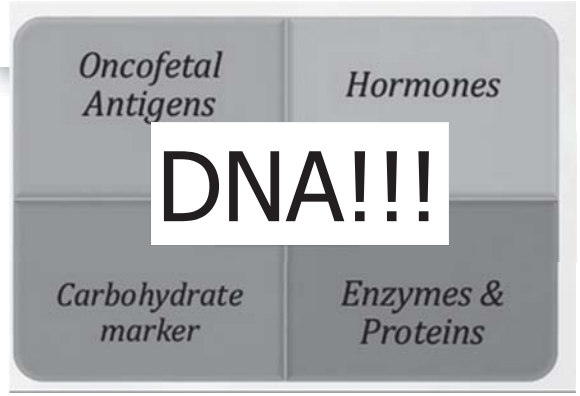
# Advancing Patient Advocacy with Common Questions in Chemistry: Tumor Markers

Mary Ann McLane, PhD, MLS(ASCP)CM
Professor, Department of Medical Laboratory Sciences
University of Delaware
mclane@@udel.edu
302-740-3114

## TUMOR MARKERS

- Not useful for diagnosis?
- Useful in tumor staging, monitoring therapeutic response, detecting cancer recurrence
- Ideally…
  - Measured easily
  - Diagnostic sensitivity
  - Diagnostic specificity
  - Cost-effective
  - Results contribute to patient care and outcome




| Tumor marker | Cancer types | Tissue used | Information |
|---|---|---|---|
| ALK gene rearrangements | NSC lung, anaplastic large cell lymphoma | Tumor | Determine tx, prognosis |
| BRAF V600 mutations | Cutaneous melanoma, colorectal | Tumor | Appropriateness of targeted tx |
| C-kit/CD117 | GI stromal, mucosal adenoma | Tumor | Tx response, recurrence |
| EGFR gene mutation | NSC lung | Tumor | Determine tx, prognosis |
| Estrogen/progesterone receptor | Breast | Tumor | Appropriateness of targeted tx |
| HER2/neu | Breast, gastric | Tumor | Appropriateness of targeted tx |
| KRAS gene mutation | Colorectal, NSC lung | Tumor | Appropriateness of targeted tx |

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National Cancer Institute, http://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-markers-fact-sheet; Examples of Tumor Markers, https://labtestsonline.org/understanding/analytes/tumor-markers/start/2

| Tumor marker | Cancer types | Tissue used | Information |
|---|---|---|---|
| Programmed death ligand 1 | NSC lung | Tumor | Appropriateness of targeted tx |
| Plasminogen activator inhibitor | Breast | Tumor | Determine aggressiveness, guide tx |
| Urokinase plasminogen activator | Breast | Tumor | Determine aggressiveness, guide tx |
| 21-gene signature (Oncotype DX®) | Breast | Tumor | Recurrence risk |
| 70-Gene signature (Mammaprint®) | Breast | Tumor | Recurrence risk |

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| Tumor marker | Cancer types | Tissue used | Information |
|---|---|---|---|
| Alpha fetoprotein | Liver, germ cell | Blood | Tx response, staging, prognosis |
| β-2 microglobulin | Multiple myeloma, CLL, some lymphomas | Blood, urine, CSF | Tx response, prognosis |
| β-hCG | Choriocarcinoma, germ cell | Blood, urine | Staging, prognosis, tx response |
| BRCA1, BRCA2 | Ovary | Blood | Appropriateness of targeted tx |
| BCR-ABL (Philadelphia chromosome) | CML, ALL, AML | Blood, BM | Confirm diagnosis, appropriateness of targeted tx, tx response |
| CA15-3 | Breast | Blood | Tx response, recurrence |

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| Tumor marker | Cancer types | Tissue used | Information |
|---|---|---|---|
| CA19-9 | Pancreas, gallbladder, bile duct, gastric | Blood | Tx response |
| CA125 | Ovary | Blood | Tx response, recurrence |
| CA27.29 | Breast | Blood | Tx response, recurrence |
| Calcitonin | Medullary thyroid | Blood | Tx response, recurrence |
| Carcinoembryonic antigen | Colorectal | Blood | Tx response, recurrence |
| CD20 | Non-Hodgkin lymphoma | Blood | Appropriateness of targeted tx |
| Chromogranin A | Neuroendocrine | Blood | Tx response, recurrence |
| Chromosomes 3, 7, 17, 9p21 | Bladder | Urine | Recurrence |

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| Tumor marker | Cancer types | Tissue used | Information |
|---|---|---|---|
| Circulating tumor cells of epithelial origin (CELLSEARCH®) | Metastatic breast, prostate, colorectal | Blood | Assess prognosis |
| Cytokeratin fragment 21-1 | Lung | Blood | Recurrence |
| Des-gamma-carboxy-prothrombin | Liver | Blood | Tx response; recurrence |
| Fibrin/fibrinogen | Bladder | Urine | Tx response |
| Gastrin | Stomach | Blood | Tx response; recurrence |
| HE4 | Ovary | Blood | Plan tx, assess progression, recurrence |
| Immunoglobulins | Multiple myeloma, Waldenström macroglobulinemia | Blood, urine | Tx response; recurrence |

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| Tumor marker | Cancer types | Tissue used | Information |
|---|---|---|---|
| JAK2 mutation | Certain leukemias, polycythemia vera | Blood, BM | Help to diagnose |
| Microphthalmia transcription factor | Melanoma | Blood | Circulating melanoma cells |
| Neuron-specific enolase | SC lung, neuroblastoma | Blood | Tx response |
| Nuclear matrix protein 22 | Bladder | Urine | Tx response |
| Prostate-specific antigen | Prostate | Blood | Tx response; recurrence |
| Soluble mesothelin-related peptides | Mesothelioma | Blood | Tx response |
| T-cell receptor gene rearrangement | T-cell lymphoma | Blood | Diagnose, Tx response |
| Thyroglobulin | Thyroid | Blood | Tx response; recurrence |
| 5-Protein signature (OVA1®) | Ovary | Blood | Assess pelvic mass for suspected ovarian cancer |

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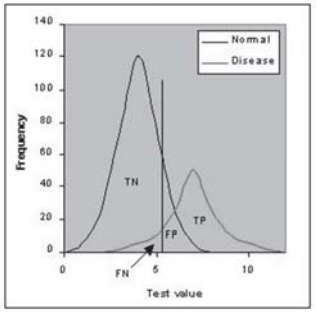
## No cancer ≠ "zero"?

- My mother was recently operated on for colon cancer (she is 79). The doctors were very optimistic about… no evidence that the cancer had spread. She then went to an oncologist who did a CEA test was 3.9 and "normal" was 3.0. She is convinced she still has cancer and refuses to go back as she has already made the decision not to seek cancer treatment. She could be convinced with facts but I can find nothing on this site that tells me about CEA levels and what is "normal". I also don't know what 3.9 means on a relative scale. I understand that the "normal" number varies with labs, but there should be some "thumbnail" rules somewhere. At what level is treatment recommended?

## Diagnostic sensitivity, specificity, PPV, NPV




## 2 by 2 table

| | | Disease + | Disease − |
|---|---|---|---|
| Test | + | True positive | False positive |
| | − | False negative | True negative |

## IF a test had perfect discrimination…

| | | Disease + | Disease − |
|---|---|---|---|
| Test | + | True positive | |
| | − | | True negative |

## Diagnostic Sensitivity

| | | Disease + | Disease − |
|---|---|---|---|
| Test | + | a | b |
| | − | c | d |

**Proportion of people with the disease who have a positive test.**

**Sensitivity = a / a + c**

## Diagnostic Specificity

| | | Disease + | Disease − |
|---|---|---|---|
| Test | + | a | b |
| | − | c | d |

**Proportion of people without the disease who have a negative test.**

**Specificity = d / b + d**

## Alpha-fetoprotein data

| | With liver CA | Without liver CA | total | |
|---|---|---|---|---|
| test + | 90 | 39 | 129 | |
| test - | 17 | 2079 | 2096 | |
| total | 107 | 2118 | 2225 | |
| | Sensitivity= | Specificity= | | |
| | xxxx% | xxxx% | | |

## Alpha-fetoprotein data

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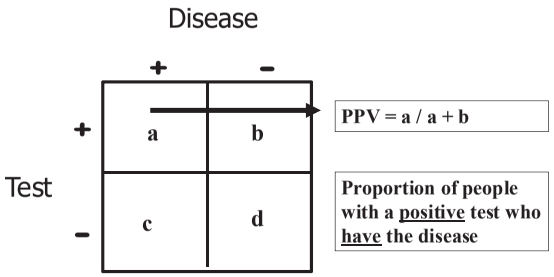
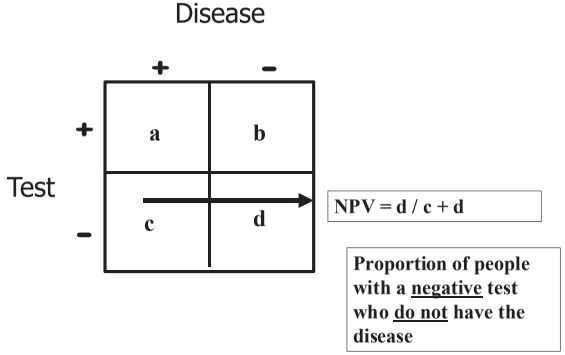
| test + | 90 | 39 | 129 | |
| test - | 17 | 2079 | 2096 | |
| total | 107 | 2118 | 2225 | |
| | Sensitivity= | Specificity= | | |
| | 84% | 98% | | |
| | With disease, test + | No disease, test - | | |

## positive predictive value (PPV)




## negative predictive value (NPV)




| | With liver CA | Without liver CA | total | |
|---|---|---|---|---|
| test + | 90 | 39 | 129 | PPV = xxxxxx |
| test - | 17 | 2079 | 2096 | NPV = xxxxxx |
| total | 107 | 2118 | 2225 | |
| | Sensitivity | Specificity | | |
| | 84% | 98% | | |

| | With liver CA | Without liver CA | total | | |
|---|---|---|---|---|---|
| test + | 90 | 39 | 129 | PPV = 70% | Test +, have disease |
| test - | 17 | 2079 | 2096 | NPV = 99% | Test -, no disease |
| total | 107 | 2118 | 2225 | | |
| | Sensitivity | Specificity | | | |
| | 84% | 98% | | | |

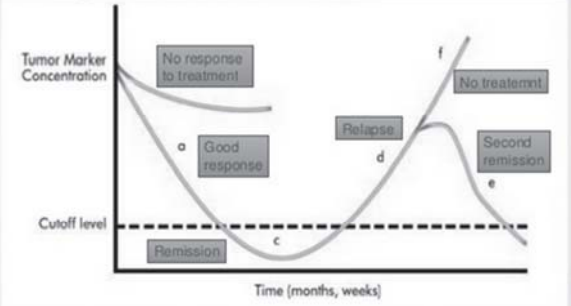
## When is tx working?

- The tumor was removed from the colon and she has had a infusion pump placed with FU5. Her CEA levels originally for the first colon surgery were 2635. Five weeks later (infusion pump put in) = 3200. Two weeks after pump inserted = 4000. Is it logical for the levels to still rise at two weeks after the infusion pump? She will begin systemic chemo next week. When should you see a decrease in the level to know if it working?

## When is tx working?

- My mom has breast cancer that has spread to her bones. She had a historectomy back in Jan 2004 and they found the cancer has spread like a web materail all over her abdomen and colon. They took what they could. Her tumor markers before the surgery were around 1100. She went through cemo and her tumor markers have come down. She had every test in the book before the surgery and everything came back normal. They couldnt see the caner on the ct/mri etc... She has been doing pretty good. Her tumor markers went way down, around 200. For the past several months they are going up and up. Her Dr keeps telling her not to worry about them. This past month there up to 560??? from last months 330. Her Dr says to not really relie on them. Is this true? should we be concerned? He says he will issue maybe another ct/mri but they never show anything. Do you have any advice? thank you

## Changes in tumor marker concentration during the course of disease:



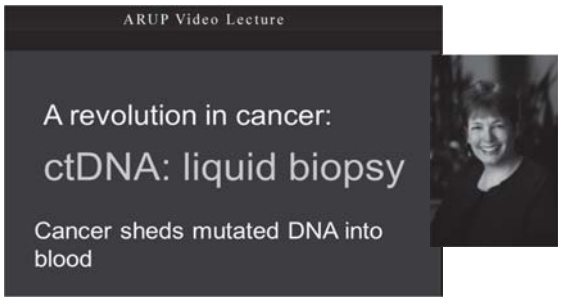

## No cancer = "zero"?

- Would a woman who never had cancer have a result of zero?
  - Depends on the test? ✔
  - Depends on the type of cancer? ✔

## Circulating tumor cells

http://arup.utah.edu/media/ctDNA/ctDNA_video_review.html

# Mary Bronner, MD (ARUP)

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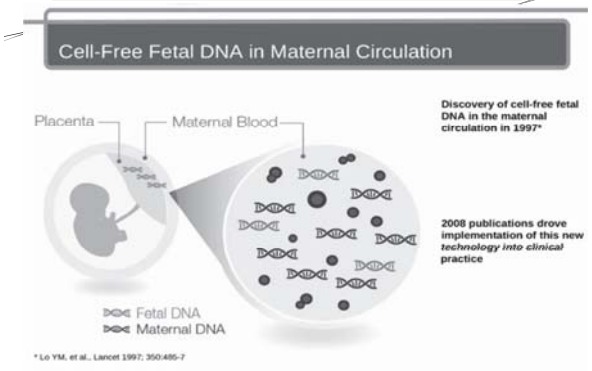


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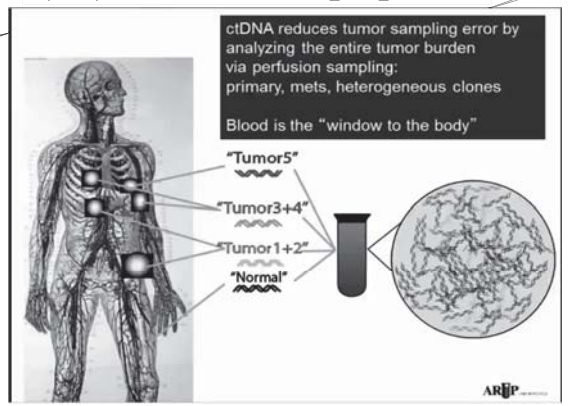


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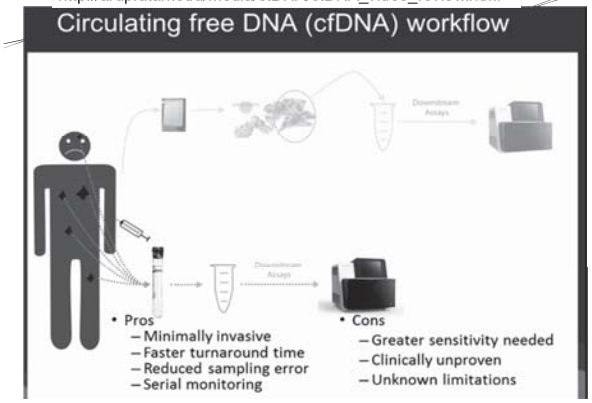



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J Clin Lab Anal. 2013 Jul; 27(4): 305–311. PMCID: PMC3748765
Published online 2013 Jul 12. doi: 10.1002/jcla.21603

**A New Blood Collection Device Minimizes Cellular DNA Release During Sample Storage and Shipping When Compared to a Standard Device**

Sheila E Norton, Kristin K Luna, Joel M Lechner, Jianbing Qin, and M Rohan Fernando*

**Results**

Shaking and shipping blood in $K_3$EDTA tubes showed significant increases in pDNA, whereas no change was seen in BCTs. Blood in $K_3$EDTA tubes incubated at 6°C, 22°C, and 37°C showed increases in pDNA while pDNA from BCTs remained stable.

**Conclusions**

BCTs prevent increases in gDNA levels that can occur during sample storage and shipping. This new device permits low abundance DNA target detection and allows accurate cfDNA concentrations.

formaldehyde-free preservative
stabilizes nucleated blood cells
prevents the release of cellular genomic DNA
inhibits nuclease mediated degradation of cfDNA
stable up to 14 days at 6-37°C

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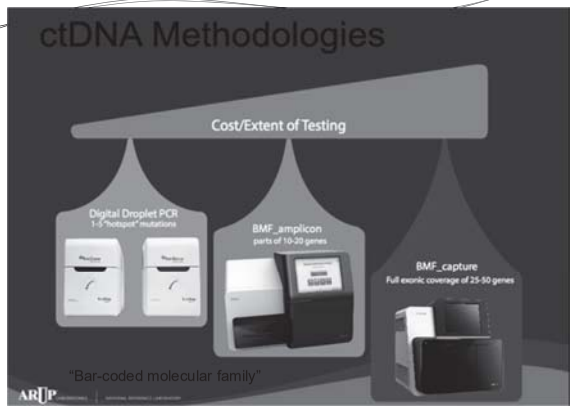


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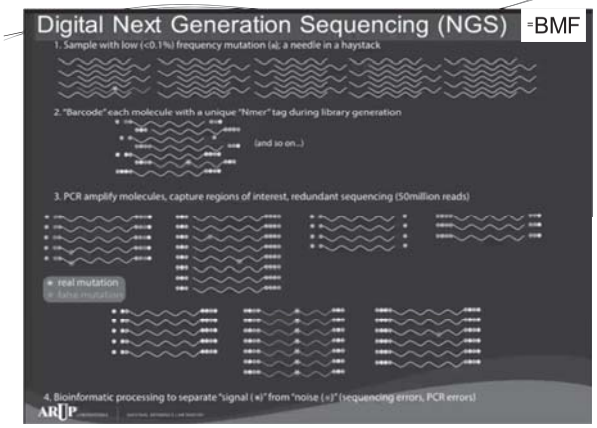


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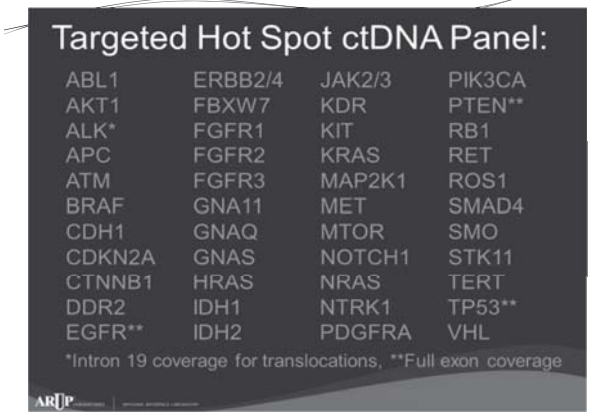


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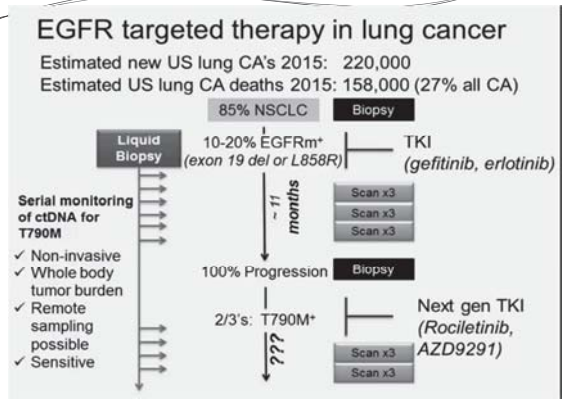

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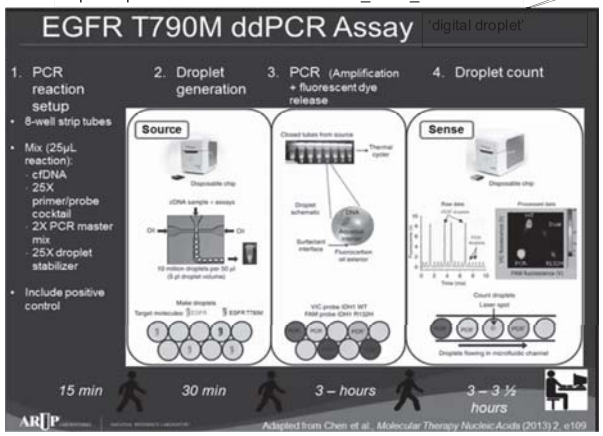



## Tumor markers you've probably never heard of…

- Microphthalmia transcription factor
  - Important for melanocyte development
  - Marker for circulating melanoma cells in blood
  - Detects subclinical metastasis?
  - Predicts treatment outcome?

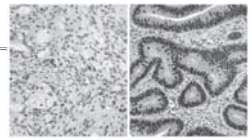
## GT198


Mivechi, Maihle, Ko

- Gene for repairing DNA
- When mutated, appears in both early onset breast cancer and ovarian cancer


Possible biomarker?
Treatment target?

## CDX2



- Dalerba et al., 2016
- Regulates cell differentiation
- Colon cancer stage 2 tumors which **do** express CDX2 = responsive to chemotherapy compared to those who tumors **do not** express CDX2

## dtectDx Breast Assay

- Provista Diagnostics
- IL-8, IL-12, VEGF, CEA, Hepatocyte Growth Factor
- 'multiple tumor-associated autoantibodies'
- Currently in clinical trial

## Questions?

Mary Ann McLane
mclane@udel.edu