TUMOR MARKERS IN SUPPORTING CANCER REGISTRATION

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AIRTUM - Monopoli – October, 3rd 2018

My Audience: Cancer Registrars

- 2015 Commentary

*"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

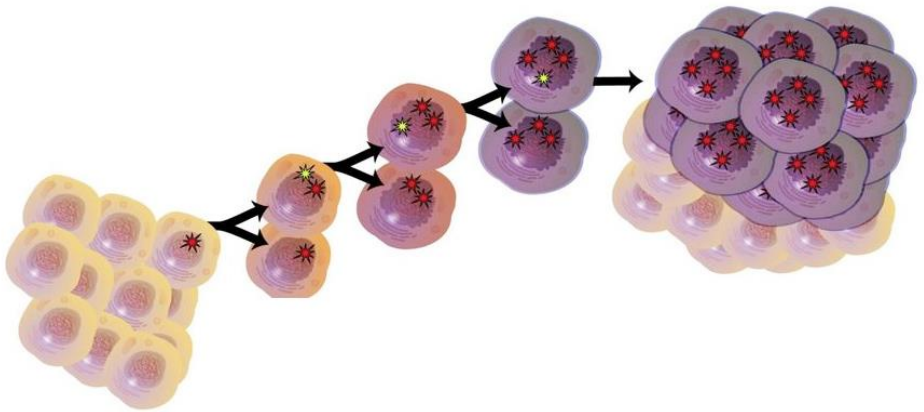
TUMOR REGISTRY SETTING

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

TUMOR REGISTRY SETTING

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).

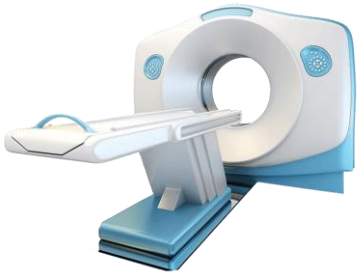
Sometimes it's not clear where a cancer may have started. When cancer is found in one or more metastatic sites but its primary site cannot be determined, it is called **CUP**. This happens in a small portion of cancers.

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.

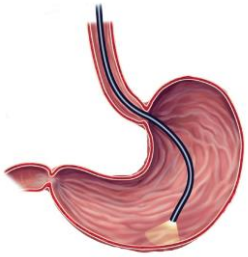
… WHERE MIGHT HAVE IT STARTED ?

MEDICAL HISTORY

IMAGING
INCLUDING SCINTIGRAFY



ENDOSCOPY



BLOOD TESTS

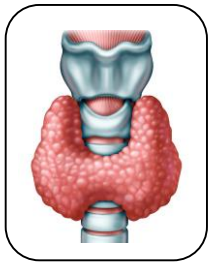
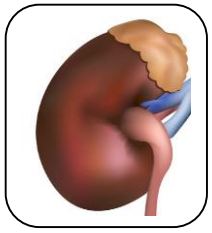
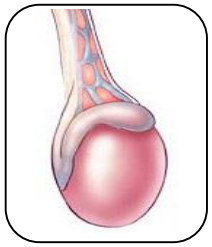
TISSUE SAMPLES

… WHERE MIGHT HAVE IT STARTED ?

BLOOD TESTS

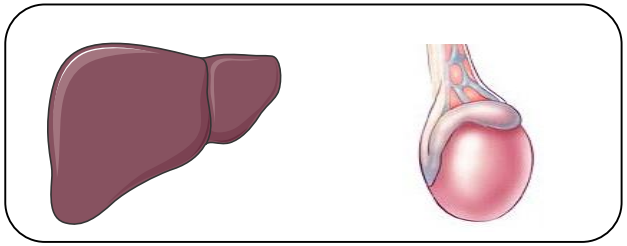
TISSUE SAMPLES

HORMONES

Calcitonin		Thyroid Medullary cancers
Catecolamine		Pheochromocytoma
Human Chorionic Gonadotropin		Trophoblastic testicular tumors Non-seminomatous testicular tumors
Ectopic hormones		Paraneoplastic syndromes

ONCOPHETAL ANTIGENS

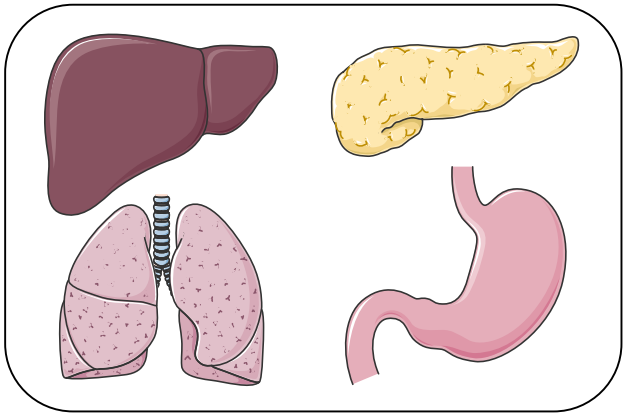
Alfa-fetoprotein



Liver cancer

Testicular tumors

Carcino-embryonic antigen



Liver cancer

Pancreas cancer

Lung cancer

Stomach cancer

ISOENZYMES

Prostatic acid phosphatase

Prostate cancer

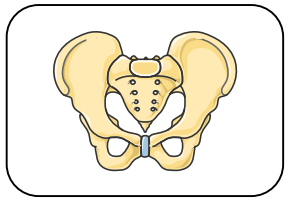
Neuron specific enolase

Neuroendocrine tumors (different primary sites)

PROTEINS

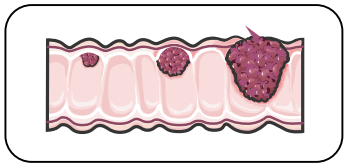
PSA-PSMA — Prostate cancer

Immunoglobulins — Multiple Mieloma



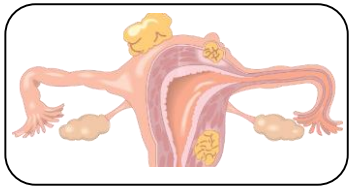
MUCINS-GLICOPROTEINS

C19.9



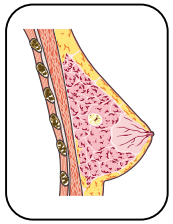
Colon cancer

C125



Ovary cancer

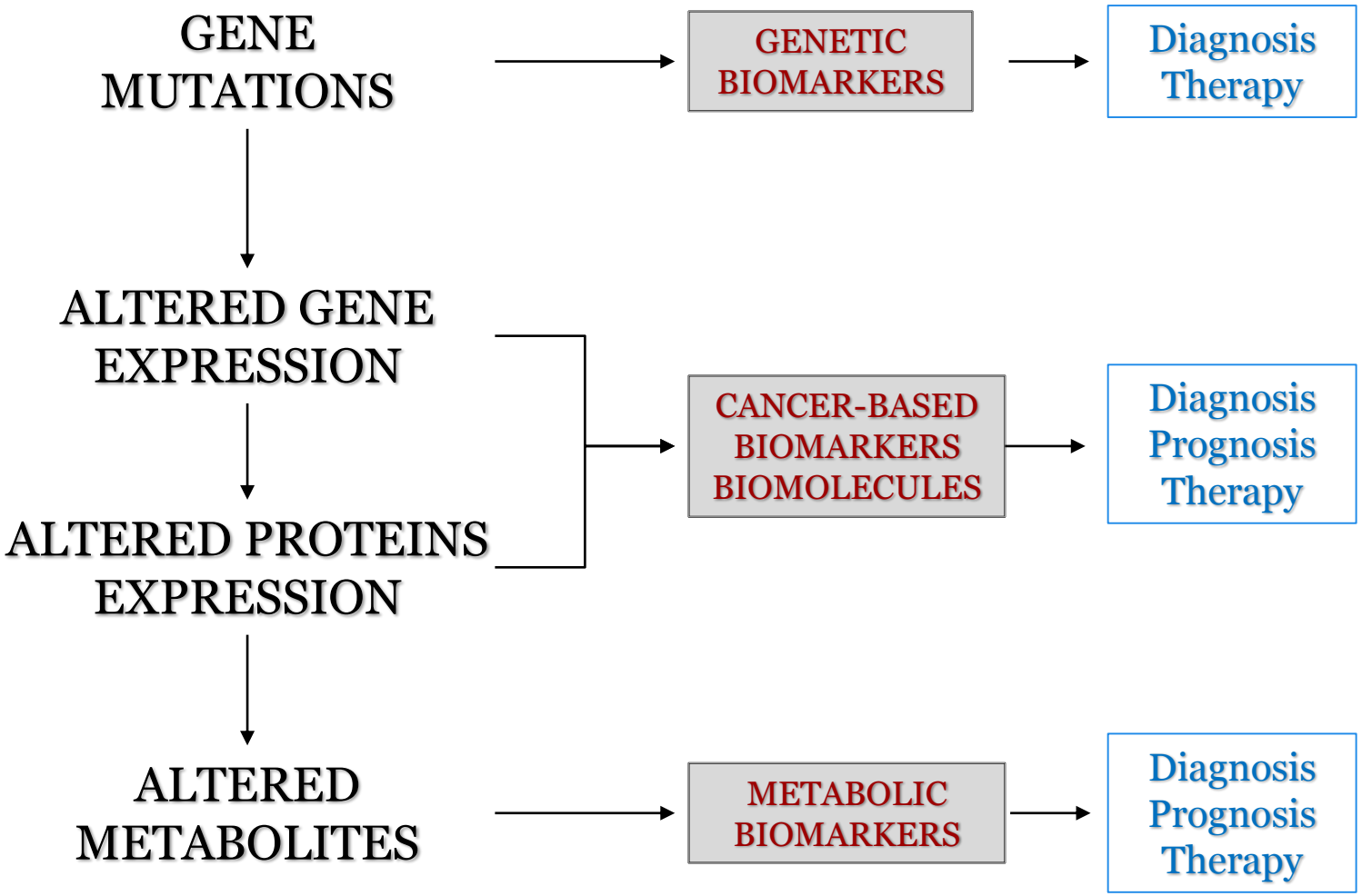
C15.3



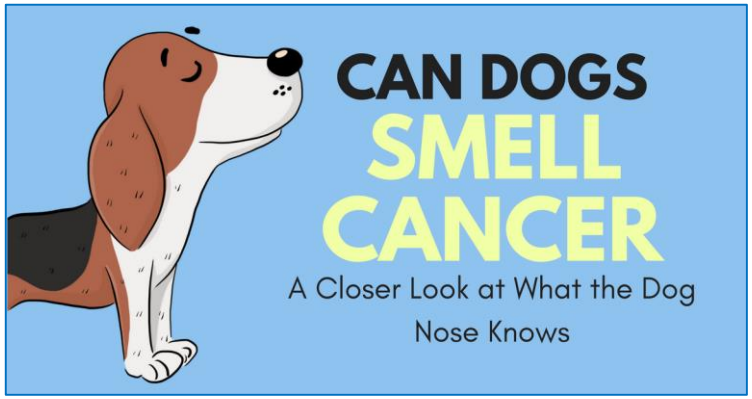
Breast cancer

BIOMARKERS IN THE ONCOGENETIC CASCADE

ONCOGENETIC CASCADE & «BIOMARKERS OPPORTUNITIES»



… WHERE MIGHT HAVE IT STARTED ?



Types of Cancer Dogs Can Detect

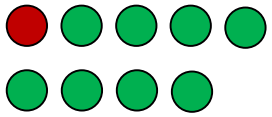
- Bowel cancer
- Bladder cancer
- Breast cancer
- Cervical cancer
- Endometrial cancer
- Lung cancer
- Ovarian cancer
- Prostate cancer
- Skin cancer

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): HighHCG levels suggest a germ cell tumor originating from testis/ovary, mediastinum, or retroperitoneum

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TESTIS CANCER:	**Seminomas**	Classical: 95% (HCG ±) Spermatocytic: 5% (HCG ±)
↓ **90%** →	**Non-seminomas** (Germ Cell Tumor in both M/F)	Embryonal carcinoma (HCG ⬆, AFP ⬆) Yolk sac carcinoma (AFP ⬆) Choriocarcinoma (HCG ⬆) Teratomas (AFP **±**)

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)**

TESTIS CANCER:

Seminomas	Classical, (HCG ±) Spermatocytic (HCG ±)
Non-seminomas (Germ Cell Tumor in both M/F)	Embryonal carcinoma (HCG ⬆, AFP ⬆) Yolk sac carcinoma (AFP ⬆) Choriocarcinoma (HCG ⬆) Teratomas (AFP **±**)

HCC

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

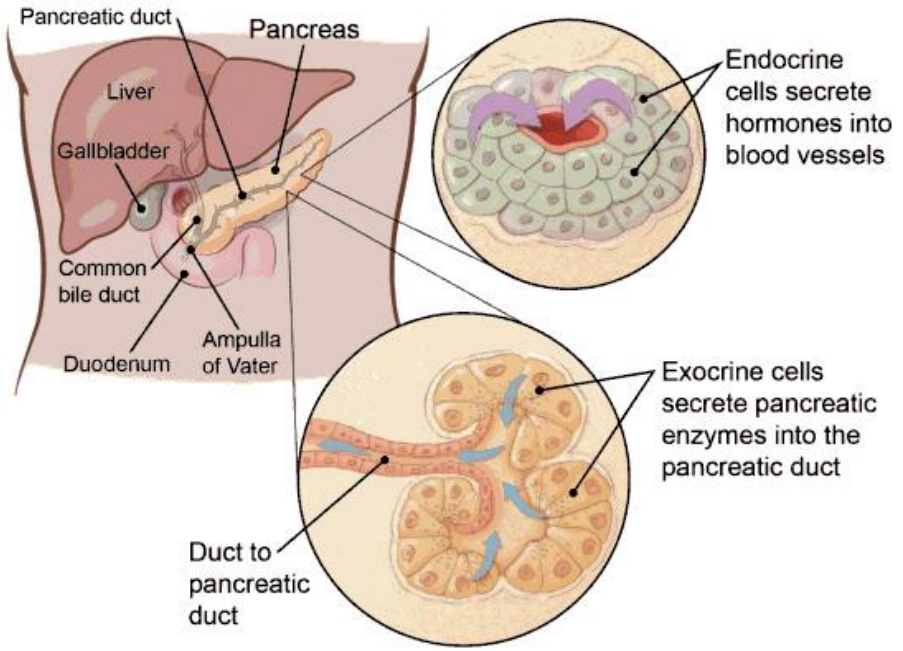
AFP is normally present at high levels in fetuses' blood (shortly drops after birth). In adults, AFP can go up from liver disease, HCC, or other cancers. Because HCC isn't the only reason for high AFP levels and HCC may have normal AFP, **it isn't very helpful in HCC diagnostic assessment**.

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

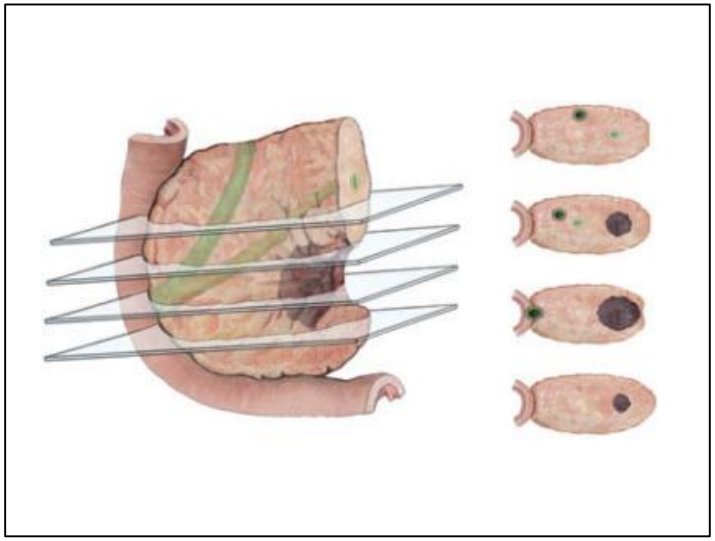


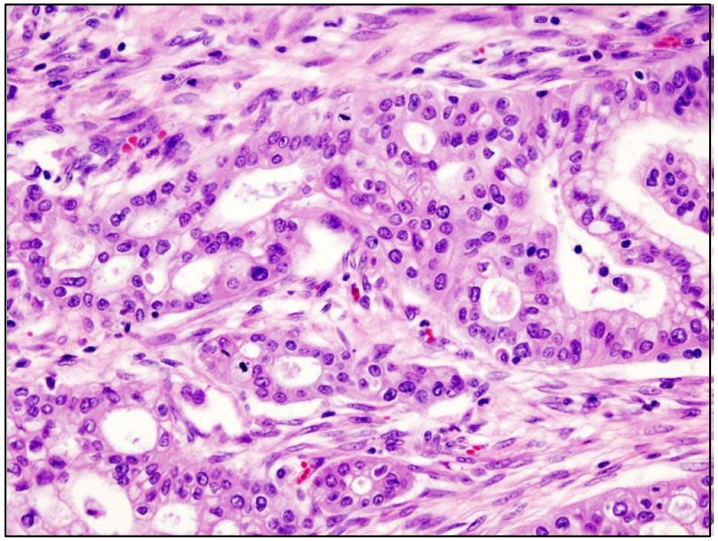
→ Neuroendocrine Markers

→ 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)

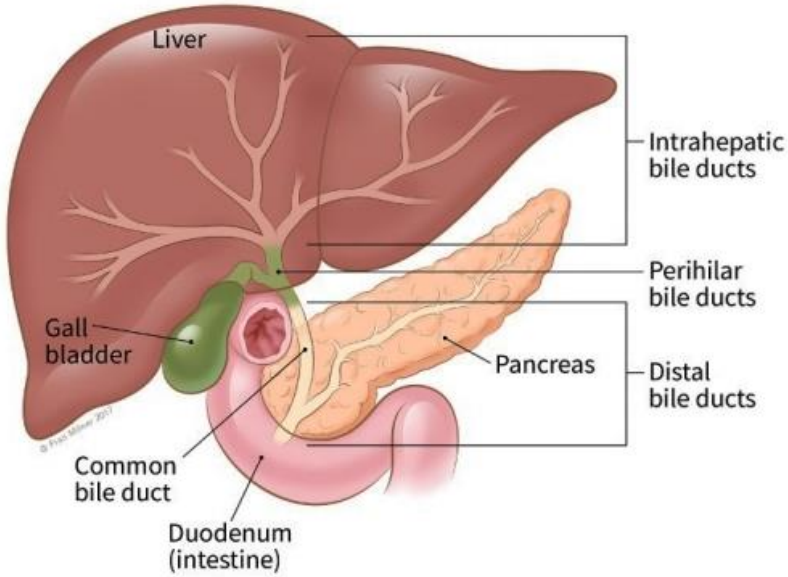
CA 19-9 and CEA are not accurate in the assessment of pancreas epithelial malignancy.
Levels of these tumor markers are not high in all people with pancreatic cancer, and some people who don't have pancreatic cancer might have high levels of these markers for other reasons. Still, these tests can sometimes 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 cholagiocarcinoma 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 descibed) may suggest ovarian and/or breast cancer

SPECTRUM NEUROENDOCRINE TUMORS

Insulin (for Insulinomas ++),

C-peptide (for Insulinomas ++)

Gastrin (for Gastrinomas ++),

Glucagon (for Glucaconomas),

Somatostatin (for Somatostatinomas),

Pancreatic polypeptide (PPomas),

Vasoactive intestinal peptide (VIPomas)

Chromogranin A (CgA; for any NE-Tumor),

Neuron-specific enolase (NSE; for NE-Tumors),

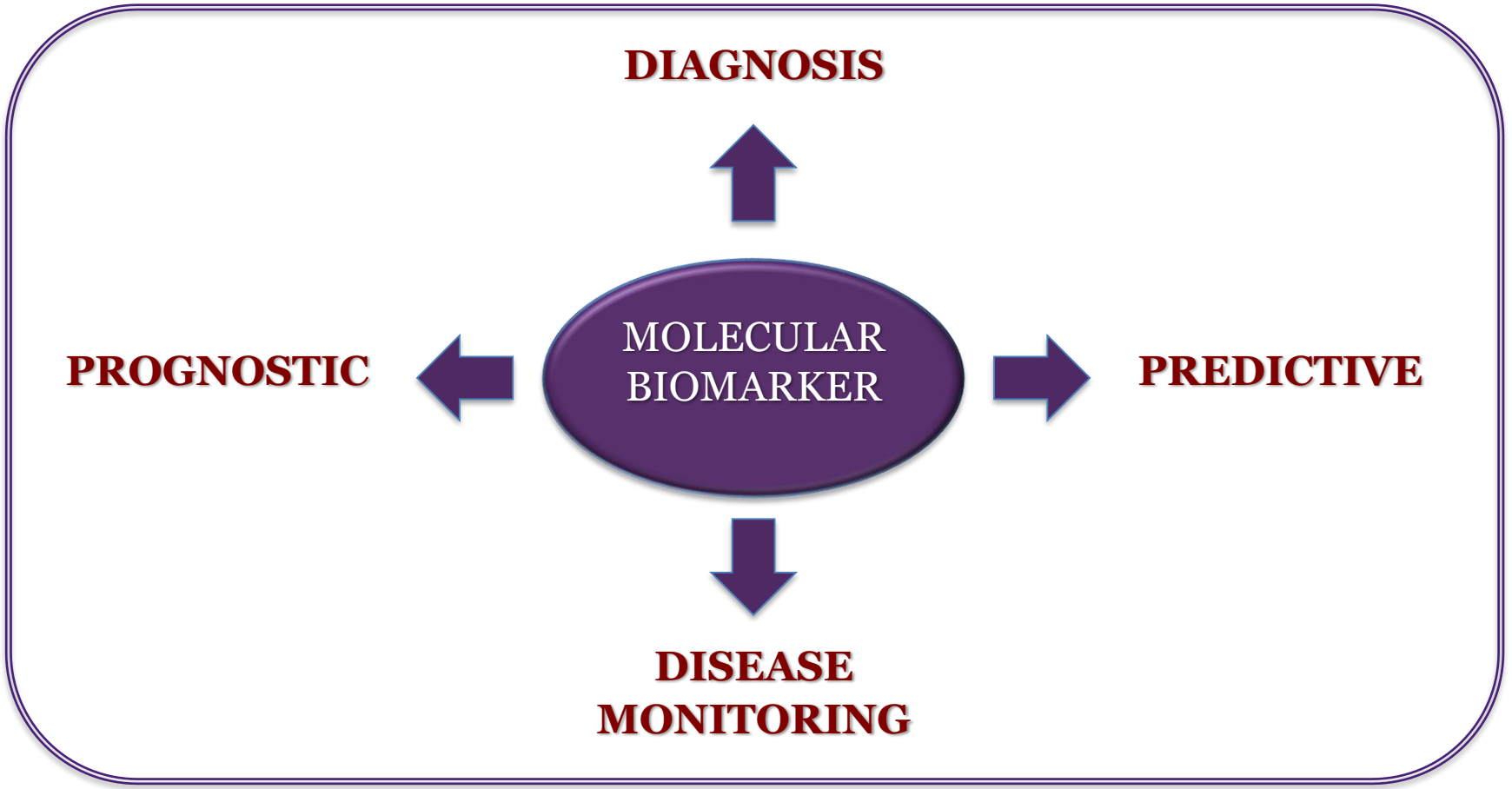
Substance P (for Carcinoid)

Thyroid
Thymus
Esophagus
Lung
Stomach
Pancreas
Small Bowel
Large Bowel
Appendix
Rectum

As a consequence...


N°5
CHANEL
PARIS
EAU DE PARFUM

… moving to “-omics”…



The increasing clinical impact of molecular profiling of cancer patients requires robust, validated tests (sensitivity, specificity, & detection limits).

MOLECULAR BIOMARKER USED IN CLINICAL PRACTICE TO GUIDE DIAGNOSIS & THERAPY

DIAGNOSIS

Myeloproliferative Diseases

JAK2 mutations confirm diagnosis of clonal MPD

Sarcomas

- *SS18-SSX1/SSX2* Synovial sarcoma
- *PAX3/PAX7-FOXO1A* Alveolar rhabdomyosarcoma
- *EWSR1-FLI1; EWSR1-ERG* Ewing's sarcoma
- *EWSR1-NR4A3; TAF15-NR4A3* Extra-skeletal myxoid chondrosarcoma
- *EWSR1-ATF1* Clear cell sarcoma (and angiomatoid fibrous histiocytoma)
- ……

PREDICTIVE

Non-small Cell Lung Cancer

- *EGFR* mutations predict response to TKI
- *ALK* Rearrangements predict response to ALK-inhibitors

Gastrointestinal Stromal tumors

- *KIT & PDGFRA* mutations predict response to c-KIT/PDGFRA inhibitors
- CRC *KRAS* mutations predict lack of response to anti-EGFR antibodies
- ……

PROGNOSTIC

Metastatic CRC

- *BRAF* mutations are indicative of poor outcome
- ……

DISEASE MONITORING

Chronic Myeloid Leukemia

- *BCR-ABL1* Minimal residual disease detection

Acute Promyelocytic Leukemia

- *PML-RARA* Minimal residual disease detection
- ……

VOLUME 30 NUMBER 34 DECEMBER 1 2012

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Publication of Tumor Marker Research Results: The Necessity for Complete and Transparent Reporting

Lisa M. McShane and Daniel F. Hayes

THE PROBLEM: FEW TUMOR MARKERS ARE OF CLINICAL UTILITY

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.**

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REVIEW ARTICLE

Publication of Tumor Marker Research Results: The Necessity for Complete and Transparent Reporting

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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.

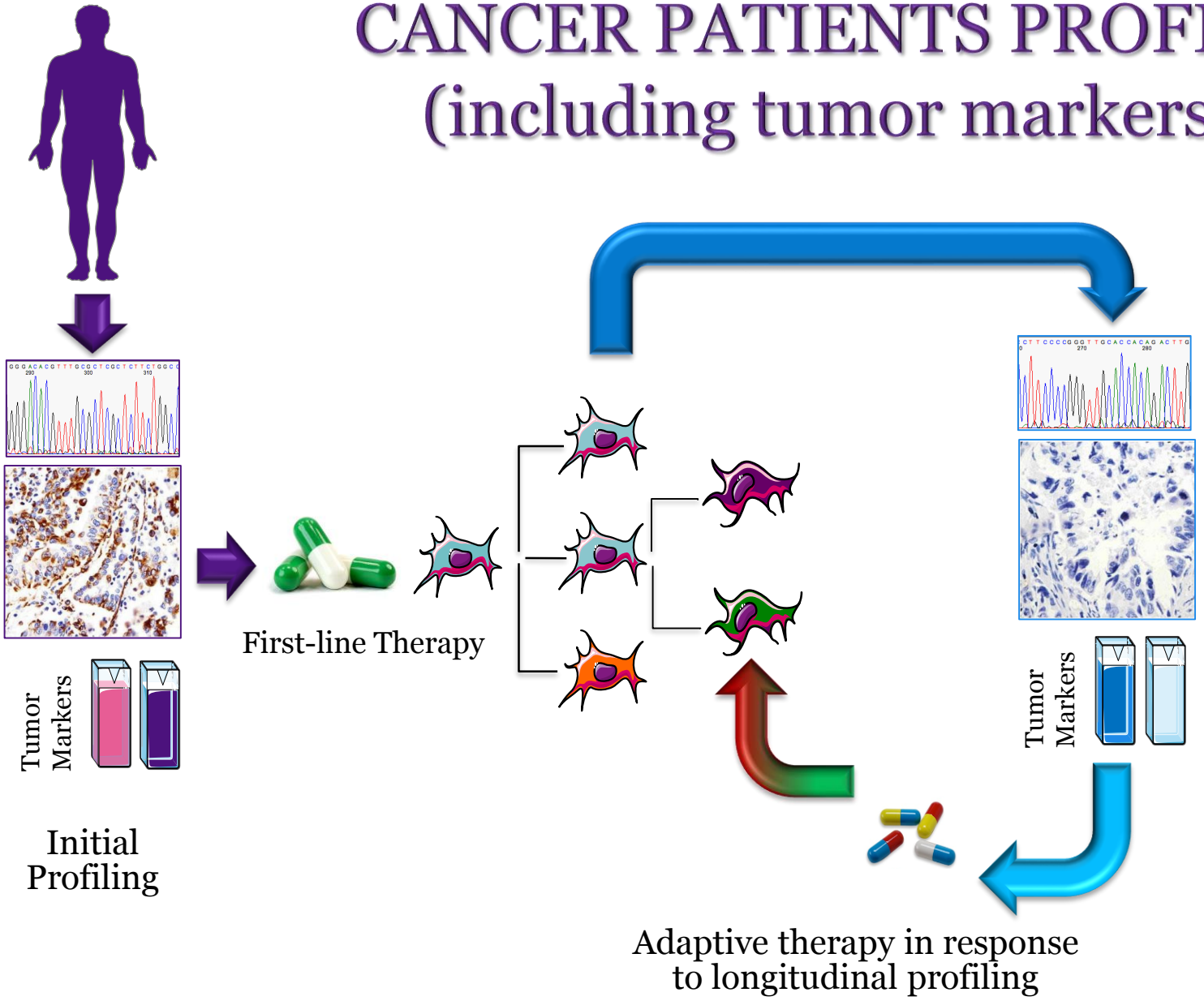
In **CRC**, testing for ***KRAS* mutations** is recommended for Ab-anti-EGFR treatment.

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)



CANCER REGISTRARS: AN EDUCATIONAL PERSPECTIVE

National Cancer Registrars Association

NCRA's Center *for* Cancer Registry Education

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.

NCRA is the premier education and training resource for the cancer registry community.
The Center for Cancer Registry Education provides easy access to high-quality educational programming to support both seasoned professionals and those new to the field.
This site offers a variety of services, allowing to **tailor training and manage continuing education credits**.
The center provides information on how to become a cancer registrar and earn the Certified Tumor Registrar (CTR®) credential

Summary

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;

Summary

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.

THANK YOU

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

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Monopoli – October, 2018