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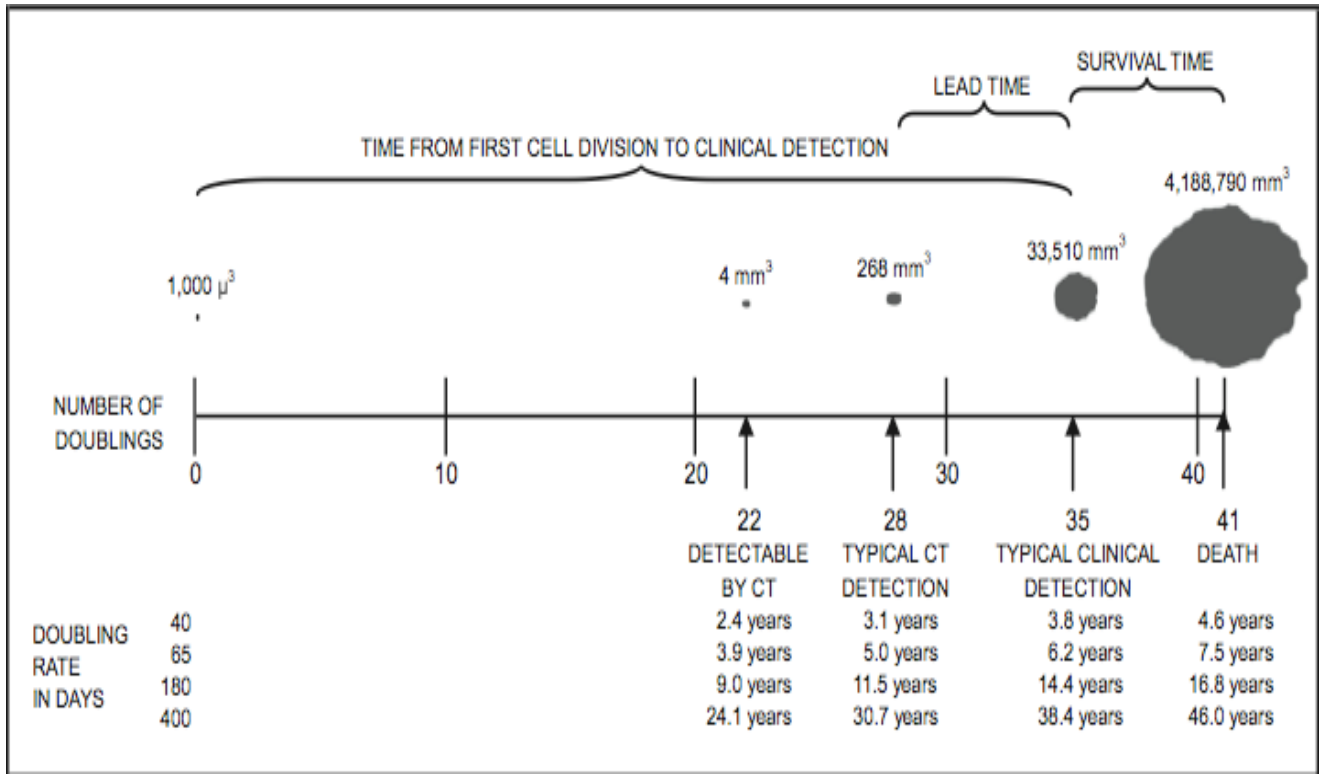
BASIC PRINCIPLES OF DIAGNOSIS MALIGNANT DISEASES

- Cancer is a major global public health problem; there were 10 million deaths from cancer worldwide in 2020.
- For nearly all cancers, the chances of survival increase significantly if the disease is detected, diagnosed, and treated at an early stage.

- Tumors consist of cells whose growth and morphological characteristics are markedly different from those of normal cells. Criteria for malignancy include increased cell proliferation, loss of differentiation, infiltrative growth and metastasis to other organs.

- Malignant transformation is a multistage process, typically a progression from benign lesions to malignant tumors . This evolution of malignant cells is caused by the sequential accumulation of alterations in genes responsible for the control of cellular proliferation, cell death and the maintenance of genetic integrity.

- The development of cancer may be initiated by environmental agents (chemical carcinogens, radiation, viruses) and inherited genetic factors (germline mutations).



In preclinical phase <1 x 10(9) malignant cells
A tumor reaching the size of 1 cm^3 (approximately 1 g wet weight) is commonly assumed to contain 1 x 10^9 cells.

Modern clinical PET scanners have a resolution limit of 4 mm, corresponding to the detection of tumors with a volume of 0.2 ml (7 mm diameter) in 5:1 Tumor/Background ratio.

SYMPTOMS AND SIGNS OF MALIGNANT DISEASE

- are caused by local and regional tumor growth, growth of distant metastases and paraneoplastic syndrome
- they are usually non-specific and easily overlooked
- they are often missing for a long time when internal organs are involved
- they are easily misinterpreted as a sign or symptom of some other disease

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Work on cancer screening and early detection
Think about the possibility of a malignant disease
In case of doubt, begin diagnostic procedures without delay, thus reducing lost time
A malignant disease diagnosed on time usually means a curable disease

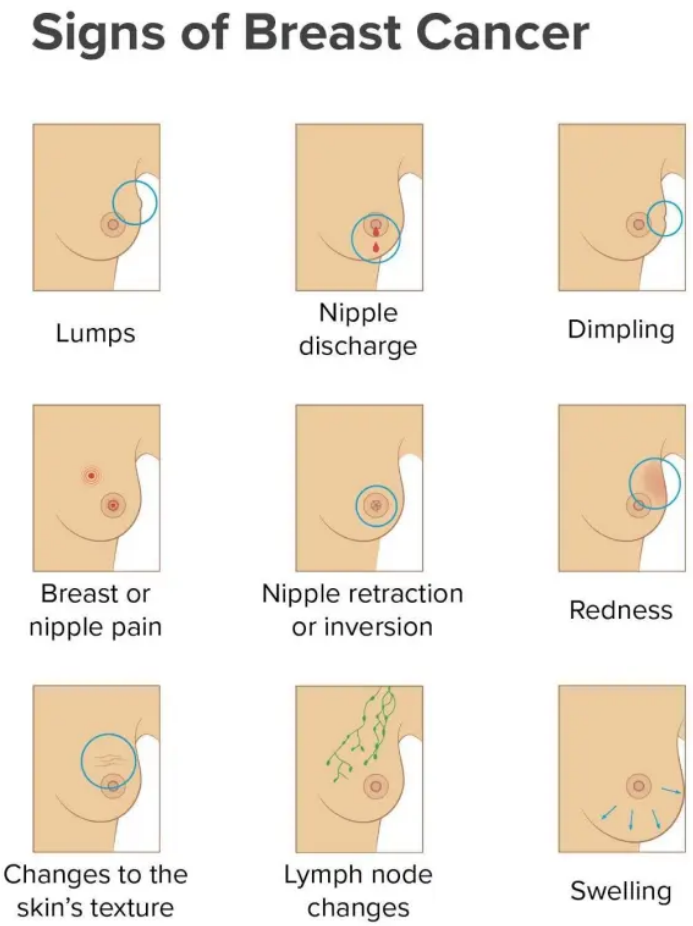
First symptoms of cancer

- Fatigue or extreme tiredness that doesn't get better with rest.
- Weight loss or gain for no known reason
- not feeling hungry, trouble swallowing, abdominal pain, or nausea and vomiting
- Change in bowel habits, such as constipation or diarrhea, or a change in how your stools look
- Thickening or lump in the breast or other part of the body
- Mouth changes such as sores, bleeding, pain, or numbness
- Skin changes such as a lump that bleeds or turns scaly, a new mole or a change in a mole, a sore that does not heal, or a yellowish color to the skin or eyes *(*jaundice*)*.
- Cough or hoarseness that does not go away
- Unusual bleeding or bruising for no known reason
- Bladder changes such as pain when passing urine, blood in the urine
- Fever or nights sweats
- Headaches
- Vision or hearing problems

- Pain from the cancer can be caused by a tumor pressing on nerves, bones, or organs. Pain is a late sign of malignant diseases

Breast cancer clinical presentation

• a lump, lumpiness or thickening, especially in just one breast
• a change in the size or shape of the breast or swelling
• a change to the nipple – change in shape, crusting, sores or ulcers, redness, pain, a clear or bloody discharge, or a nipple that turns in (inverted) when it used to stick out
• a change in the skin – dimpling or indentation, a rash or itchiness, unusual redness or other color changes
• swelling or discomfort in the armpit
• ongoing, unusual pain in one breast only



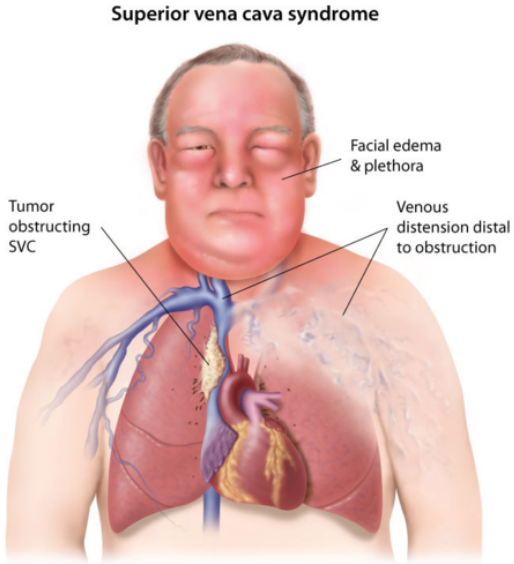
Colon Cancer Clinical Presentation

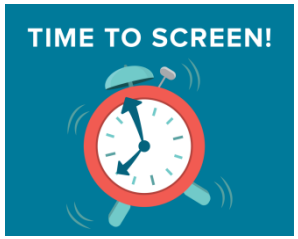
- Colon cancer is now often detected during screening procedures. Common clinical presentations include the:
- Iron-deficiency anemia
- Rectal bleeding
- Abdominal pain
- Change in bowel habits
- Intestinal obstruction or perforation
- Right-sided lesions are associated with younger age, and common presenting signs include bleeding and/or diarrhea.
- Left-sided tumors are associated with older age, and patients commonly present with bowel obstruction.

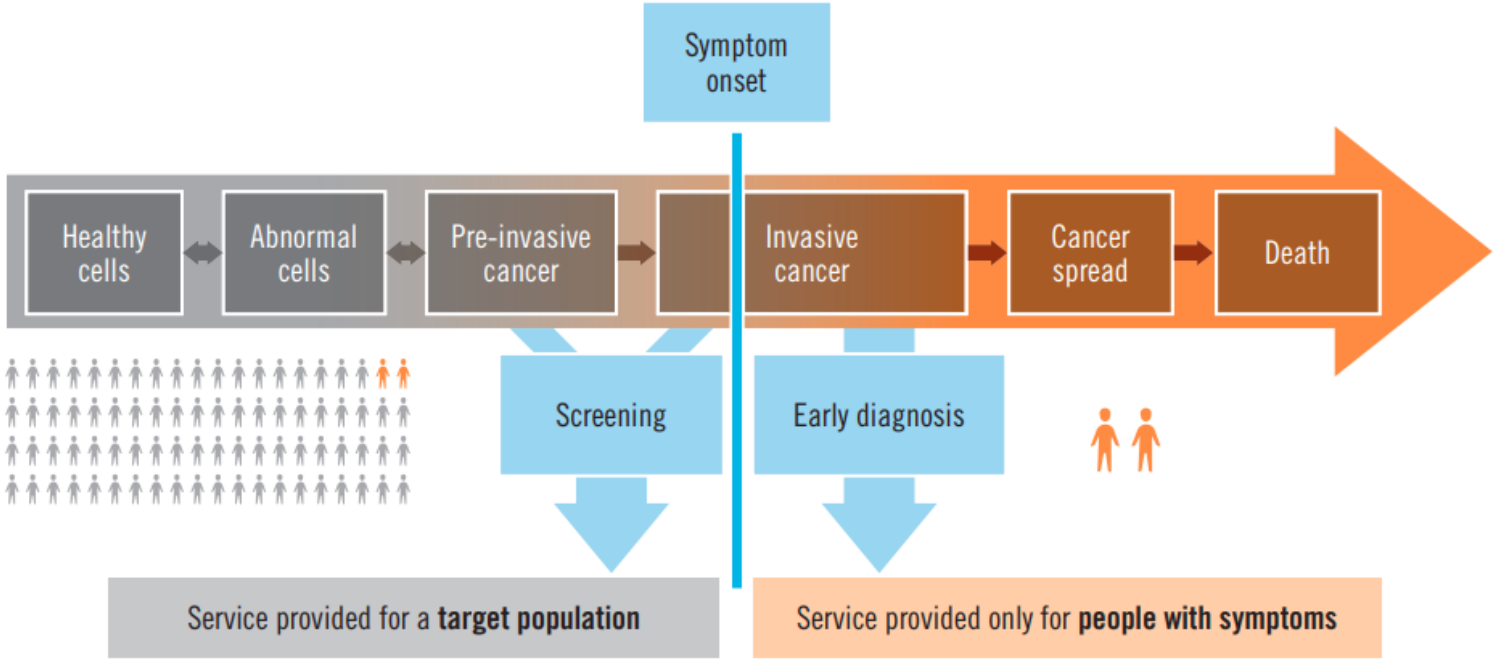
CLINICAL PRESENTATION OF LUNG CANCER

- Symptoms can be caused by the local tumor, intrathoracic spread, distant metastases, or paraneoplastic syndromes.
- cough (33.9%); dyspnoea (26.7%); pain (23.8%); and weight loss (21%), coughing up blood (hemoptysis), infections such as bronchitis and pneumonia that don’t go away or keep coming back, new onset of wheezing.
- Cough was the most frequent symptom in never/ex/and current smokers.
- The presence of haemoptysis was twice as frequent in ever smokers than in never smokers (12% vs 6%, respectively)
- 31.5% of patients displayed no symptoms at diagnosis,
- 7.5% had four or more.

- **Pancoast tumors** refers to superior sulcus tumors along with ipsilateral shoulder and causes shoulder pain, paresthesias, paresis and atrophy of the thenar muscles of the hand and Horners syndrome (ptosis, miosis, and anhidrosis).
- **Superior vena cava (SVC) syndrome**: Tumors in upper part of the right lung can press on the SVC, which can cause the blood to back up in the veins. This can lead to swelling in the face, neck, arms, and upper chest (sometimes with a bluish-red skin color). It can also cause headaches, dizziness, and a change in consciousness if it affects the brain. While SVC syndrome can develop gradually over time, in some cases it can become life-threatening.
- **Paraneoplastic syndromes**: Some common syndromes include: SIADH (syndrome of inappropriate anti-diuretic hormone): Cushing syndrome (the cancer cells make ACTH), Nervous system problems (SCLC can lead to Lambert-Eaton syndrome, SCLC can also cause other nervous system problems, such as muscle weakness, sensation changes, vision problems, or even changes in behavior), **hypercalcemia**.

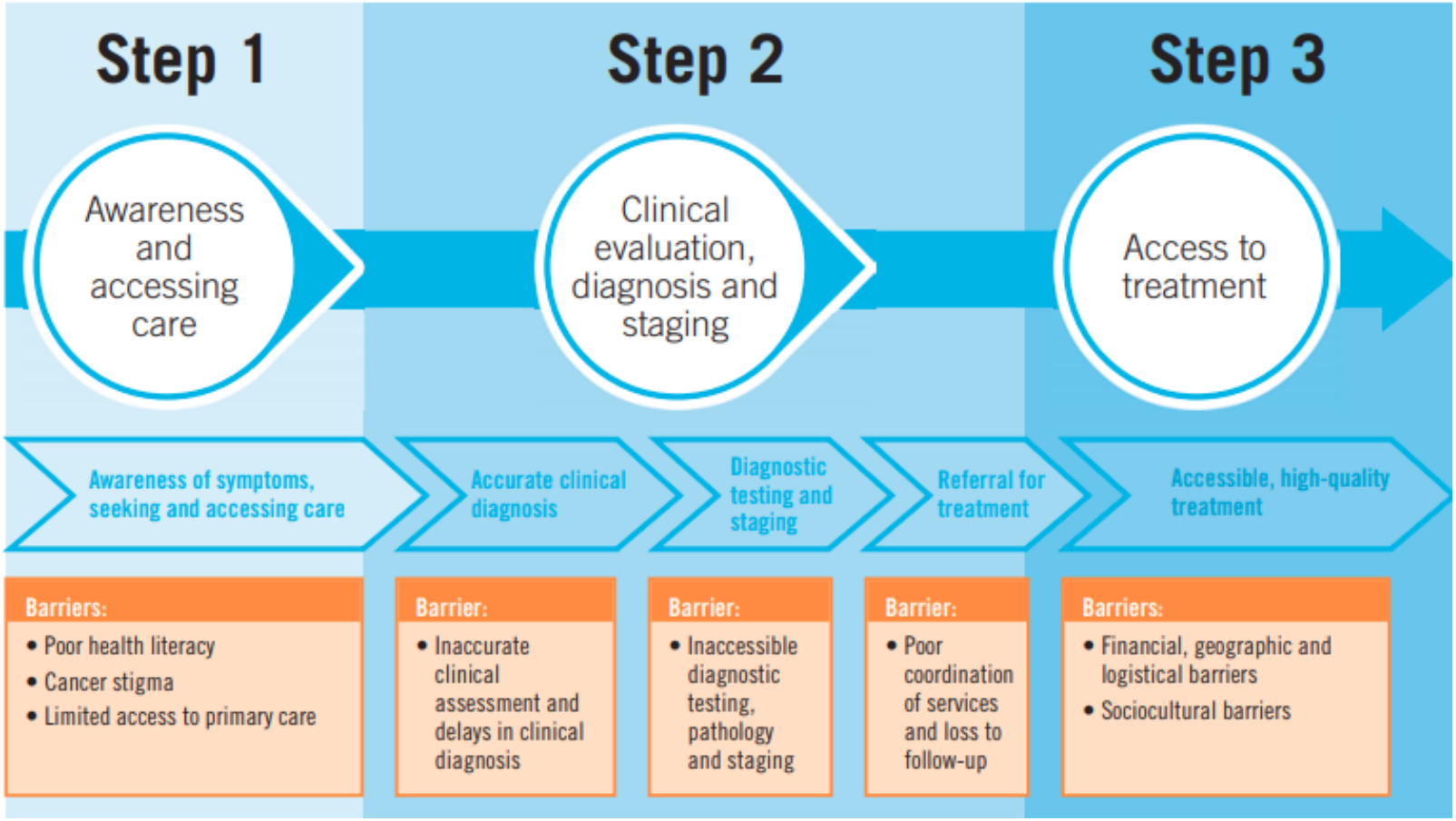






- Early diagnosis is defined as the early identification of cancer in patients who have symptoms of the disease.
- Cancer screening that seeks to identify unrecognized (pre-clinical) cancer or pre-cancerous lesions in an apparently healthy target population.
- Cancer early diagnosis and screening are both important components of comprehensive cancer control, but are fundamentally different in resource and infrastructure requirements, impact and cost.

STEPS OF EARLY DIAGNOSIS



What should oncologist address for each cancer patients?

- Is diagnosis confirmed (clinicaly, laboratory , patohystologicaly)?
- What is the stage of disease?
- Can this patient be cured?
- If the disease not curable, what is the best aproach to help patient?

The diagnosis of malignant disease

- The diagnosis of malignant disease is divided into clinical and cytological/histological
- Clinical diagnosis aims to determine the localization, as well as the local, regional and systemic extension of the disease
- Cytological/histological diagnosis aims (in addition to the goals of clinical diagnosis) to definitively confirm the existence of a malignant disease, determine the histological type of the tumor and the degree of its differentiation
- The diagnosis of malignant disease is complete only when we have both diagnoses

The diagnosis of malignant disease

- Anamnesis
- family health history
- physical examination
- laboratory workup
- Imaging results (X-ray, MSCT, MRI, US, scintigraphy, PET-CT, endoscopy) will confirm the presence of malignancy and determine the best site for a biopsy
- Histopathological image analysis

Laboratory diagnosis

- Routine bloodwork will not detect most cancers.
- Blood chemistry and complete blood count are not diagnostic for cancer, but if abnormalities are seen, it may indicate the need for further evaluation
- Tumor markers are cellular products that are helpful in the detection and diagnosis of certain cancers

a. Cell surface markers have become essential to the diagnosis and typing of certain malignancies. An important example are the clusters of differentiation (CD) antigens on cells, in diagnosing and typing hematopoietic malignancies.

b. **Genetic markers** are useful for diagnosis and prognosis of a variety of cancers. They may also be useful for selected patients with family histories of a hereditary cancer syndrome in which identification provides early detection (BRCA-1, KRAS, BRAF V600e…)

Types of tumor markers

c. Serum markers are usually normal cell components that are abnormally elaborated and released by malignant cells; can be useful in monitoring the response of some cancers to treatment, in detecting recurrence or progressions of cancers, in prognosis, and in helping to make an early diagnosis of a few tumors.

d. Oncofetal proteins are substances found normally in larger amounts during fetal development. Cancers derived from the fetal counterpart of adult tissues often elaborate these proteins in increased quantities.

-α-Fetoprotein (α-FP) is increased in about 80% of patients with hepatomas, 60% of patients with non-seminoma germ cell cancers.

-Carcinoembryonic antigen (CEA) is a useful marker for monitoring breast, colon, and small cell lung cancers.

* Elevations of CEA blood levels (usually less than 10 ng/mL) are found in smokers and in patients with chronic obstructive lung disease, inflammatory or peptic bowel disease, liver inflammation or cirrhosis of any cause, renal failure, and fibrocystic breast disease.

e. Hormones

- Human chorionic gonadotropin (b-HCG) is found in a normal blood product in women during pregnancy. It is never found in normal males, high levels are almost always pathognomonic of a germ cell neoplasm in this setting
- Thyrocalcitonin is produced by thyroid C cells and medullary thyroid cancer. It is an effective way to screen patients with first-degree relatives affected by medullary thyroid cancer and multiple endocrine neoplasia type 2 (MEN 2).

f. Enzymes

-Prostate-specific antigen (PSA) correlates closely with tumor burden and response to therapy for men with prostate cancer

-Lactic dehydrogenase (LDH) blood level is elevated in association with many types of malignancy.

- Neuron-specific enolase (NSE) is a glycolytic enzyme found in association with several neuroendocrine tumors. It is clinically useful as a prognostic factor in neuroblastoma.

g. Cancer antigens (CAs) : A large number have been associated with various malignancies, none is useful for cancer screening.

- CA 125 is detected by monoclonal antibodies against cystadenocarcinoma cell lines. It is useful for monitoring patients with known ovarian cancer when blood levels correlate closely with extent of disease, response to therapy, and recurrence. *CA 125 is useless as a general screening test for ovarian cancer.*

- CA 15-3 may be elevated in patients with breast, ovarian, prostate, and lung cancer. For breast cancer, CA 15-3 has a 75% correlation with measurable disease and is useful for monitoring disease that cannot be measured after treatment.

-CA 19-9 is found in increased levels in gastrointestinal cancers. It is helpful in the diagnosis and monitoring of pancreatic cancer, in which it has a 70% specificity and a 90% sensitivity.

h. Miscellaneous markers: b2-Microglobulin (increased in myeloma, lymphomas, poor renal function) ferritin (hepatoma), thyroglobulin (well-differentiated thyroid cancer).

Histopathology : Biopsy

- Histologic proof of malignancy is the cornerstone of diagnosis and treatment. Neoplasms can masquerade as benign or inflammatory conditions, and vice versa. The site that is least risky and most likely to provide the necessary information is tested.
- Cytology sampling:

*Exfoliative (brush) Superficial lesions of hollow organs =intraepithelial or invasive tumors (cervix, small bronchus, biliary duct system)

*Liquid-Cytology of Liquids: Body cavity effusions of neoplastic or inflammatory origin, cyst content, other fluids than blood (e.g. peritoneal, pleural, pericardial, urine)

*Fine needle aspiration (FNA)

- Tissue sampling
    - *By excision (direct, open surgical, video-assisted)
    - *Incisional biopsy
    - *Core needle biopsy
    - *By endoscopy
    - *Punch biopsy
    - *sentinel node biopsy

Cytology vs tissue sampling

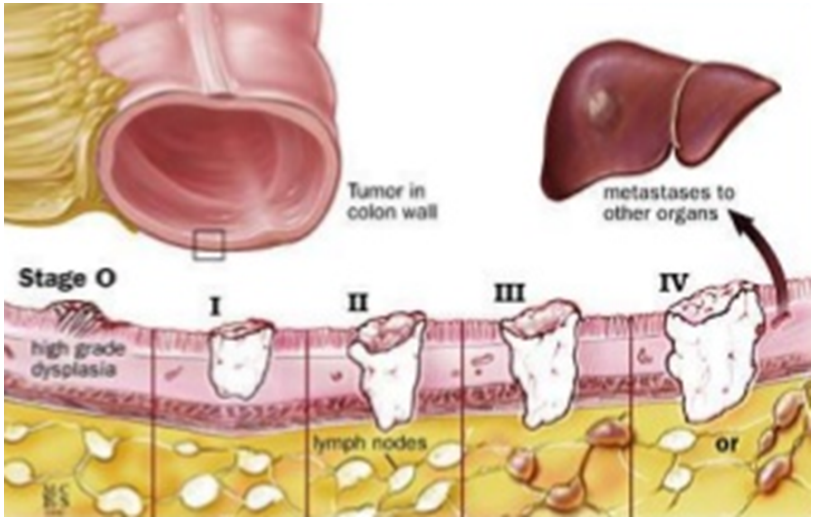
	Cytology	Histology
Advantages	•fast •Simple tools •Minimally invasive, complications rare	• Several slides from the same sample •Ideal if immunohistochemistry evaluation is needed
Disadvantages/limitations	•Limited sample(smear) •Ancillary exams (e.g. immunohistochemistry) limited	•Time consuming processing •More expensive, lab requirements •Invasive, complications may occur
Diagnostic evaluation(tumors)	•Dignity •Type – main tumor type •Low grade/high grade •Invasion – limited	•Dignity •Type –more accurate tumor typing •Grade-assessment of proliferation •Invasion
Setting	•Before surgery •in case of a metastatic disease clarify etiology	•Before surgery •Systemic therapy planning •Some special tumors (e.g.lymphomas)
Both techniques require experience!!!! Unsatisfactory samples are not diagnostic-unnecesary invasive intervention!		

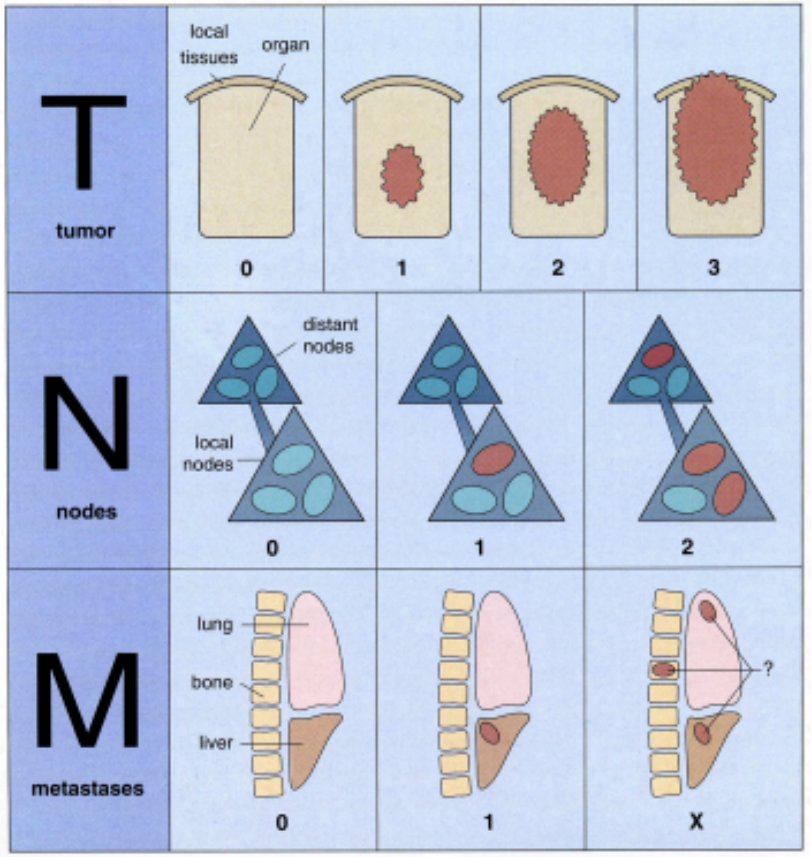
Histopathological report

- the origin of the tissue examined and the method of obtaining the sample
- histological type of tumor (plano, adeno, giganto, microcellular type, neuroendocrine tumor, etc. - in lung carcinoma)
- degree of tumor differentiation - histological grade, nuclear grade, mitotic index
- data on **T**(umor)**N**(odus)**M**(etastasis) status
- data on the presence of invasion (perineural, venous and lymphatic invasions)
- residual status
- other information of significance

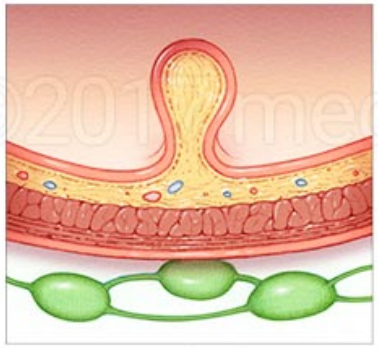
The TNM system for the classification of malignant tumours

- T - the primary tumour
- N - regional lymph nodes
- M - distant metastases

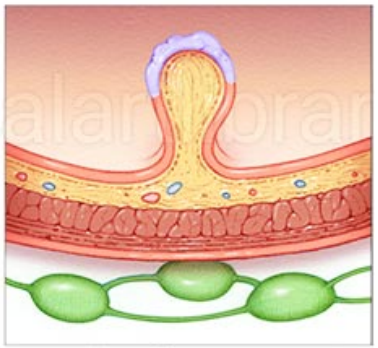




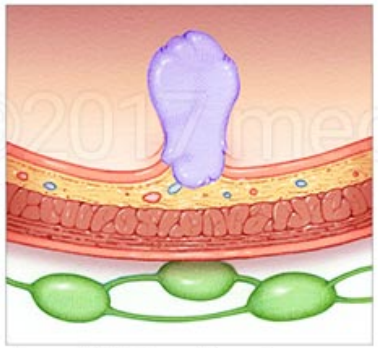
Colon Cancer Staging



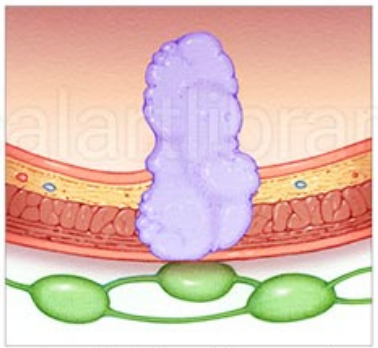
normal poylp



stage 0 - mucosa

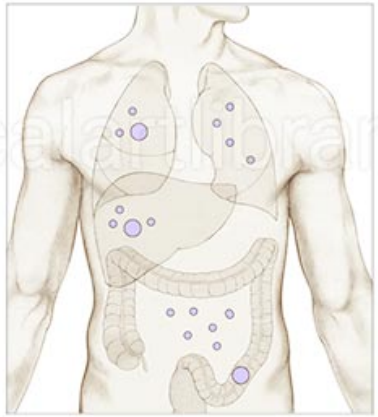


stage 1 (Dukes A) - submucosa



stage 2 (Dukes B) - muscle

stage 3 (Dukes C) - lymph nodes



stage 4 (Dukes D) - metastases

Screening

- synonym for secondary prevention
- the goal is to discover the disease in the asymptomatic (early) phase in "healthy" individuals
- enables more efficient treatment
- reduces mortality
- it should be based on scientific evidence
- to be applicable to a large part of the population
- good relation of costs and efficiency
- to be sensitive enough
- that in case of a positive finding it is followed immediately by further diagnosis and possible treatment

Colorectal cancer diagnosis

- Medical history and physical exam
- The Digital Rectal Examination
- Colonoscopy-biopsy, histopathological examination
- Molecular tests: If the cancer is advanced, the cancer cells will probably be tested for specific gene and protein changes that might help tell if targeted therapy drugs could be options for treatment (KRAS, NRAS, and BRAF genes, as well as other gene and protein changes)
- imaging: CT or MRI scan of the chest and abdomen, 18-FDG PET-CT
- Tumors up to 15 cm from the ano-cutaneous edge are defined as rectal tumors, those above are colon tumors.

Lung Cancer Diagnosis

- Medical history and physical examination
- Chest x-ray
- CT scan of the chest and abdomen: is more likely to show lung tumors than routine chest x-rays. It can also show the size, shape, and position of lung tumors and can find enlarged lymph nodes;CT can also be used to look for masses in the adrenal glands, liver, brain, and other organs that might be due to the lung cancer spread.
- Definitive diagnosis of lung cancer can be made in two ways: histopathological and cytopathological. Bronchoscopy specimens included: induced sputum, bronchial washing (BW), bronchial brushing (BB), endobronchial ultrasound- guided or transesophageal FNA.
- Molecular tests for gene changes, especially for NSCLC : KRAS, EGFR, ALK, RET, RAS
- Other diagnostics according to symptoms: PET-CT, bone scan, MRI

Breast cancer diagnosis

- Medical history and physical exam
- US/mammography/Breast MRI
- CT scan of the chest and abdomen
- Biopsy and histopathological diagnosis
- Other diagnostics according to symptoms: PET-CT, bone scan, MRI

Assessment of Risk Factors for Breast Cancer

- **Female Gender**-Breast cancer accounts for over 32% of all invasive cancers in women and only 1% in men.
- **Age**-The risk of breast cancer increases with age
- **Personal history of cancer**- Previously diagnosed breast cancer, increases the risk by 4 times of breast cancer in the opposite breast. Previous ovarian, endometrial or colon cancer ↑1-2 times risk
- **Family history of cancer and genetics**-Those with a family history (mother, sister, or daughter) of breast cancer are between 2-4 times more likely to develop breast cancer. Mutation of the BRCA1 or BRCA2 tumour suppressor genes have a significant lifetime risk of developing breast cancer,
- **Hormonal Factors-**Early menarche (before 12), late menopause (after 55) menses ↑ risk of breast cancer.
- **Nulliparity** and first full-term pregnancy after 30 is associated with an increased risk of breast cancer.

Asssessment os Risk Factors for Breast Cancer

- **Oral Contraceptives or hormone replacement therapy** can increase the risk of breast cancer especially when HRT includes the addition of progestin and use is prolonged (over 5 years).
- **Lactation-** reduction in risk of 4% is associated per 12 months of breast feeding for all parous women
- **Benign Breast Disease**-proliferation of abnormal looking cells, with atypia within ducts or lobules, 2-4 times increased risk of breast cancer.
- **Obesity and Dietary Fat-** Obesity is associated with higher levels of insulin and other hormones, which increase the risk of cancer diagnosis and increase risk of cancer recurrence two-fold.
- **Radiation exposure**-Women exposed to ionizing radiation of the chest have been shown to be at an increased risk of developing breast cancer
- **Mamography breast density**-breast cancer risk rises with increasing breast density

Breast cancer screening

- **Average risk**

breast examination by a physician:

-every 3 years in women 20-40 years

-annual examination in women >40 years

The European guidelines: mammography screening in all women aged 45 to 74 years.

-For age 50 to 69 is recommended every 2 years;

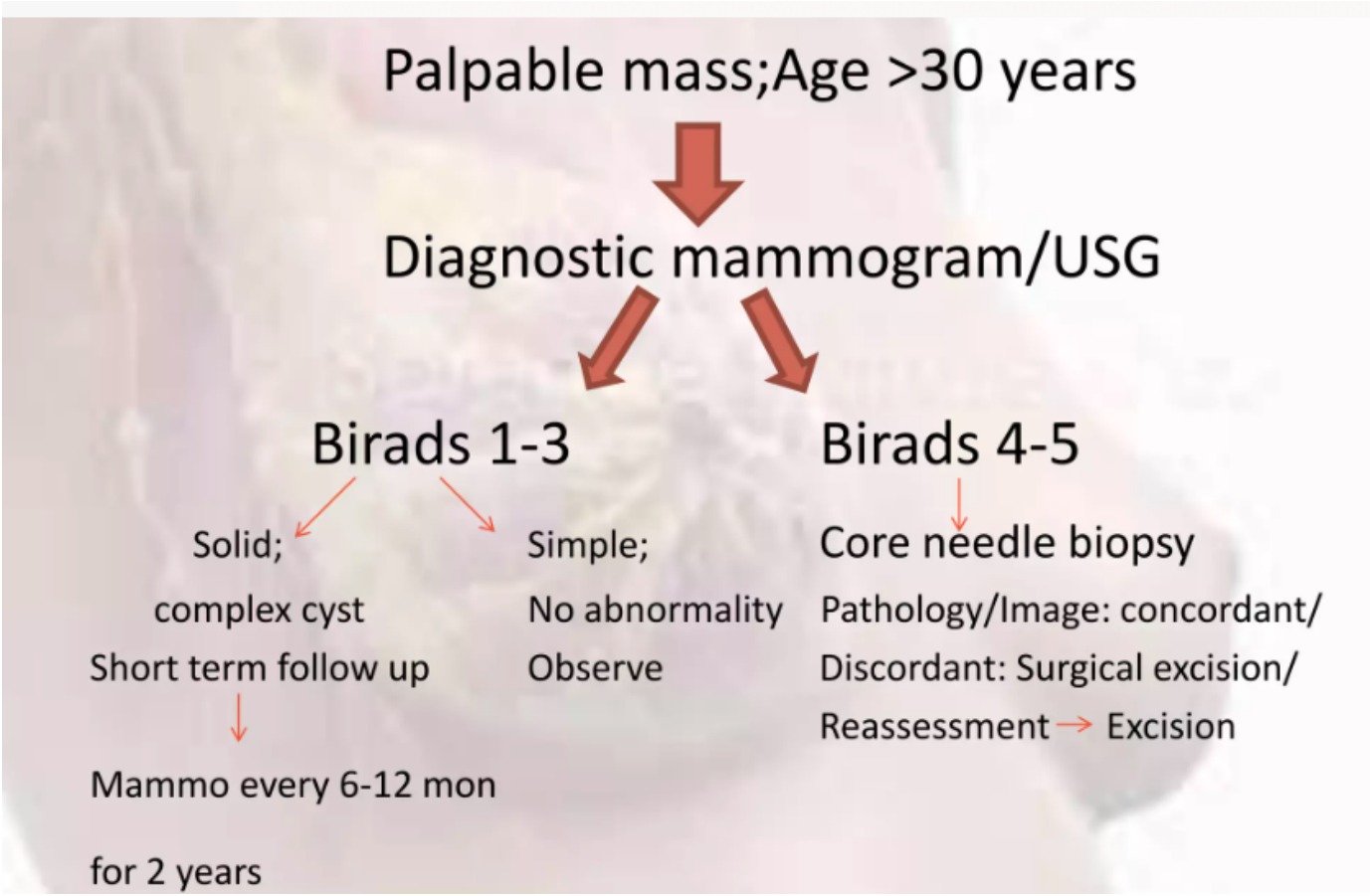
-for age 45 to 49 years, every 2-3 years;

-for age 70 to 74, every 3 years.

- **High risk:** women with a calculated life-time risk of breast cancer ≥20%
- breast examination by a oncologist 1-2/ year
- the screening of choice is breast MRI.
- annual MRI starting age 25-30
- For those who qualify for but cannot undergo breast MRI, mammography (CEM) or US could be considered.
- annual digital mammography, starting at age 30 (*mammographic screening can delay until age 40 if annual breast MRI is performed as recommended*).

All women >20 years of age should examine their breasts 5 days after each menstrual period.
Postmenopausal women or those with irregular menses should examine their breasts on the same day each month.

Possible algorithm for women over 30 years with the complaint of a breast mass



BI-RADS (Breast Imaging Reporting and Data System) categories, which range from category 1 (not cancer) to category 6 (high likelihood of cancer)
(American College of Radiology)

Final Assessment Categories			
Category		Management	Likelihood of cancer
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	n/a
1	Negative	Routine screening	Essentially 0%
2	Benign	Routine screening	Essentially 0%
3	Probably Benign	Short interval-follow-up (6 month) or continued	>0 % but ≤ 2%
4	Suspicious	Tissue diagnosis	4a. low suspicion for malignancy (>2% to ≤ 10%) 4b. moderate suspicion for malignancy (>10% to ≤ 50%) 4c. high suspicion for malignancy (>50% to <95%)
5	Highly suggestive of malignancy	Tissue diagnosis	≥95%
6	Known biopsy-proven	Surgical excision when clinical appropriate	n/a

Cervical cancer–risk factors

- **Infection by the human papillomavirus** HPV is the most important risk factor
- **sexual history** : becoming sexually active at a young age <18 years old, having many sexual partners, having high risk partner (someone with HPV infection or who has many sexual partners)
- **Smoking:** Women who smoke are about twice as likely as those who don't smoke to get cervical cancer.
- **weakens the immune system** (HIV) puts people at higher risk for HPV infections
- **Chlamydia infection-**hlamydia bacteria may help HPV grow
- **taking oral contraceptives for a long time** (>5 years) increases the risk of cancer of the cervix.
- **Having multiple full-term pregnancies:** Women who have had 3 or more full-term pregnancies have an increased risk of developing cervical cancer.

Cervical cancer–risk factors

- **Young age at first full-term pregnancy:** women with first full-term pregnancy <20 years are more likely to get cervical cancer later in life, than women who get pregnant >25 years
- **Economic status:** Many low-income women do not have easy access to adequate health care services, including cervical cancer screening with Pap tests and HPV tests.
- **A diet low in fruits and vegetables:** Women whose diets don't include enough fruits and vegetables may be at increased risk for cervical cancer.

- **Factors that may lower risk**
- **Intrauterine device (IUD) use:** Some research suggests that women who had ever used an intrauterine device (IUD) had a lower risk of cervical cancer. The effect on risk was seen even in women who had an IUD for less than a year, and the protective effect remained after the IUDs were removed.

Risk factors that cannot be changed

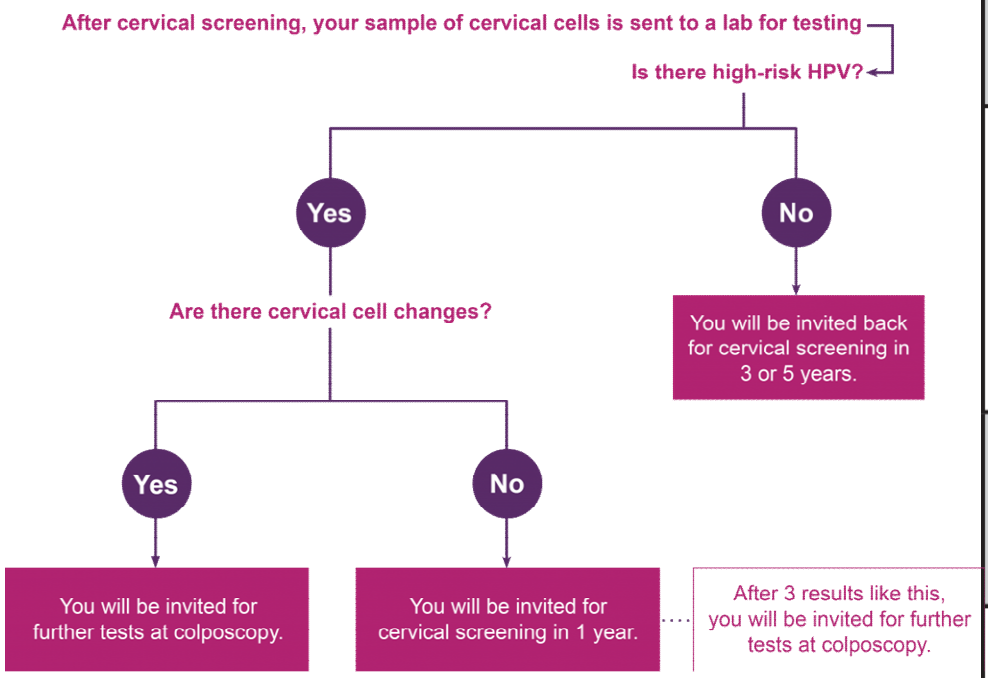
- **Diethylstilbestrol (DES):** DES is a hormonal drug that was given to some women between 1938 and 1971 to prevent miscarriage. Women whose mothers took DES (when pregnant with them) develop clear-cell adenocarcinoma of the vagina or cervix more often than would normally be expected. These types of cancer are extremely rare in women who haven't been exposed to DES. DES daughters may also be at increased risk of developing squamous cell cancers and pre-cancers of the cervix linked to HPV.
- **Having a family history of cervical cancer:** Cervical cancer may run in some families. Some researchers suspect that some rare instances of this familial tendency are caused by an inherited condition that makes some women less able to fight off HPV infection than others.

Cervical Cancer Screening

The introduction of vaccines targeting the most common cancer-causing HPV genotypes has advanced the primary prevention of cervical cancer. As vaccination coverage increases, HPV prevalence is expected to continue to decline . This could prompt future changes to screening guidelines.

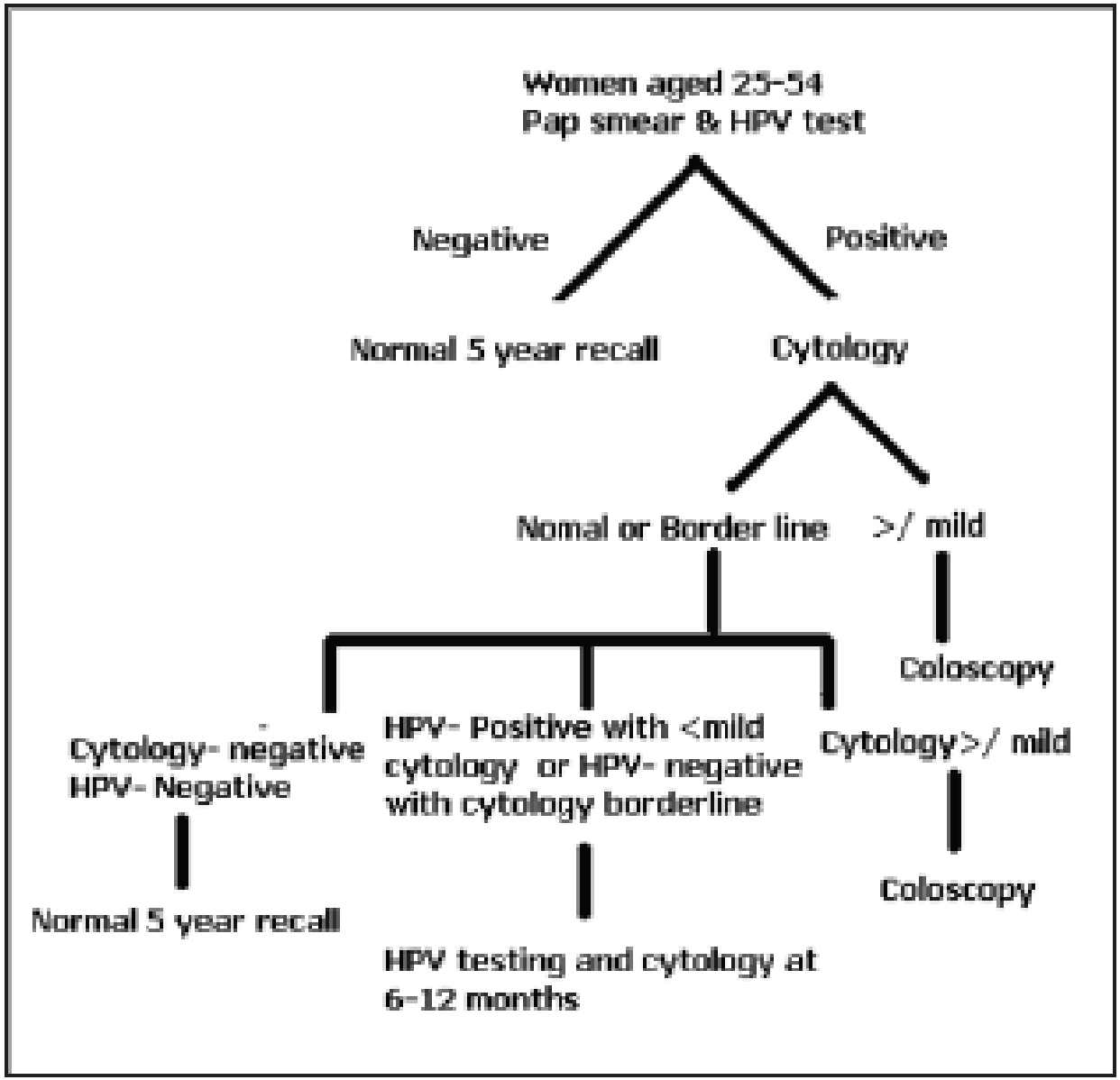
Population*	Recommendation
Aged less than 21 years	No screening
Aged 21–29 years	Cytology alone every 3 years‡
Aged 30–65 years	Any one of the following: • Cytology alone every 3 years • FDA-approved primary hrHPV testing alone every 5 years • Cotesting (hrHPV testing and cytology) every 5 years
Aged greater than 65 years	No screening after adequate negative prior screening results§
Hysterectomy with removal of the cervix	No screening in individuals who do not have a history of high-grade cervical precancerous lesions or cervical cancer

Cervical Cytology (Papanicolau system) and Histopathological Cervical Biopsy Findings (Bethesda System)



Papanicolaou System	*Bethesda System*
Inadequate sample	Unsatisfactory result/ inadequate sample
PA I Normal result	Negative for intraepithelial lesion or malignancy, NILM
PA II Present inflammation, benign reactive and reparative changes	Present inflammation, benign reactive and reparative changes Negative for intraepithelial lesion or malignancy (no observed abnormality), NILM
IIIa Atypical cells of undetermined significance •squamous • glandular	ASC-US (in favour of reactive changes)) ASC-H (in favour dysplasia) AGC (atypical glandular cells)
IIIb Dyskariosis of a light degree Dyskaryosis of a medium degree	L-SIL (CIN 1) H-SIL (CIN 2)
IV Dyskariosis of a severe degree	H-SIL (CIN 3) AIS
V malignant cells	invasive carcinoma

Possible algorithm for cervical cancer management



Risk Factors for Developing Colon Cancer

Risk Classification	Characteristics
Average Risk	Age >50 Absence of history of adenoma Absence of history of inflammatory bowel disease Absence of family history of colon cancer
Increased Risk	Personal history of adenoma Personal history of colorectal cancer Personal history of endometrial or ovarian cancer prior to the age of 60 Personal history of inflammatory bowel disease Family history of colorectal cancer or adenoma Family history of hereditary nonpolyposis colortectal cancer
Highest Risk	History of colon cancer in family members younger than age 50 Family history of polyposis Personal history of polyposis syndrome Personal history of hereditary nonpolyposis colorectal cancer

National Comprehensive Cancer Network. Colorectal Screening. Practice Guidelines in Oncology-v.1.2008.

Hereditary CRC syndromes

- **FAP** — and its variants (Gardner syndrome, Turcot syndrome, and attenuated familial adenomatous polyposis [AFAP]) account for less than 1% of CRCs. In typical FAP, numerous colonic adenomas appear during childhood. Symptoms appear at an average age of approximately 16 years and colonic cancer occurs in 90 percent of untreated individuals by age 45. FAP is caused by germline mutations in the adenomatous polyposis coli (*APC*) gene
- **Lynch syndrome** — is more common than FAP and accounts for approximately 3% of all colonic adenocarcinomas. Lynch syndrome can be suspected on the basis of a strong family history of CRC, endometrial, and other cancers.
- defect in one of the DNA mismatch repair (MMR) genes
- Extracolonic cancers are very common in Lynch syndrome, particularly endometrial carcinoma, in up to 60% of female mutation carriers. Other sites at increased risk of neoplasm formation include the ovary, stomach, small bowel, hepatobiliary system, brain and renal pelvis or ureter, and possibly breast and prostate.

RISK FACTORS

- **Hereditary CRC syndromes —** Familial adenomatous polyposis (FAP) and Lynch syndrome are the most common of the familial colon cancer syndromes
- **Inflammatory bowel disease (Crohn disease, Ulcerative colitis) —** There is a well-documented association between chronic ulcerative colitis and colonic neoplasia
- **Abdominopelvic radiation —** Cancer survivors who received abdominopelvic radiation therapy in childhood (adult survivors of pediatric cancer), or as adults are at significantly increased risk of subsequent gastrointestinal neoplasms, the majority being CRC
- **Cystic fibrosis —** Patients with cystic fibrosis (CF) have an elevated risk of CRC
- **Personal or family history of sporadic CRCs or adenomatous polyps —**are at risk for the future development of colon cancer.

- **Race and sex** — Screening strategies do not differ with regard to race. CRC mortality is approximately 33% higher in males than in females. Both colonic adenomas and CRCs appear to have a more proximal distribution in females.
- **Obesity** — Obesity is a risk factor for CRC . The risk was highest for those in the highest weight gain category. Obesity also appears to increase the likelihood of dying from CRC.
- **Diabetes mellitus and hyperinsulinemia** are associated with an elevated risk of CRC
- **Red and processed meat** — long-term consumption of red meat or processed meats appears to be associated with an increased risk of **CRC.**
- **Cigarette smoking, alcohol consumption** has been associated with increased incidence and mortality from CRC

The Amsterdam criteria

- **Amsterdam Criteria I (**Initial description in 1991)
- > or equal to 3 relatives with colorectal cancer (CRC)
- > or equal to 1 case in a first degree relative
- > or equal to 2 successive generations should be affected
- > or equal to 1 tumor should be diagnosed before the age of 50 years
- FAP should be excluded
- tumors should be confirmed with histology

- **Amsterdam Criteria II** Revision in 1996, is one of the most widely used criteria along with Bethesda guidelines.
- > or equal to 3 relatives with colorectal cancer (CRC) or with an HNPCC associated cancer (endometrial carcinoma, small bowel adenocarcinoma, ureter or renal pelvis cancer
- One must be the first degree relative to the other two
- > or equal to 2 successive generations should be affected
- > or equal to 1 tumor should be diagnosed before the age of 50 years
- FAP should be excluded
- tumors should be confirmed with histology

Cancer Risk in Individuals with HNPCC to Age 70 Compared to the General Population

Cancer	General Population Risk	HNPCC Risk	Mean Age of Onset In HNPCC
Colon	7 %	70-80%	45 years
Endometrium	2.3%	20-60%	46 years
Stomach	<1%	13-19%	56 years
Ovary	1.5%	9-12%	42.5 years
Hepatobiliary tract	<1%	2-7%	54 years
Urinary tract	<1%	4-5%	~55 years
Small Bowel	<1%	1-2%	49 years
Brain / CNS	<1%	1-4%	50 years

from: http://www.genetests.org

The Genetics Education Project

Colorectal cancer screening guidelines for average risk individuals

Risk Group	Screening Tool	Onset (Age)	Frequency
• Asymptomatic • Family history limited to non-first degree relatives	Faecal Occult Blood Testing	50 years	Annually
	Colonoscopy	50 years	Every 10 years
	CT Colonography	50 years	Every 5 years

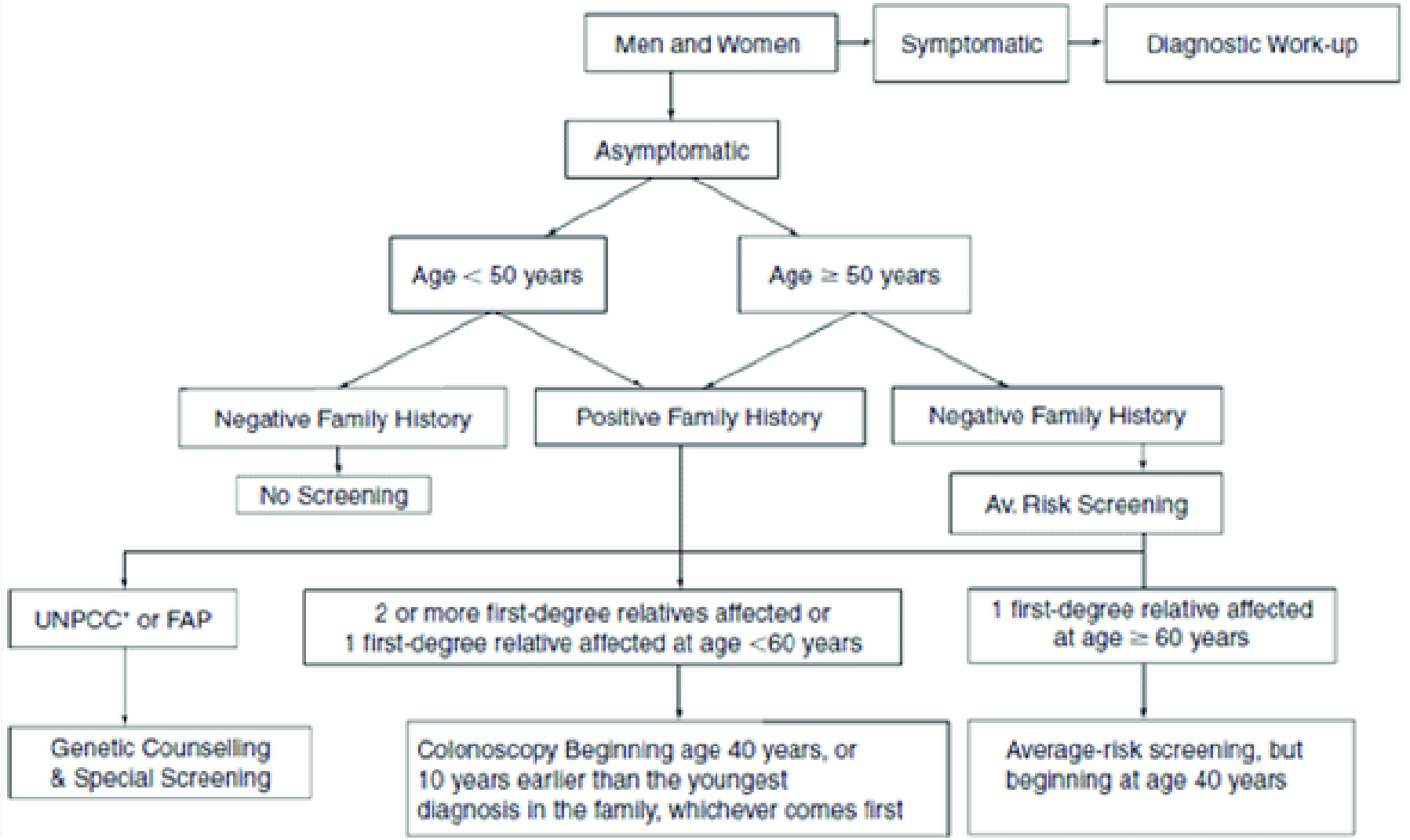
* Screening tool alternatives are arranged in order of supporting evidence

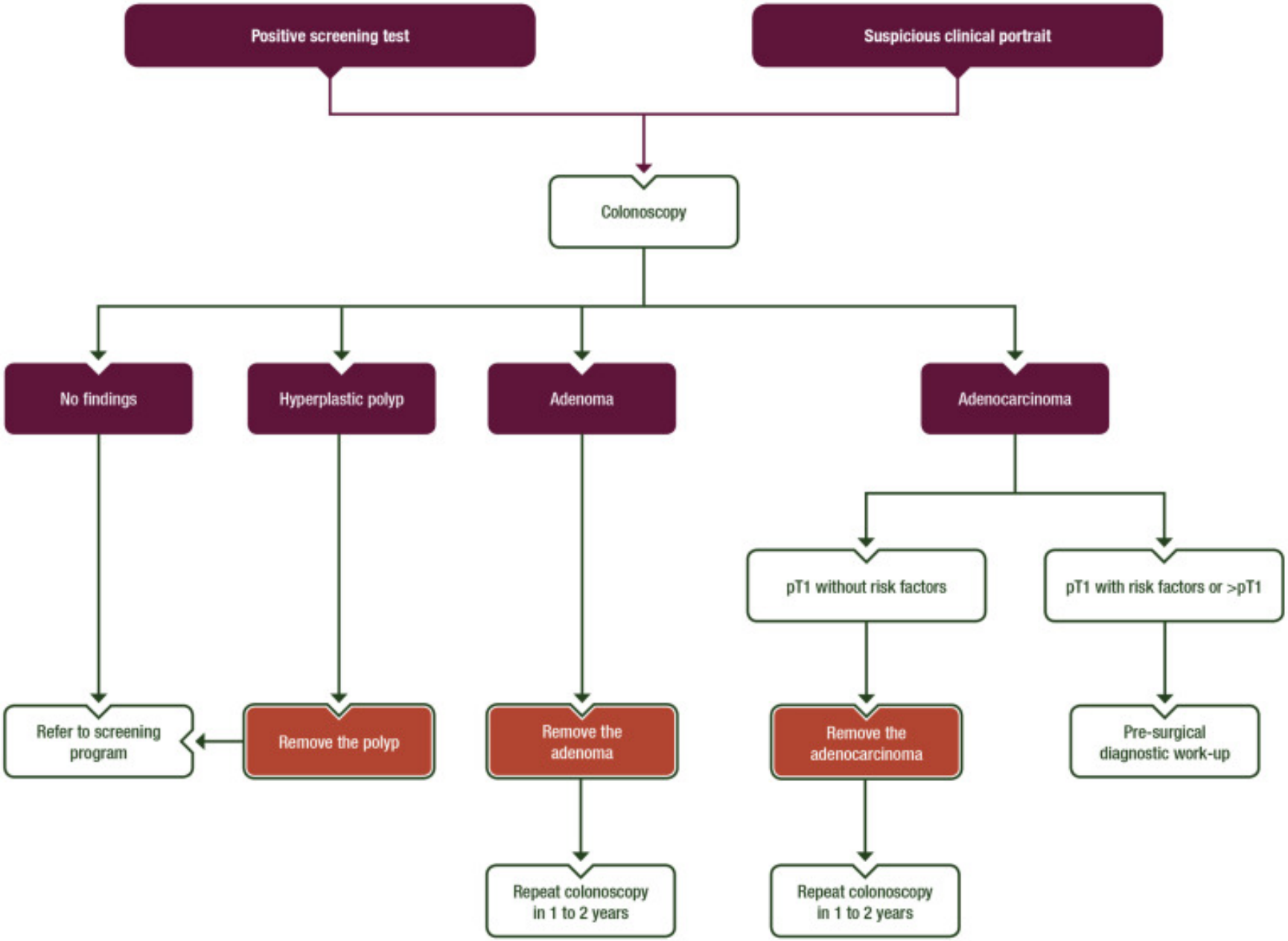
Colorectal cancer screening guidelines for increased risk individuals

Risk Group	Screening Tool	Onset (Age)	Frequency
Colorectal cancer in first degree relative age 60 years or younger, or 2 or more first degree relatives	Colonoscopy	10 years prior to youngest case in the family or age 40 years, whichever is earlier	Every 5 years
Colorectal cancer in first degree relative over the age of 60 years		10 years prior to youngest case in the family or age 50 years, whichever is earlier	Every 10 years
Personal history of colorectal polyps		3 years after polypectomy in the presence of high risk features (>1 cm, multiple, villous architecture); otherwise, 5 years after polypectomy for low risk polyps	-
Personal history of colorectal malignancy		One year after resection	Every 3 years
Personal history of ovarian or endometrial cancer		One year after resection	-

Colorectal cancer screening guidelines for high risk individuals

Risk Group	Screening Tool	Onset (Age)	Frequency
Family history of familial adenomatous polyposis	Flexible sigmoidoscopy (switch to colonoscopy if adenomas identified); consider genetic counselling and testing	10 to 12 years (from puberty)	Every 5 years
Family history of hereditary non-polyposis colorectal cancer	Colonoscopy; consider generic counselling and testing	20 to 25 years	Every 10 years
Inflammatory bowel disease A. Left-sided colitis B. Pan-colitis	Colonoscopy	A. From 15th year of diagnosis onwards B. From 8th year of diagnosis onwards	Every 1 to 2 years


Men and Women
Symptomatic
Diagnostic Work-up
Asymptomatic
Age < 50 years
Age ≥ 50 years
Negative Family History
Positive Family History
Negative Family History
No Screening
Av. Risk Screening
UNPCC* or FAP
2 or more first-degree relatives affected or
1 first-degree relative affected at age <60 years
1 first-degree relative affected
at age ≥ 60 years
Genetic Counselling
& Special Screening
Colonoscopy Beginning age 40 years, or
10 years earlier than the youngest
diagnosis in the family, whichever comes first
Average-risk screening, but
beginning at age 40 years


Positive screening test
Suspicious clinical portrait
Colonoscopy
No findings
Hyperplastic polyp
Adenoma
Adenocarcinoma
pT1 without risk factors
pT1 with risk factors or >pT1
Refer to screening program
Remove the polyp
Remove the adenoma
Remove the adenocarcinoma
Pre-surgical diagnostic work-up
Repeat colonoscopy in 1 to 2 years
Repeat colonoscopy in 1 to 2 years