TUMOR MARKERS
IN SUPPORTING CANCER REGISTRATION

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"Critical to improving data quality are cancer registrars. They are personnel with specialized training to abstract pertinent information with regard to the history, diagnosis, treatment and surveillance of cancer patients."

My Purpose:

... enabling a judicious use of widely performed serum cancer markers as (potential!) support in cancer registration.
“Tumor markers are not the primary modalities for cancer diagnosis rather they can be used as laboratory test to support the diagnosis.”

Can tumor markers be useful in driving and/or making easier/more consistent cancer registration?
Testing for a Cancer of Unknown Primary

Tumor Registry Setting

Exploiting (serum) Biomarkers in Looking for Cancer of Unknown Primary
TUMOR REGISTRYSETTING

EXPLOITING (SERUM) BIOMARKERS IN LOOKING FOR CANCER OF UNKNOWN PRIMARY

... WHERE MIGHT IT HAVE STARTED?
... WHERE MIGHT IT HAVE STARTED?

A Cancer of Unknown Primary (CUP)!
Cancers are named based on their primary site.

Cancers often spread from their primary site to one or more metastatic sites (example: a lung cancer that spreads to the liver is still classified as lung cancer).

Sometimes it’s not clear where a cancer may have started. When cancer is found in one or more metastatic sites but its primary site cannot be determined, it is called CUP. This happens in a small portion of cancers.

Further tests (cancer biomarkers?) may eventually «disclose» the primary cancer site. When this happens, the CUP is renamed and treated according to where it started.
... WHERE MIGHT HAVE IT STARTED?

MEDICAL HISTORY

IMAGING INCLUDING SCINTIGRAFY

ENDOSCOPY

BLOOD TESTS

TISSUE SAMPLES
... WHERE MIGHT HAVE IT STARTED?

BLOOD TESTS

TISSUE SAMPLES
HORMONES

Calcitonin

Thyroid Medullary cancers

Catecolamine

Pheochromocytoma

Human Chorionic Gonadotropin

Trophoblastic testicular tumors
Non-seminomatous testicular tumors

Ectopic hormones
Paraneoplastic syndromes
**ONCOPHETAL ANTIGENS**

- Alfa-fetoprotein
  - Liver cancer
  - Testicular tumors

- Carcino-embryonic antigen
  - Liver cancer
  - Pancreas cancer
  - Lung cancer
  - Stomach cancer

**ISOENZYMES**

- Prostatic acid phosphatase
  - Prostate cancer

- Neuron specific enolase
  - Neuroendocrine tumors (different primary sites)
**PROTEINS**

- PSA-PSMA: Prostate cancer
- Immunoglobulins: Multiple Mieloma

**MUCINS-GLICOPROTEINS**

- C19.9: Colon cancer
- C125: Ovary cancer
- C15.3: Breast cancer
BIOMARKERS IN THE ONCOGENETIC CASCADE
ONCOGENETIC CASCADE & «BIOMARKERS OPPORTUNITIES»

GENE MUTATIONS → ALTERED GENE EXPRESSION → ALTERED PROTEINS EXPRESSION → ALTERED METABOLITES

GENETIC BIOMARKERS → CANCER-BASED BIOMARKERS BIOMOLECULES → METABOLIC BIOMARKERS

Diagnosis Therapy
Diagnosis Prognosis
Diagnosis Prognosis Therapy
... WHERE MIGHT HAVE IT STARTED?

In some cases, the source of the cancer is undetermined (CUP). Even when pathologists do autopsies on people who have died of cancer of unknown primary, they may be still unable to find the site where the cancer started. The main reason to look for the primary site of a Cancer of Unknown Primary is to guide treatment.

In cancer registration workup, however, to assign a cancer to a specific site may have significant epidemiological consequences.
**Prostate-specific antigen (PSA):** A high PSA level suggests that a CUP may have started in the prostate.

About 1/9 man will suffer of prostate cancer during his lifetime. It is **rare before age 40.** The average age at the time of diagnosis is about 66.

Most men without prostate cancer have blood PSA levels under 4 nanograms per milliliter.  
The chance of having prostate cancer goes up as the PSA level goes up.  
When cancer develops, the PSA level usually goes above 4 (a level <4 does not guarantee that a man doesn’t have cancer; 15% of men with a PSA <4 have cancer on a biopsy).  
Men with PSA level between 4-10 have about a 1/4 chance of having cancer.  
**Men with PSA level >10 have over 50% chance of having cancer.**
Human chorionic gonadotropin (HCG): High HCG levels suggest a germ cell tumor originating from testis/ovary, mediastinum, or retroperitoneum.

<table>
<thead>
<tr>
<th>Seminomas</th>
<th>Classical: 95% (HCG ±)</th>
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<tbody>
<tr>
<td>Non-seminomas</td>
<td>Spermatocytic: 5% (HCG ±)</td>
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<tr>
<td>(Germ Cell Tumor in both M/F)</td>
<td>Embryonal carcinoma (HCG ↑, AFP ↑)</td>
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<tr>
<td></td>
<td>Yolk sac carcinoma (AFP ↑)</td>
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<tr>
<td></td>
<td>Choriocarcinoma (HCG ↑)</td>
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<tr>
<td></td>
<td>Teratomas (AFP ±)</td>
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Worldwide incidence rate of testicular cancers is reported as increasing (mostly seminomas).
Testicular cancer is uncommon: 1/250 males will develop testicular cancer at some point during their lifetime.
The average age at the time of diagnosis is about 33. It is largely a disease of young/middle-age.
About 6% of cases occur in children/teens; about 8% occur in men >55 yrs old.
Cancer can usually be treated successfully (lifetime dying risk: ± 1/5,000).
Alpha-fetoprotein (AFP): Is produced by:
i) some germ cell tumors: ii) some liver cancers (HCC)

<table>
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<th>Testis Cancer:</th>
<th>HCC</th>
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<tr>
<td><strong>Seminomas</strong></td>
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**HCC**

Mostly occurs in men >55 yrs old (strictly linked to cirrhosis incidence)

AFP is normally present at high levels in fetuses’ blood (shortly drops after birth). In adults, AFP can go up from liver disease, HCC, or other cancers. Because HCC isn’t the only reason for high AFP levels and HCC may have normal AFP, it isn’t very helpful in HCC diagnostic assessment.

**DKK1** as a serum marker for HCC. DKK1 is overexpressed in HCC tissue but is not detectable in non-cancer liver tissue (attractive candidate as HCC-marker)
PANCREATIC CANCERS: DIFFERENT HISTOGENESIS RESULTING INTO DIFFERENT SERUM MARKERS

NORMAL ANATOMY

CANCER SIDE

Neuroendocrine Markers

Epithelial Markers
**CA 19-9:** High levels suggest that the cancer started in the pancreas or biliary tree (*CEA* is not used as often as CA 19-9)

**CA 19-9 and CEA are not accurate in the assessment of pancreas epithelial malignancy.** Levels of these tumor markers are not high in all people with pancreatic cancer, and some people who don’t have pancreatic cancer might have high levels of these markers for other reasons. Still, these tests can sometimes support a histogenetic hypothesis (along with other tests).
**CA 19-9:** High levels of this tumor marker suggest that cancer started in the pancreas or biliary tree (**CEA** is not used as often as CA 19-9)

Biliary tract cancer (cholangiocarcinoma) may have high blood levels of **CEA** & **CA 19-9**. High **CEA/CA 19-9** can also result from other types of cancer, or even by non-cancer diseases. Not all bile duct cancers ↑**CEA/CA 19-9** (low or normal levels can not exclude cancer).

Cholangiocarcinoma is rare and includes both intra-hepatic and extra-hepatic bile duct cancers. Bile duct cancer rarely occur at young age; the average age of diagnosis for both intra- and extra-hepatic cholangiocarcinoma ranges between 70-72 yrs.
CA-125: A high levels suggests ovarian, fallopian tube, or primary peritoneal cancer.

Germ cell cancers may cause elevated blood levels of HCG, AFP, and/or lactate dehydrogenase (LDH). Some ovarian stromal tumors may associate with increased the blood levels of Inhibin and both Estrogen/Testosterone.

REMIND

OVARIAN CANCER: Germ Cell Tumors

- Embryonal carcinoma (HCG ↑, AFP ↑)
- Yolk sac carcinoma (AFP ↑)
- Choriocarcinoma (HCG ↑)
- Teratomas (AFP ±)

Ovary cancer ranks fifth among women in cancer deaths (more deaths than any other cancer of the ♂ reproductive system). A woman's risk of getting ovarian cancer during her lifetime is about 1/78. The lifetime chance of dying from ovarian cancer is about 1/108 (excluding low malignant potential ovary tumors).

NB: Pre-assessed BRCA1 or BRCA2 mutations (>1,000 BRCA mutations have been described) may suggest ovarian and/or breast cancer
<table>
<thead>
<tr>
<th>Spectrum Neuroendocrine Tumors</th>
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<tbody>
<tr>
<td><strong>Insulin</strong> (for Insulinomas ++),</td>
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<tr>
<td><strong>C-peptide</strong> (for Insulinomas ++)</td>
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<tr>
<td><strong>Gastrin</strong> (for Gastrinomas ++),</td>
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<td><strong>Glucagon</strong> (for Glucagonomas),</td>
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<tr>
<td><strong>Somatostatin</strong> (for Somatostatinomas),</td>
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<tr>
<td><strong>Pancreatic polypeptide</strong> (PPomas),</td>
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<tr>
<td><strong>Vasoactive intestinal peptide</strong> (VIPomas)</td>
</tr>
<tr>
<td><strong>Chromogranin A</strong> (CgA; for any NE-Tumor),</td>
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<tr>
<td><strong>Neuron-specific enolase</strong> (NSE; for NE-Tumors),</td>
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<tr>
<td><strong>Substance P</strong> (for Carcinoid)</td>
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**Organ Sites**: Thyroid, Thymus, Esophagus, Lung, Stomach, Pancreas, Small Bowel, Large Bowel, Appendix, Rectum
As a consequence...
... moving to “-omics”...
The increasing clinical impact of molecular profiling of cancer patients requires robust, validated tests (sensitivity, specificity, & detection limits ).
<table>
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<tr>
<th>MOLECULAR BIOMARKER USED IN CLINICAL PRACTICE TO GUIDE DIAGNOSIS &amp; THERAPY</th>
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<tr>
<td><strong>DIAGNOSIS</strong></td>
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<tr>
<td>Myeloproliferative Diseases</td>
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<tr>
<td><em>JAK2</em> mutations confirm diagnosis of clonal MPD*</td>
</tr>
<tr>
<td>Sarcomas</td>
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<tr>
<td>• <em>SS18-SSX1/SSX2</em> Synovial sarcoma</td>
</tr>
<tr>
<td>• <em>PAX3/PAX7-FOXO1A</em> Alveolar rhabdomyosarcoma</td>
</tr>
<tr>
<td>• <em>EWSR1-FLI1; EWSR1-ERG</em> Ewing’s sarcoma</td>
</tr>
<tr>
<td>• <em>EWSR1-NR4A3; TAF15-NR4A3</em> Extra-skeletal myxoid chondrosarcoma</td>
</tr>
<tr>
<td>• <em>EWSR1-ATF1</em> Clear cell sarcoma (and angiomatoid fibrous histiocytoma)</td>
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<td>• .........</td>
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<tr>
<td><strong>PREDICTIVE</strong></td>
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<tr>
<td>Non-small Cell Lung Cancer</td>
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<tr>
<td>• <em>EGFR</em> mutations predict response to TKI</td>
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<tr>
<td>• <em>ALK</em> Rearrangements predict response to ALK-inhibitors</td>
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<tr>
<td>Gastrointestinal Stromal tumors</td>
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<tr>
<td>• <em>KIT &amp; PDGFRA</em> mutations predict response to c-KIT/PDGFRA inhibitors</td>
</tr>
<tr>
<td>• <em>CRC KRAS</em> mutations predict lack of response to anti-EGFR antibodies</td>
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<td>• .........</td>
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<tr>
<td><strong>PROGNOSTIC</strong></td>
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<tr>
<td>Metastatic CRC</td>
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<tr>
<td>• <em>BRAF</em> mutations are indicative of poor outcome</td>
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<td>• .........</td>
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<tr>
<td><strong>DISEASE MONITORING</strong></td>
</tr>
<tr>
<td>Chronic Myeloid Leukemia</td>
</tr>
<tr>
<td>• <em>BCR-ABL1</em> Minimal residual disease detection</td>
</tr>
<tr>
<td>Acute Promyelocytic Leukemia</td>
</tr>
<tr>
<td>• <em>PML-RARA</em> Minimal residual disease detection</td>
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<td>• .........</td>
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Regrettably, most tumor marker studies fail to rigorously address analytic validity or clinical utility. Rather, most publications simply demonstrate clinical validity with a marker assay that is often poorly described and not demonstrated to be accurate, reliable, and reproducible outside of the respective research laboratory that developed it.

Few tumor marker tests have been studied with sufficient rigor to generate the kind of high-level evidence needed to determine whether they have clinical utility. Indeed, 40 years into the remarkable biologic observations from the revolution in molecular biology and more than a decade after initiation of the “-omics” era, only a few tumor markers are supported by evidence that would be considered Level 1.
EXAMPLES:
The only tissue-based markers recommended for breast cancer (ASCO Guidelines) are: i) estrogen & progesterone receptor testing for decisions about delivery of endocrine therapy, ii) HER2 testing for anti-HER2 therapy, and iii) urinary plasminogen activator & plasminogen activator inhibitor 1 assay to determine prognosis.

The situation in other solid tumors is even more dismal.

In CRC, testing for KRAS mutations is recommended for Ab-anti-EGFR treatment.

In lung cancer, testing for ALK translocations (likelihood of sensitivity to crizotinib), and for EGFR mutations, (associated with benefit from tyrosine kinase inhibitor therapy), are recommended.

Among the many other promising markers reported for prognosis/prediction of benefit from both targeted and routine therapies, few have advanced beyond the clinical validity phase.
... moreover
CANCER PATIENTS PROFILE (including tumor markers)

Initial Profiling

First-line Therapy

Adaptive therapy in response to longitudinal profiling

Tumor Markers

Tumor Markers
NCRA is the premier education resource for the cancer registry community. Whether you are beginning your career, preparing to take the CTR exam, NCRA provides a wide variety of training that is uniquely focused on the needs of the cancer registry profession.

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The clinical information achievable by “traditional” cancer-biomarkers is controversial; it may become potentially useful only when supported by “adjunctive clinical traces”;

... “omics-biomarkers” are equally “weak”: they suffer of significant inter-laboratory inconsistency; such as the “traditional” biomarkers, -omics become supportive only when interpreted in a wider context of clinical information;
In supporting the **new mission(s)** of Cancer Registries, -omics information is currently limited to high-resolution registries.
In such a context, the collection of omics-data needs elective/dedicated procedures.

Educational “clinical” programs should support Cancer Registrars in the interpretation/registration of **controversial CUP cases**. The educational profile of cancer Registrars needs to be specifically addressed.
In clinical practice, cancer markers it refers to a molecule that can be detected in plasma and body fluids.

Tumor markers are measurable biochemicals associated with a malignancy. These markers are either produced
i) by tumor cells (tumor-derived) or
ii) by the body, in response to tumor cell (tumor-associated). They are typically substances that are released into the circulation and thus measured in the blood. Tumor markers are not the primary modalities for cancer diagnosis rather they can be used as laboratory test to support the diagnosis.
Cancer is a cluster of diseases involving alterations in the status and expression of multiple genes that confer a survival advantage and undiminished proliferative potential to somatic or germinal cells.[3] Alterations primarily in three main classes of genes, namely (proto) oncogenes, tumor suppressor genes, and DNA repair genes collectively contribute to the development of cancer genotype and phenotype that resists the natural and inherent death mechanism(s) embedded in cells (apoptosis and like processes), coupled with dysregulation of cell proliferation events [Figure 1].[1]
Tumor Markers in supporting cancer registration

REGISTER NOW!

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Monopoli – October, 2018