

MedCAC Public Comment:
miRview[®] mets²
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COI and Safe Harbor



Conflict of Interest

- I am a full-time employee of Rosetta Genomics.
- Rosetta Genomics' CLIA-certified, CAP-accredited clinical laboratory provides the miRview® mets² assay for cancer of unknown primary origin, which is a specific topic of discussion at this MEDCAC meeting.

Safe Harbor

Except for historical information, the statements made in the following presentation are forward-looking statements. Such forward-looking statements involve significant risks and uncertainties that may cause actual results and events to differ materially and adversely from those implied by the forward-looking statements. Risks and uncertainties include, amongst others, the uncertainties set forth under "Risk Factors" in Rosetta's Annual Report on Form 20-F for the year ended December 31, 2012, filed with the Securities and Exchange Commission. Rosetta is presenting this information as of the date of the presentation and expressly disclaims any duty to update the information contained in this presentation. This presentation contains information from third-party sources, including data from studies conducted by others and market data and industry forecasts obtained from industry publications. Although Rosetta Genomics believes that such information is reliable, we have not independently verified any of this information and we do not guarantee the accuracy or completeness of this information.

By the 1970s, the Problem of CUP had Been Well-Defined, but Without a Solution

[JAMA](#). 1979 Jan 26; 241(4):381-3.

Identifying the primary site in metastatic cancer of unknown origin. Inadequacy of roentgenographic procedures.

[Nystrom JS](#), [Weiner JM](#), [Wolf RM](#), [Bateman JR](#), [Viola MV](#).

[Semin Oncol](#). 1977 Mar;4(1):53-8.

Metastatic and histologic presentations in unknown primary cancer.

[Nystrom JS](#), [Weiner JM](#), [Heffelfinger-Juttner J](#), [Irwin LE](#), [Bateman JR](#), [Wolf RM](#).

X-ray

Exploratory Surgery

Microscopy

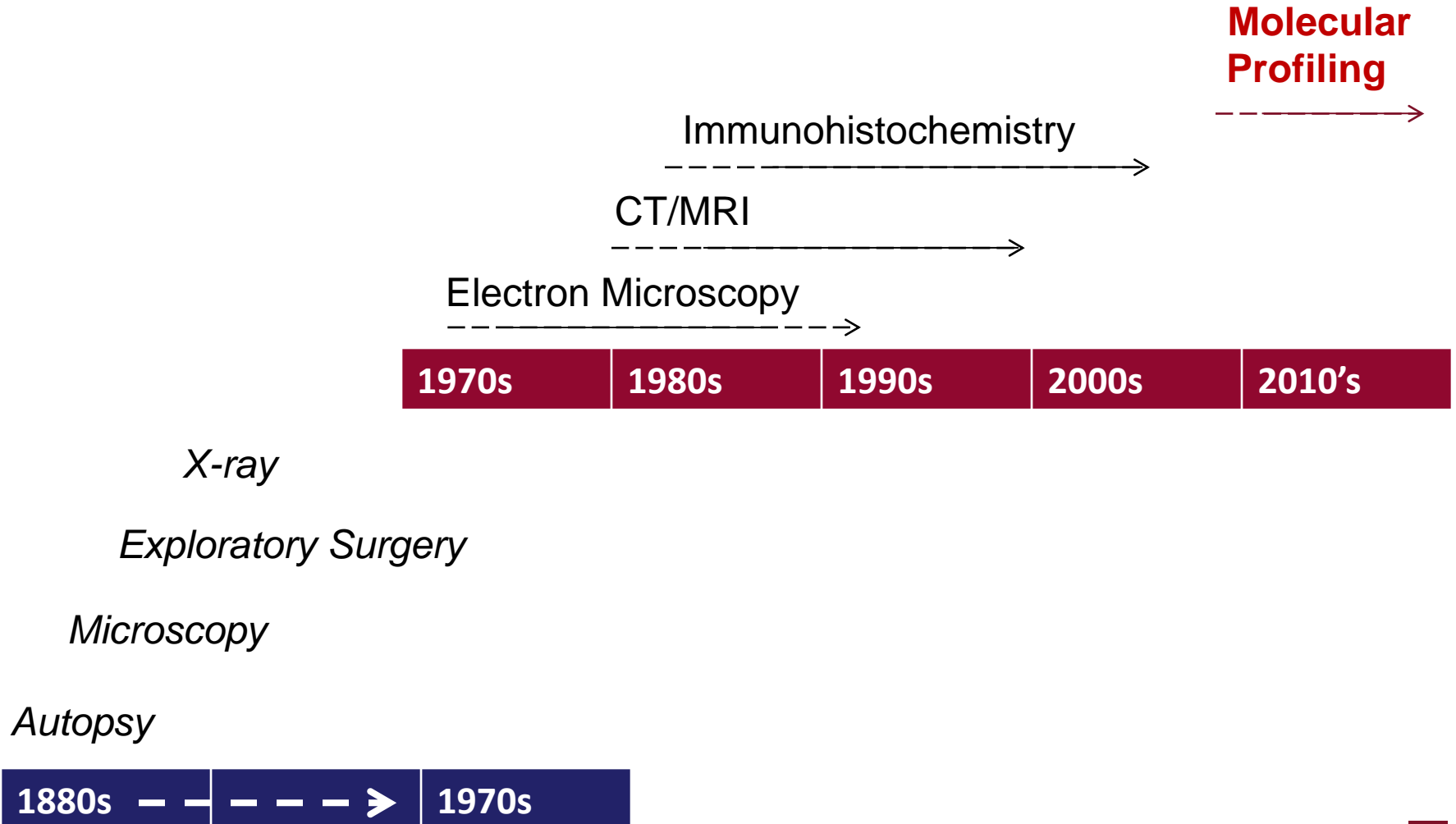
Autopsy

1880s



1970s

Each Decade has Brought more Powerful Modalities for CUP Diagnosis



Molecular profiling: Value for Physicians and Patients



Historical Work-up (Nystrom 1970s)	CT/MRI	Immunohisto-chemistry	Molecular Profiling
<ul style="list-style-type: none"> Entry point to our modern understanding of CUP 	<ul style="list-style-type: none"> Avoid exploratory surgery Identify targets for biopsy 	<ul style="list-style-type: none"> Identify <u>some</u> cases previously “CUP” Ability to rule-in, rule-out <u>limited</u> by “noisy” markers 	<ul style="list-style-type: none"> Successfully “fingerprint” genomic expression Identify ~90% or more of today’s CUP cases

Oncologists

- Reach a diagnosis
- Select optimal therapy
- Rational decision-making with patient and family

Pathologists

- Resolve challenging cases
- Confirm tentative diagnoses
- Select additional tests, if indicated

Patients:

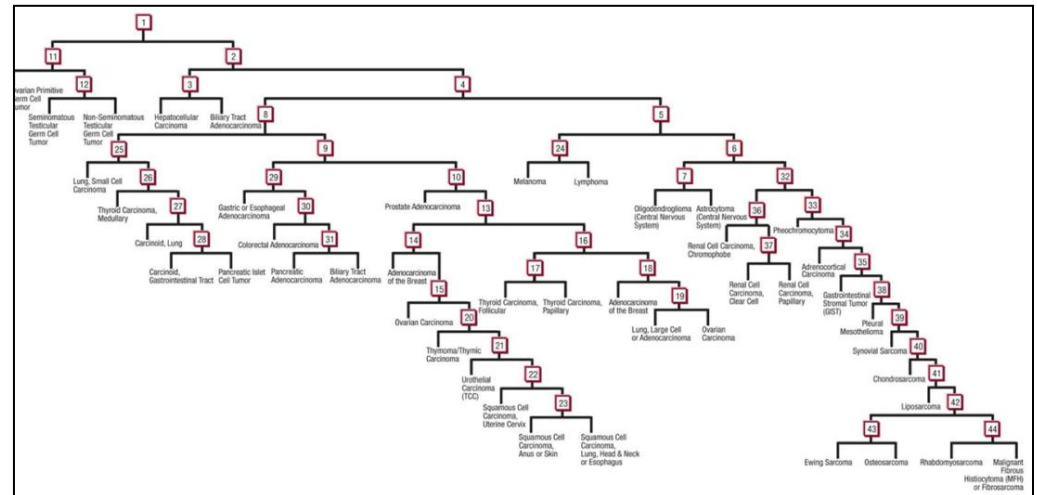
End diagnostic odyssey and indicate therapy

<i>Primary</i>	<i>Specific Tx</i>	<i>Outcome (OS)</i>	<i>FOLFOX or similar (OS)</i>
Breast	Anthracycline, taxane, capecetabine	24 mo	6 mo
Colorectal	Oxaliplatin/irinotecan; 5FU/capecetabine; Bevacizumab/Cetuximab	24 mo	16 mo
Lung	Platinum regimens	13 mo	9 mo
Ovary	Carboplatin/paclitaxel; pegylated doxorubicin	50 mo	18 mo

MicroRNAs are Excellent Biomarkers



- ▶ Tissues have highly specific microRNA signatures
- ▶ Upstream control of fundamental processes of tissue differentiation
- ▶ Very high demonstrated stability in clinical samples, including FFPE
- ▶ MicroRNAs represent a biological basis for cancer classification



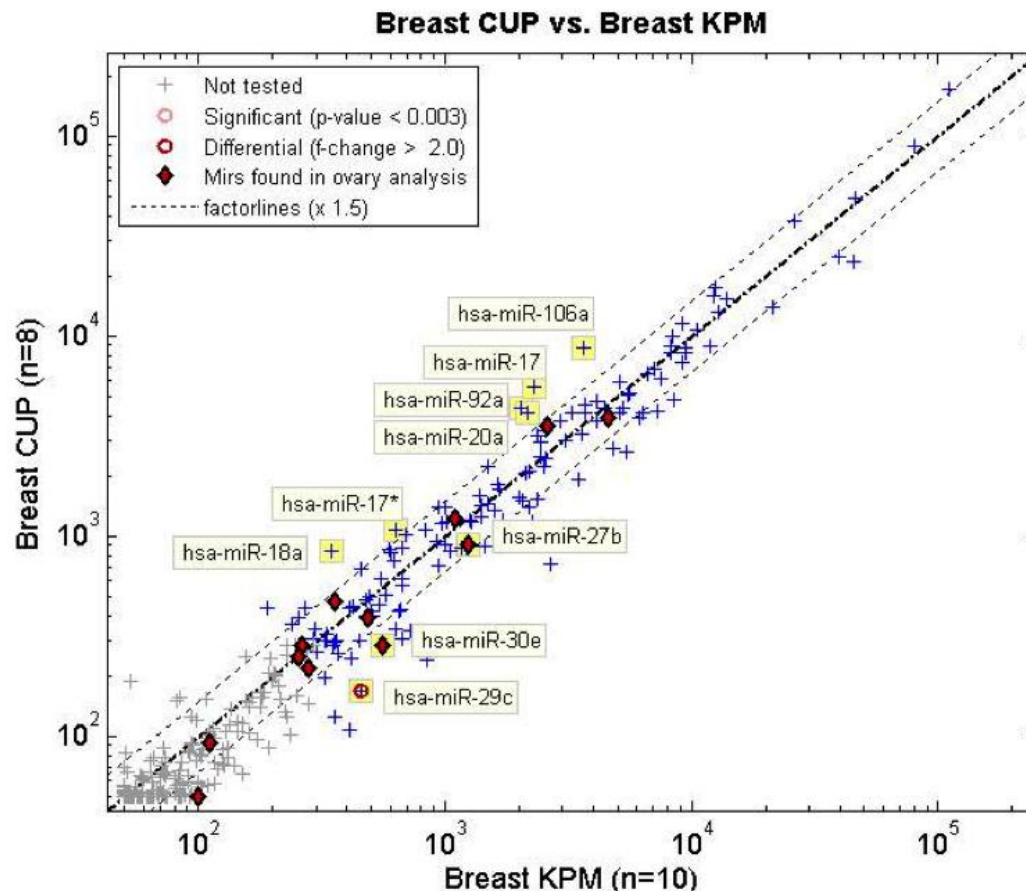
Report Performance Metrics



- ▶ Delivers single-call tissue of origin in 82% of cases with 90% sensitivity
- ▶ Delivers two-call report or tumor category report in most remaining cases
- ▶ As Technology Assessment notes, CUP is a unique problem – by definition, there is no prior “gold standard,” the cancer is of “unknown” primary
- ▶ Close “fingerprint” match with known tumors is an extremely important benchmark (next slide)

Cancer of Unknown Primary Maps Closely to Cancer of Known Primary

Global microRNA profiling in favorable prognosis subgroups of cancer of unknown primary (CUP) demonstrates no significant expression differences with metastases of matched known primary tumor



Pentheroudakis et al.
Clin Exper Metastasis
Epub ahead of print 11/4/2011
DOI 10.1007/s10585-012-9548-3

Current Platform Further Improves Specificity and Accuracy



Oncologist (2012) 17:801-12

A Second-Generation MicroRNA-Based Assay for Diagnosing Tumor Tissue Origin

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- Overall assay sensitivity (positive agreement), measured blindly on a validation set of 509 independent samples, was 85%.
- The sensitivity reached 90% for cases in which the assay reported a single answer (>80% of cases).
- A clinical validation study on 52 true CUP patients showed 88% concordance with the clinicopathological evaluation of the patients.

Is the Real Question not “Whether” but “When” to use Genomic Profiling?



Boyland et al. (2008) J Palliative Med 22:177-183

Patients' experience of carcinoma of unknown primary site

- Confirmed that patients find it particularly hard to accept a cancer diagnosis without a primary origin
- Patients describe undergoing extensive series of tests (“they looked everywhere”) to no avail
- Suddenly told the final bad news with “enormous urgency”

Bridgewater et al. (2008) Brit J Cancer 98:1425-1430

Gene expression profiling may improve diagnosis in patients with carcinoma of unknown primary

- Primary site can be predicted in a majority of patients
- Prediction is robust
- Total costs of all investigations is high and could be reduced if molecular profiling was used early
- Evidence has progressed much further since this report, and converges on the accuracy of profiling and the close match of most CUPs to a definitive molecular tissue type

Indications for CUP Testing

- ▶ Diagnosis is unknown/uncertain primary
- ▶ Basic panel (8-10 IHC) cannot indicate a definitive diagnosis
- ▶ Diagnosis requires verification before therapy decisions
- ▶ Clinical picture does not make sense

Case Study:

70 year old female presented with suspicious R breast lesion on screening mammogram

Dx: poorly differentiated primary ductal breast carcinoma; IHC c/w “triple negative”

Rx: breast resection + local radiotherapy

8 months later, 3x4 cm brain met with same histology & IHC profile & similarly, an axillary node

The brain met was analyzed by miRview™ mets and classified as **metastatic melanoma**, as well as original primary and axillary node met

Further IHC reassessment as c/w miRview™ mets Dx of **melanoma** (IHC: HMB45+, S-100+ and MELAN A+)

CUP Assays have a Critical Position in the Diagnostic Workup of these Patients



- ▶ CUP assays show that most tumors of uncertain origin have a very close genomic match to known tumors
- ▶ CUP assays “fingerprint” the tumor type in most cases of CUP
- ▶ CUP assays are both more accurate and better-validated than individual immunohistochemical markers
- ▶ The miRview® mets² assay is very highly validated and leverages fundamental and stable processes of tissue differentiation
- ▶ Diagnostic accuracy becomes increasingly important as targeted therapies are available