13 of the KRAS gene on formalin-fixed, paraffin-embedded tissue from the primary tumor or a metastasis.
- In June 2017, the FDA approved PRAXIS Extended RAS Panel, next-generation sequencing (NGS) kit. The kit detects 56 specific RAS mutations in DNA extracted from formalin-fixed, paraffin-embedded colorectal cancer tissue samples.

CIRCULATING TUMOR CELLS AND CIRCULATING TUMOR DNA

- Circulating tumor DNA (ctDNA) and Circulating Tumor Cells (CTCs) present in the bloodstream of patients are considered promising biomarkers for the management of CRC.

- An automated CTC counting algorithm to eliminate the variability in manual counting of CTCs has been validated on colorectal cancer. By using this approach, CTCs were identified and morphological features extracted from images stored by the CellSearch system. The automated CTC counts were strongly correlated with clinical outcomes in metastatic colorectalcancers.

Systematic review of blood diagnostic markers in colorectal cancer

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Abstract

Go to: ⊡

The purpose of this systematic review was to compare the diagnostic ability of

PROMISING DIAGNOSTIC BLOOD MARKERS FOR PRIMARY HUMAN COLORECTAL CANCER

In a systematic review of the literature for diagnostic blood markers for primary human colorectal cancer over the last 5 years the markers were divided in broadly four groups:

- nucleic acids (RNA/DNA/messenger RNA/microRNAs),
- cytokines,
- antibodies,
- and proteins.

- The most promising circulating markers identified among the nucleid acids were NEAT_v2 non-coding RNA, SDC2 methylated DNA, and Septin9 methylated DNA.
- The most promising cytokine to detect CRC was interleukin 8,
- and the most promising circulating proteins were CA11-19 glycoprotein and DC-SIGN/DC-SIGNR.

- None of the studies showed promising enough results for antibodies use in diagnosis of CRC.
- With the exception of Septin 9 which is now commercially available and implemented as a screening test for CRC If combined with fecal immunochemical test (FIT) all other markers lacked reproducibility and standardization and were studied in relatively small population samples.

- Another new study suggests MYO5B a protein within the myosin family, as a prognostic marker for colorectal cancer.
- The study found that the concentration of the protein decreases as the disease progresses.
- These new findings could lead to new classifications allowing some CRC patients to be labeled "high-" or "low-" risk.
- This stratification could potentially help oncologists to choose the best treatment plan.

GENOME-WIDE ASSOCIATION STUDIES

- Recent findings Genome-wide association studies have recently linked CRC to 10 common genetic variants or single-nucleotide polymorphisms that map to chromosomes 8q23, 8q24, 10p14, 11q23, 14q22, 15q13, 16q22, 18q21, 19q13 and 20p1. However, the causal significance of these variants is not understood, and some are located in poorly characterized genomic regions or gene deserts.

- In addition, several microRNAs interact with genes such as *K-RAS*, *APC*, *p53*, *PTEN*, *TCF4*, *COX-2*, *DNMT3a* and *DNMT3b*. Germline hypermethylation of the DNA mismatch repair genes *MLH1* and *MSH2* may serve as predisposing events in some CRC patients.

P53 MUTATION

- Mutation in the tumour suppressor gene p53 occur in 50%-70% of all CRC and is associated with worse outcomes, including disease free survival and overall survival.

MicroRNAs and Colorectal Cancer

- miRNAs are single-stranded, small (19–25 ribonucleotides), noncoding RNAs that function as posttranscriptional gene regulators.

- miRNAs contribute to oncogenesis functioning either as tumor suppressors (*ts*miRs) or tumor promoters (*onco*miRs).

- In the last few years, several miRNAs have been shown to be up or downregulated in CRC. and of interest, expression of miR-31, miR-183, miR-17-5, miR-18a, miR-20a and miR-92 have been found to be significantly higher in CRC than normal tissues.

- whereas miR-143 and miR-145 are expressed at lower levels in CRCs. Findings from this study further revealed that CRCs with overexpression of miR-18a tended to have a poorer prognosis as compared with the tumors with lower expression of this miRNA. miR-18a functions as a tumor suppressor miRNA by targeting the *K-RAS* oncogene.

Plasma MicroRNA Signature Validation for Early Detection of Colorectal Cancer.

Herreros-Villanueva M[1], Duran-Sanchon S[2], Martín AC[1], Pérez-Palacios R[1], Vila-Navarro E[2], Marcuello M[2], Diaz-Centeno M[2], Cubiella J[3], Diez MS[4], Bujanda L[5], Lanas A[6], Jover R[7], Hernández V[8], Quintero E[9], José Lozano J[10], García-Cougil M[3], Martínez-Arranz I[11], Castells A[2], Gironella M[2], Arroyo R[1].

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- Another study identified and validated a signature of 6 miRNAs (miRNA19a, miRNA19b, miRNA15b, miRNA29a, miRNA335, and miRNA18a) as predictors that can differentiate significantly patients with CRC from those who are healthy.

ABBRAVIATIONS

- (ASCP)the American Society for Clinical Pathology,
- (CAP)the College of American Pathologists
- (AMP) the Association for Molecular Pathology