Frank malignancy requires the presence of one billion malignant cells \(10^9\).

<table>
<thead>
<tr>
<th>Characteristics of human neoplasia</th>
<th>Characteristics of precursor lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Abnormal growth and cell proliferation.</td>
<td></td>
</tr>
<tr>
<td>• Invasiveness</td>
<td></td>
</tr>
<tr>
<td>• Abnormal cell proliferation (known as metaplasia).</td>
<td></td>
</tr>
<tr>
<td>• No invasiveness.</td>
<td></td>
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<tr>
<td>• Examples:</td>
<td></td>
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<tr>
<td>✓ Colon polyps (preceding colon cancer).</td>
<td></td>
</tr>
<tr>
<td>✓ Skin dysplastic navi (preceding melanoma).</td>
<td></td>
</tr>
</tbody>
</table>

**Steps of tumorigenesis:**

- **Initiation:**
  ✓ Tumors usually arise from a single cell or clone.
  ✓ **Initiation event (mutation):**
    - Gain of function of oncogens (amplification).
    - Loss of function of tumor-suppressor genes (deletions).

- **Promotion:**
  ✓ Represented by subsequent events after the initiation event (accumulation of additional mutations).

- **Progression:**
  ✓ Benign lesions → in situ tumors → invasive cancers!

**Genetic alterations in neoplasia:**

- **Genetic mutations.**
- **Epigenetic changes:** hyper-methylation in the promoter region leading to gene silencing:
  ✓ Influence gene expression and cell behavior.
  ✓ Transmitted to daughter cells (inherited).

- A particular genetic alteration is linked to a certain cancer type (molecular marker), target for:
  ✓ Drug development.
  ✓ Molecular profiling (classification).

**Ideal tumor markers:**

- What are tumor markers?
  ✓ They are biological substances synthesized and released by cancer cells or produced by the host in response to the presence of the tumor.

- **Characteristics:**
  ✓ In healthy individuals: low concentrations.
  ✓ Being specific to the tumor.
  ✓ Levels should change in response to tumor size.
  ✓ Predict recurrences before they are clinically detectable.

- **Tumor markers are detected in:**
  ✓ Solid tumor.
  ✓ Circulating tumor cells in blood.
  ✓ Lymph nodes.
  ✓ Bone marrow.
  ✓ Body fluids (e.g. urine, stool, ascites).

- **Types of tumor markers:**
  ✓ Tumor specific proteins:
    - They are expressed only in tumor cells.
    - They are products of mutated oncogenes and tumor suppressor genes.
  ✓ Cell-specific proteins over-expressed in malignant cells:
    - *Example:* Prostate-Specific Antigen (PSA) expressed in prostate cancer.
✓ Non-specific proteins or markers related to malignant cells:
  
  ➤ Oncofetal proteins: expressed by cells as they de-differentiate and take on embryonic characteristics:
    ➢ α-FP (alpha Fetoprotein): hepatocellular carcinoma; testicular of ovarian cancer.
    ➢ CEA (Carcino-Embryonic Antigen):
      - Detect early relapse of colorectal cancer.
      - Found in 30-50% of breast cancer and small cell lung cancer.
      - Normal pre-therapy CEA indicates lower metastasis incidence while high initial CEA indicates higher metastasis incidence.
      - CEA can also be elevated in patient with COPD and those who smoke.

• Uses of tumor markers:
  ✓ Population screening:
    ❖ Screening tests:
      - Cancer must be common.
      - Natural history of the cancer should be understood.
      - Effective treatments must be available.
      - The test must be acceptable to both patients and physicians.
      - The test must be safe and relatively inexpensive.
  ✓ Diagnosis.
  ✓ Establishing prognosis and staging.
  ✓ Post-operative evaluation.
  ✓ Monitor treatment response.
  ✓ Surveillance for recurrence.
  ✓ Targets for therapeutic intervention.

• Breast cancer markers:
  ✓ HER-2-neu (Human epidermal growth factor receptor 2): it is an oncogen. If it is overexpressed in breast cancer, this indicates poor prognosis.
  ✓ BRCA-1 (Breast cancer type 1) gene on chromosome 17 indicates familial breast-ovarian cancer syndrome.

• Estrogen Receptor (ER):
  ✓ They are implicated in: breasts, ovaries, endometrium, prostate, colon and cancers.
  ✓ There are two isoforms:
    ❖ ERα: better prognosis; predictor of relapse.
    ❖ ERβ: correlates with low-grade tumor and negative involvement of axillary lymph nodes.

• Cervical squamous cell carcinoma:
  ✓ Squamous cell carcinoma antigen (SCC):
    ❖ Not sensitive enough for screening early-stage carcinoma.
    ❖ Used for prognosis and monitoring.

• Cancer Antigen 19-9 (CA 19-9):
  ✓ It is not recommended for screening, diagnosis, surveillance or monitoring of therapy for colon or pancreatic cancers!! (JUST A USELESS EXTRA INFO BECAUSE YOU ARE A MEDICAL STUDENT 😊!)