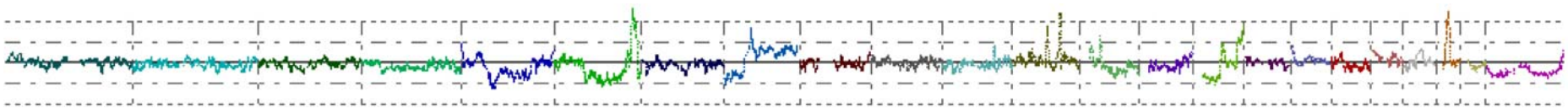
The LIS Redesign Challenges Prompted by Emerging Molecular Diagnostic Testing

Federico A. Monzon M.D.

Medical Director of Molecular Diagnostics

The Methodist Hospital

Houston, TX



Outline

- What's so special about molecular diagnostics?
- What challenges are prompted by emerging molecular tests?
- What needs to change in the LIS to cope with this new environment?

Informatics for Molecular Diagnostics Labs

- The volume and complexity of data related to molecular labs testing surpasses capabilities of current systems.
- Information generated by the molecular and other specialty laboratories does not fit existing LIS models.
- An increase in tests performed makes effective laboratory information management crucial to the laboratories' success and to quality patient care.

Some Challenges

- Complex QC of samples
  - Impacting decision making or downstream options
  - Responses needed on QC/QA information
- Documented specimen processing
  - Non-standardized protocols across laboratories
  - User-Defined Protocols
  - Barcode specimen tracking
- Complicated, dynamic and frequently updated testing workflows
  - Multiple or multistep methods
  - Extensive use of calculations
  - Tracking of samples during workflow and status report
  - Complex laboratory worksheets

More Challenges

- Reagent and inventory tracking
  - Ability to retrieve reagent info for QC/QA
- Extensive data analysis for interpretation
  - Combination of discrete values and complicated interpretive reports
  - Customized reporting
- Instrument platforms still in development & refinement
  - Continuous updates of instrument platforms
  - No existing specification for data handling and interfaces

Current Status

- Most information systems cannot handle molecular data, so…
  - Vast majority of data embedded in text
  - Difficult/unable to analyze data over time
  - No workflow/specimen/aliquot tracking
  - Lack of support for…
    - Scientific notation
    - Log calculations
    - Large numbers (i.e. 50,000,000 IU/mL HCV)

One Non-Emerging Example

- After a “successful” LIS upgrade I receive an email

  “The infectious disease tests (except for HIVQ) are set up as numeric with alpha responses defined as normal or abnormal. However, the LIS does not recognize the alpha responses with a “<” or “>” and flags as abnormal those results with these signs. The alpha responses with no numbers flags as absurd.”

- This issue did not exist before the upgrade
- Problem: all our viral-load assays require reporting of “Not-detected”, “<##”, “###” and “> ###”
- Need to accept alphanumeric responses and handle them appropriately
- If Excel can do it, why can’t my LIS?

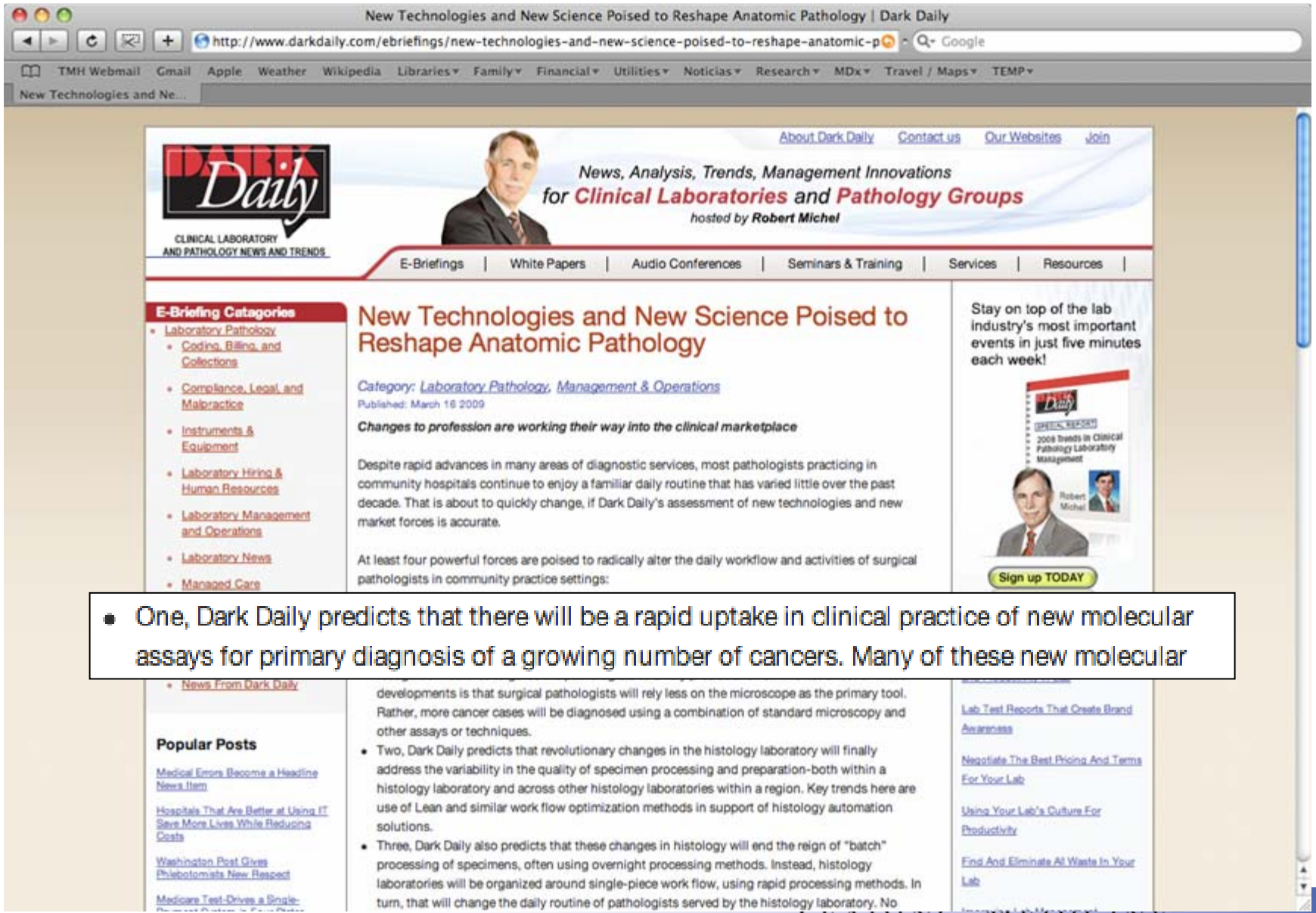
Industry is Responding

- LIS vendors with dedicated modules for molecular diagnostics laboratories
  - Cerner Helix
  - Soft Genetics
- Other vendors trying to integrate AP and CP systems to handle molecular data
- Multiple niche products in genetics, cytogenetics, etc..

More Problems

- Many automated molecular instruments lack interface capability
  - No standard interfacing rules as of yet
- No standards for common data elements for molecular data in general
- Molecular techniques are advancing at a much more rapid pace than information systems can keep up
- We haven't solved the current issues and new challenges keep arising

Consulting the Oracle



- One, Dark Daily predicts that there will be a rapid uptake in clinical practice of new molecular assays for primary diagnosis of a growing number of cancers. Many of these new molecular

Emerging Molecular Tests - 1

- Companion tests for drug eligibility
  - *ERBB2* (Her2Neu) by IHC for Breast Cancer
    - Response to Trastuzumab (Herceptin)
    - Detection by FISH, direct protein, other ERBB members
  - EGFR mutations in Lung Cancer
    - Response to anti-EGFR agents Gefitinib and Erlotinib
  - KRAS mutations in metastatic Colon Cancer
    - Response to anti-EGFR agents Cetuximab and Panitumumab

Emerging Molecular Tests - 2

- IVDMIAs (In vitro diagnostic multivariate index assays)
  - Breast Cancer Prognosis
    - Oncotype DX - 21 gene profile
    - Mammaprint - 70 gene profile
  - Tumors of Unknown Origin
    - Pathwork Tissue of Origin Test - 1500 gene profile
    - Rossetta Genomics miRView Mets - 48 miRNA profile
  - Heart Transplant Rejection
    - XDx AlloMap - 20 gene profile

Emerging Molecular Tests - 3

- Pharmacogenomics
  - Breast Cancer
    - Cytochrome P450 2D6 (*CYP2D6*) polymorphisms determine response to Tamoxifen therapy
  - Warfarin Sensitivity
    - Polymorphisms in *CYP2C9* and *VKOR* genes determine metabolism of Warfarin
    - Algorithm determines optimal dosing for a given patient

Futuristic Report (circa 2005)

Department of Pathology
5230 Centre Avenue
Pittsburgh, PA 15232
(412) 62
(412) 68

Pathology Report

Accession #:	**SYS05-0011**	*Patient Name:*	**WASHING**
Accession Date:	**1/1/2004 12:28**	*MRN:*	**999802433**
Collection Date:	**1/1/2004 10:00**	*Location:*	**Amb Surg Cen**
Attending Physician:	**Bill Clinton, M.D.**	*DOB/Age/Sex:*	**8/27/1955 (Age**
Procedure Physician/Copies To:	**John Kerry, M.D.** **George W. Bush M.D.**	*Account #:*	**006213650453**
		Patient Type:	**Day Surgery (S**
		Specimen Class:	**SYSG, SY Sur**
		Bench Designate:	**Breast (SY)**

PATIENT HISTORY:

5PRE-OP DIAGNOSIS: History of breast cancer.
POST-OP DIAGNOSIS: Same.
PROCEDURE: Left breast biopsy.
TW/kmr

PRELIMINARY DIAGNOSIS:

LEFT BREAST, BIOPSY Ğ

A. INVASIVE DUCTAL CARCINOMA, 3.5 CM, AT UPPER INNER QUADRANT.
B. NOTTINGHAM SCORE 9 (TUBULE FORMATION, 3; NUCLEAR PLEOMORPHISM
C. FOCAL DUCTAL CARCINOMA IN SITU (DCIS), OF SOLID TYPE, WITH HIGH NU LOBULAR CANCERIZATION.
D. DCIS CONSTITUTES LESS THAN 25% OF THE TUMOR MASS AND IS PRESENT THE INVASIVE COMPONENT.
E. MULTIFOCAL ANGIOLYMPHATIC INVASION IDENTIFIED
F. SURGICAL MARGINS FREE OF CARCINOMA
G. BENIGN BREAST TISSUE WITH DIFFUSE STROMAL FIBROSIS
H. TNM HISTOPATHOLOGICAL STAGING: T2 N1 Mx
I. PROTEOMIC SIGNATURE: AGGRESSIVE
J. GENOMIC SIGNATURE: BASAL CELL TYPE, AGGRESSIVE.

HD/jk

Pathologist: Howard Dean, M.D.
Fellow/Chief Resident: Dick Cheney M.D.
Resident: John Edwards, M.D.

My signature is attestation that I have personally reviewed the submitted material(s) and the final diagn

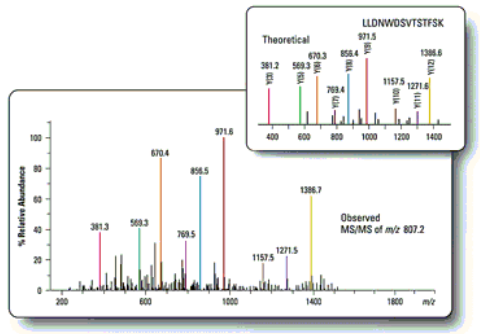
GROSS DESCRIPTION:

The specimen is received fresh identified with the patientÕs name with initials MW and labeled as Ğ single piece of yellow lobulated fibrofatty tissue measuring 6.0 x 5.0 x 4.0 cm . Serial sectioning re measuring 2.0 cm in largest dimension. The rest of the tissue is homogenous, yellow lobulated fatt white fibrous breast tissue. Representative sections are submitted in cassettes A through F (A wit DC

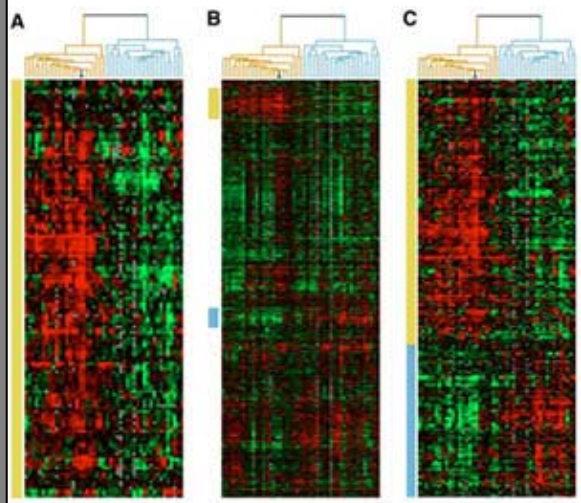
Pathology Report

SYS05-0011 **WASHINGTON, MARTHA**

GENOMICS & PROTEOMICS:



PROGNOSTIC MARKERS IN TUMOR PROTEIN PROFILE.



CLUSTERING OF PATIENT SAMPLE WITH PROGNOSTIC MARKERS.

Case Scenario #1

- 55 y/o female with Breast Cancer
  - Routine surgical pathology (with IHC for ER/PR/HER2)
- In order to provide personalized care:
  - Prognostic category
    - Oncotype DX, Mammaprint, Intrinsic Signatures
  - Testing for Hereditary Breast and Ovarian Cancer
    - BRCA1/2
  - Testing for response to Tamoxifen
    - CYP2D6
  - And possibly soon, testing for Her3 and other biomarkers of response to Herceptin therapy.

mammaprint

Customer	Specimen		Patient	
	Collection Date	06-Aug-2008	Name	
	Test Request Date	06-Aug-2008	Date of Birth	
	Accession Date	08-Aug-2008	Patient ID	
	Report Date	19-Aug-2008	Gender	
			Requisition #	00011636

Results

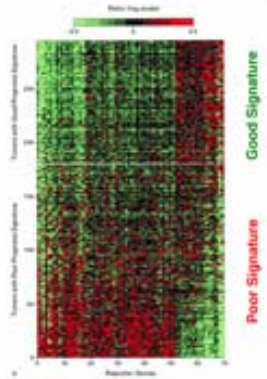
Pathology findings, H&E staining	Sample contains an average of 45% tumor, see *picture*
The sample is classified as:	LOW RISK

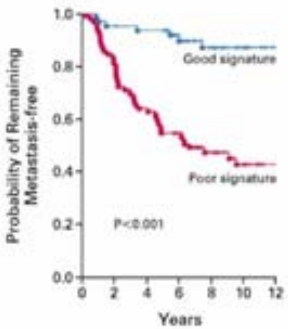
Analysis Description

The breast cancer tissue sample submitted was analyzed by MammaPrint®, a gene expression analysis of 70 prognostic genes that has been validated to correlate with high or low outcome risk for distant metastasis in women with breast cancer.

Interpretation

In the reference group as published [1], lymph node-negative patients classified as Low Risk had a 13% chance to develop distant metastases at 10 years, without adjuvant treatment. The patients classified as High Risk had a 56% chance to develop distant metastases at 10 years, without adjuvant treatment. MammaPrint® has been independently validated and shown to provide independent prognostic information to clinicopathological risk assessment for patients with lymph node-negative breast cancer.[2]





Probability of remaining metastasis-free survival, in lymph node-negative women with breast cancer.[1]

International validation in European patients [3],showed that patients with a "Good signature" had a probability of 90% of metastasis free survival at 10 years. Patients with a "Poor signature" had a probability of 70% metastasis free survival at 10 years.

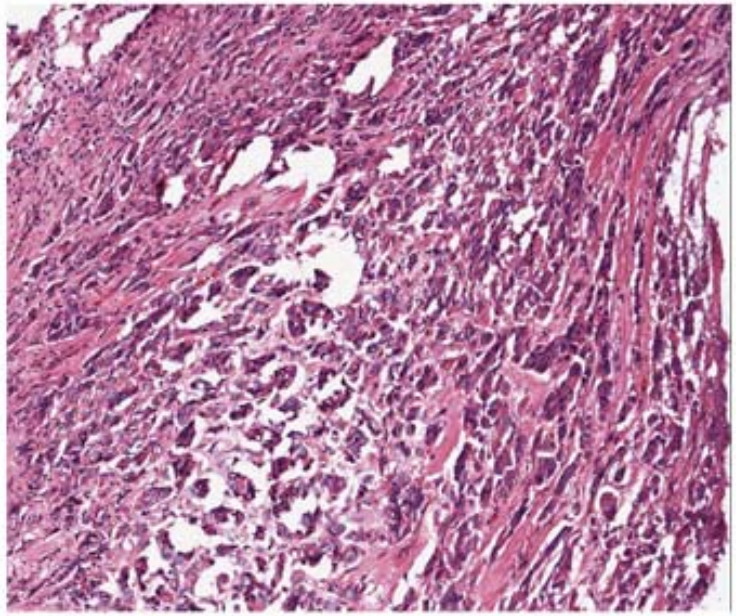
References

1.Van de Vijver MJ et al. N Engl J Med 2002 Dec 19;347(25):1999-2009.
2. Buyse M et al. JNCI 2006;98(17):1183-1192.
3. Van't Veer L et al. Nature 2002;415(31):530-536.
4. Decision summary documents at the publicly accessible FDA 510(k) database at http://www.accessdata.fda.gov website.

The MammaPrint® analysis was performed at Agendia's **CLIA** Laboratory, Kruislaan 406, 1098 SM Amsterdam, The Netherlands.

H&E Staining

Patient ID



Authorized Signature:

Dr. Laura Van t' Veer
Laboratory Director

Dr. Jan Groen
Chief Operating Officer

For *In Vitro* Diagnostic Use
Caution: Federal law restricts this device to sale by or on the order of a physician.
Agendia BV (99D1030869) is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. MammaPrint® is an aid in estimating the prognosis of patients diagnosed with breast cancer. Decisions regarding care and treatment should not be based on a single test such as this test. Rather, decisions on care and treatment should be based on the independent medical judgment of the treating physician taking into consideration all available information concerning the patient's condition, including other pathological tests, in accordance with the standard of care in a given community. MammaPrint® was developed using adjuvantly untreated lymph node negative, mainly European, patients to capture the biology of the primary tumor in a gene expression profile. Its performance characteristics and clinical utility in the United States Population have not been established. The metastasis free survival data is from an independent external patient group in Europe.

agendia

General information about MammaPrint® can be found at www.agendia.com. Detailed information regarding methodology has been published previously [1,3,4]. If you have any questions regarding this report, please contact our office at 714-849-7515 or toll free 1-866-321-BREAST or at customerservice@agendia.com

Pathwork Diagnostics

Tissue of Origin Test Clinical Report

Pathwork Diagnostics Laboratory
1196 Borregas Avenue, Suite 200
Sunnyvale, CA 94089
Toll-free: 1.877.808.0006
Fax: 1.408.400.0840
www.pathworkdx.com

Patient and Order Information

Treating Physician
John Smith, M.D. Tel: 123.456.7890
Institution Fax: 123.456.7890
Street Address
City, State Zip Code

Submitting Pathologist
Mary Lee, M.D. Tel: 987.654.3210
Institution Fax: 987.654.3210
Street Address
City, State Zip Code

Patient Information
Name: Jane Doe
Date of Birth: 04/22/1968
Sex: Female
Medical Record Number: ABC123456789

Specimen Information
Sample ID: AB-12-34-56
Date Specimen Collected: 07/28/08
Date Specimen Received: 07/29/08
Pathwork ID: TOO08-987654

Clinical Information

Specimen Type: Frozen
Biopsy Site: Lung
Clinical Data: No conclusive diagnosis

Tissue of Origin Test Results

The Tissue of Origin Test shows that the highest Similarity Score for this submitted frozen specimen is 90.2 for colorectal origin. The Similarity Scores for the remaining 14 tumor types are all below 5.

Pathology Interpretation

The most likely explanation for these Similarity Score findings is that the primary tumor is of colorectal origin with metastasis to the lung. Similarity Scores of less than 5 indicate there is a less than 5% probability that the submitted tumor specimen is of either Bladder, Breast, Gastric, Hepatocellular, Kidney, Melanoma, Non-Hodgkin's Lymphoma, Non-Small Cell Lung, Ovarian, Pancreas, Prostate, Testicular Germ Cell, Thyroid, or Soft Tissue Sarcoma origin.

The data reported above should be considered along with all other relevant clinical information in reaching a conclusion regarding the origin of this patient's carcinoma.

CLIA: 05D1080859
Laboratory Director: Meredith Halks Miller, M.D.

Meredith Halks Miller — 7/29/08
Electronic Signature of Pathwork Staff Pathologist — *Date*

This service is an adjunct to the evaluation of the submitting pathologist and does not represent a final diagnosis. A portion of the assay was performed at the Affymetrix Clinical Services Laboratory, 910 Riverside Parkway, Suite 60, West Sacramento, CA 95605.

This test was developed and its performance characteristics determined by Pathwork Diagnostics Laboratory. It has not been cleared by the U.S. Food and Drug Administration (FDA). This test is intended for clinical purposes. It should not be regarded as investigational or for research.

Pathwork Diagnostics

Tissue of Origin Test Report

Pathwork Diagnostics Laboratory
1196 Borregas Avenue, Suite 200
Sunnyvale, CA 94089
Toll-free: 1.877.808.0006
Fax: 1.408.400.0840
www.pathworkdx.com

Report Date: 29Jul2008 14:44PDT
Sample ID: AB-12-34-56
File: Sample_Data_TOO08-987654.CEL

Pathchip Serial #: 123456
Pathwork Analysis ID: 98765

Specimen Type: Frozen
Version: TOOv3.0

Data Quality: Acceptable.

TISSUE	SIMILARITY SCORE	SIMILARITY SCORE (LOW — HIGH)
Colorectal	90.2	
Pancreas	2.4	
Non-small Cell Lung	2.3	
Breast	2.1	
Gastric	1.3	
Kidney	0.6	
Hepatocellular	0.3	
Ovarian	0.3	
Soft Tissue Sarcoma	0.1	
Non-Hodgkin's Lymphoma	0.1	
Thyroid	0.1	
Prostate	0.1	
Melanoma	0.1	
Bladder	0.1	
Testicular Germ Cell	0.0	

Guide to Report Interpretation:

The Similarity Score (SS) is a measure of the similarity of the RNA expression pattern of the specimen to the RNA expression pattern of the indicated tissue. Similarity Scores range from 0 (very low similarity) to 100 (very high similarity) and sum to 100 across all 15 tissues on the panel.

SS $\geq$ 30: A single SS greater than or equal to 30 indicates the likely tissue of origin. If two or three SS are greater than or equal to 30, then one of those results indicates the likely tissue of origin.

5 < SS < 30: If every SS is between 5 and 30, then the test result is indeterminate and no tissue of origin is indicated.

SS $\leq$ 5: A SS less than or equal to 5 rules out that tissue type as the likely tissue of origin.

Limitations: The Pathwork Tissue of Origin Test is not intended to establish the origin of tumors (e.g. carcinoma of unknown primary) that cannot be diagnosed according to current clinical and pathological practice. It is not intended to subclassify or modify the classification of tumors that can be diagnosed by current clinical and pathological practice, nor to predict disease course or survival or treatment efficacy, nor to distinguish primary from metastatic tumor. Tumor types not in the Pathwork Tissue of Origin Test database may have RNA expression patterns that are similar to patterns in the database. Therefore, results cannot be used to distinguish tumor types in the database from tumor types not in the database.

Case Scenario #2

- 55 y/o male with Chronic Lymphocytic Leukemia (CLL)
  - Routine hematopathology workup (with IHC, flow cytometry)
- In order to provide personalized care:
  - Prognostic category
    - Cytogenetics
    - FISH
  - Array-based karyotyping is poised to replace these analyses

CLL FISH/LOH Panel

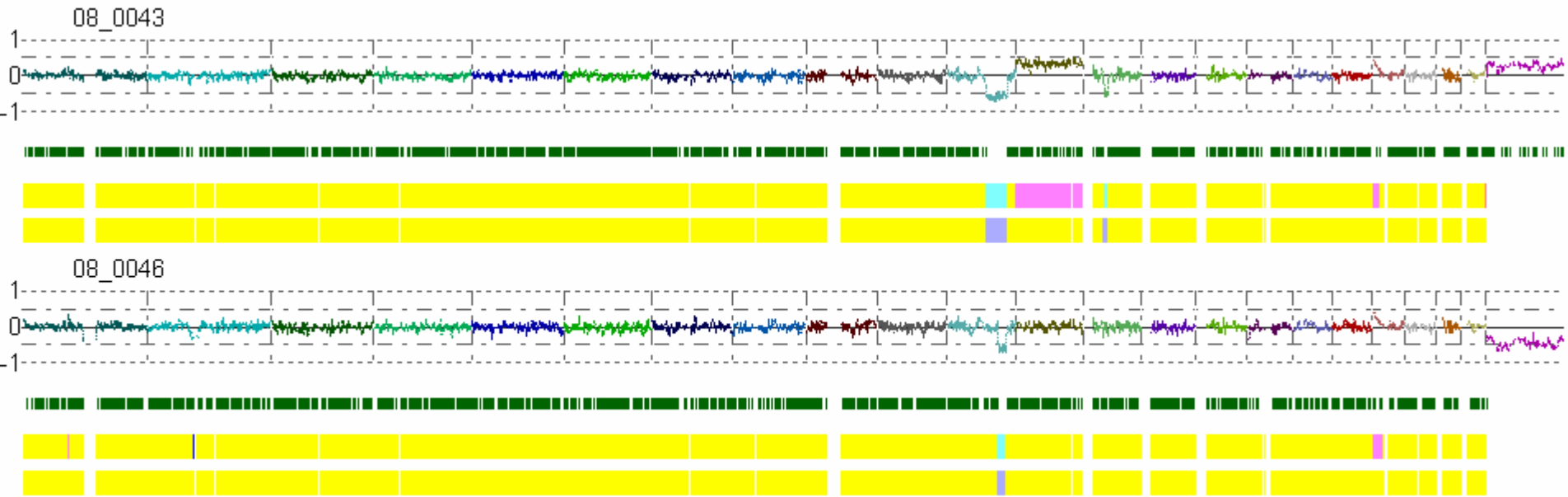
Cytogenetic Aberrations in CLL

Cytogenetic aberration	Gene(s) involved	% cases detected by FISH[a]	Prognosis (median survival)[b]
del(13)(q14)	Unknown	55–64%	Good (133 months)
Trisomy 12	Unknown	16–25%	Intermediate (114 months)
del(6)(q21–q23)	Unknown	0–6%	Intermediate
del(11)(q22.3–q23.1)	*ATM*	15–18%	Poor (79 months)
del(17)(p13)	*TP53*	7–8%	Poor (32 months)

[a] Data from refs. *54* and *55*.
[b] Data from ref. *54*.

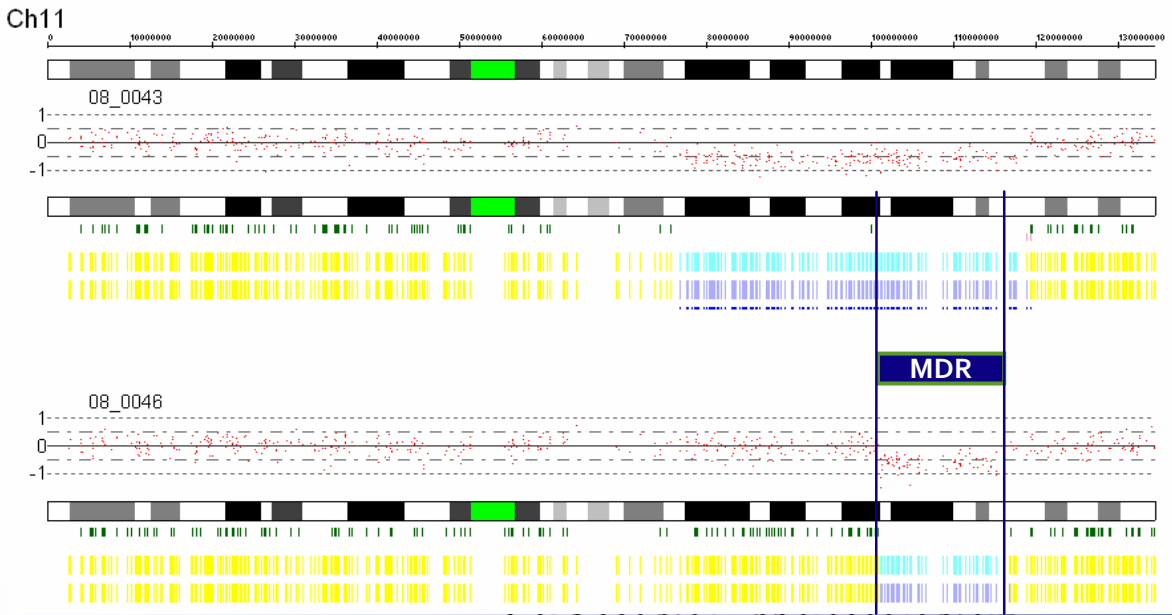
From Gerson and Keagle, The Priniciples of Clinical Cytogenetics, 2nd Ed, 2005 Humana Press, p473.

SNP array virtual karyotype results from 2 CLL cases.

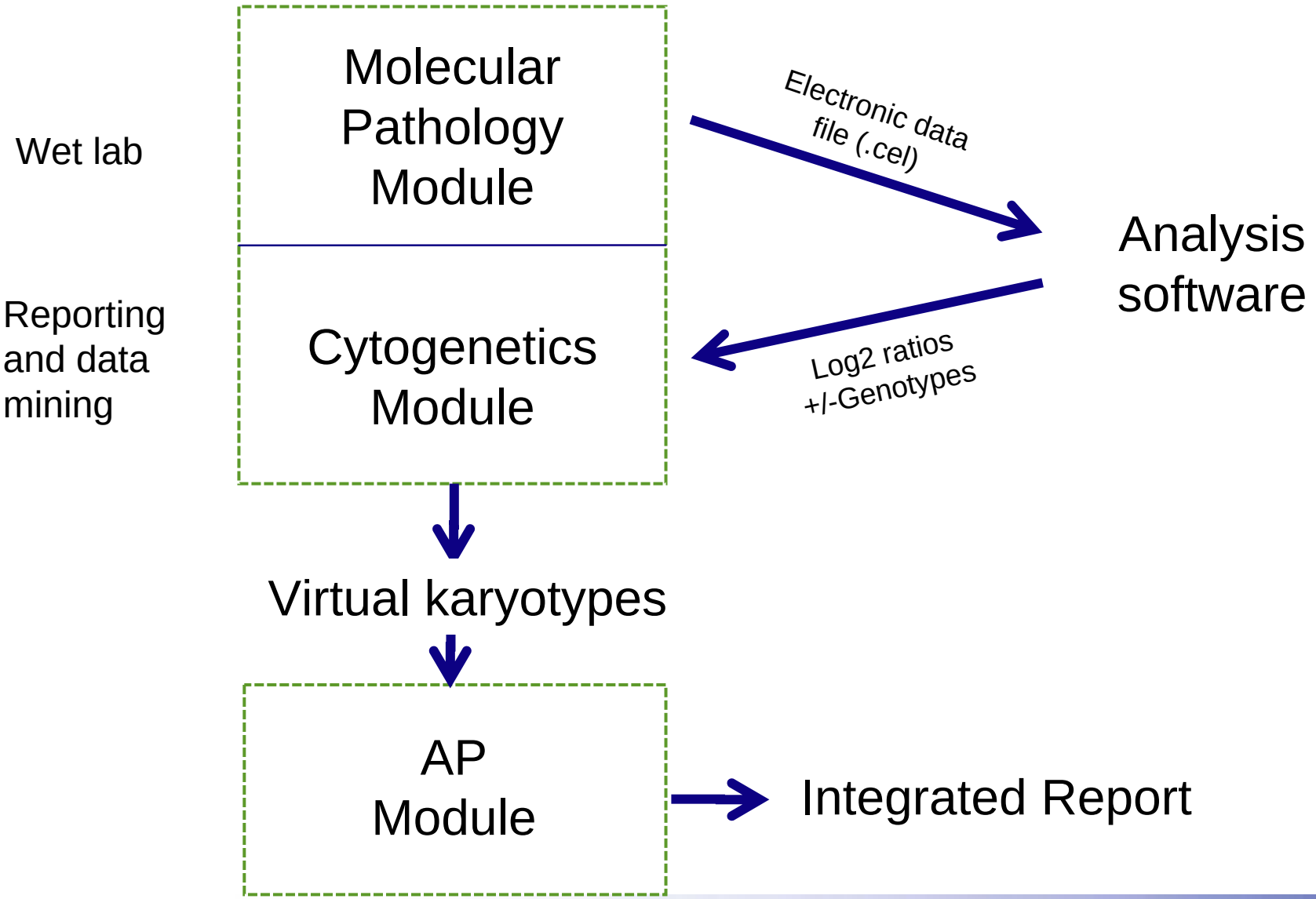


<u>08_0043</u>
67% tumor cells
Log2Ratio on 10K: -0.55
Log2Ratio on 250K: -0.40
LOH on 10K: 68
LOH on 250K: 1

<u>08_0046</u>
80% tumor cells
Log2Ratio on 10K: -0.60
Log2Ratio on 250K: -0.42
LOH on 10K: 28
LOH on 250K: 4



Data Workflow for Virtual Karyotyping



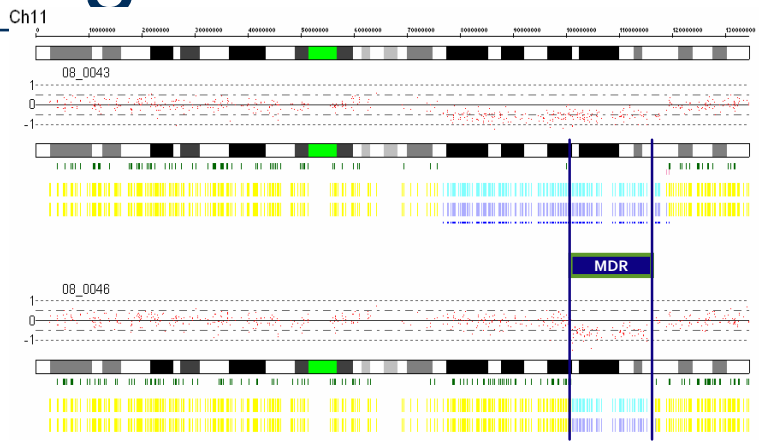
Analysis: Informatics

- Different analysis programs for different array types
  - aCGH
  - Affymetrix SNP array
    - Affymetrix Genotyping Console (GTC)
    - CNAG (www.genome.umin.jp)
    - Partek Genomics Suite
    - dChipSNP (www.biostat.harvard.edu/complab/dchip)
  - Illumina bead array → Bead studio

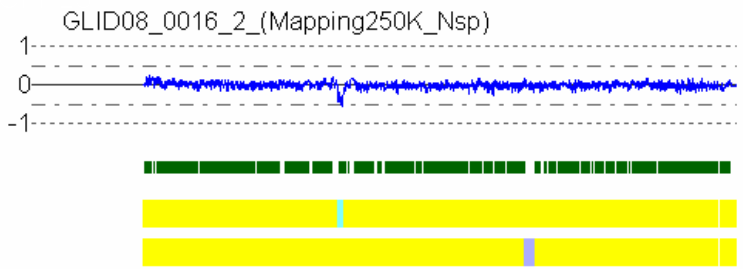
Data Mining

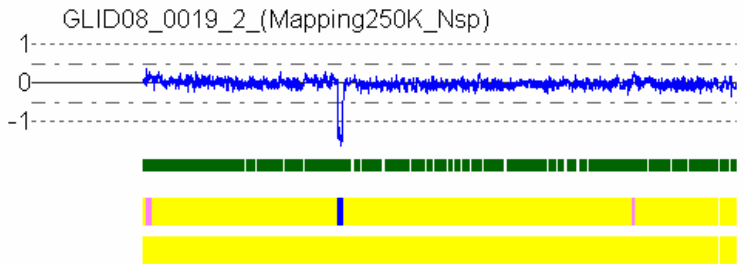
- Research and Clinical
- Recurrently deleted regions
- Minimally deleted regions
- Recurrently gained regions
- Minimally gained regions
- Recurrently amplified regions
- Minimally amplified regions
- % overlap with CNV
- Based on automated and/or manual calls

Overlapping area



Exactly the same breakpoints





Redesign Challenges

- Handling of multianalyte test data
  - Some currently done in reference labs, but they will migrate to hospital laboratories
  - New platforms add complexity – Microarrays, next generation sequencing
  - Archival of clinically generated data for research or new test applications
- Interoperability with data analysis software
  - Gene sequencing, microarray analysis, etc.

Redesign Challenges

- Integration of tumor biomarker data, genetics and pharmacogenomics
  - Integrated reports with data coming from various sources
- Interoperability with other hospital systems
  - e.g. Pharmacy for adequate therapeutic selection based on biomarker data
- Data Mining

Complete Redesign is Needed

- Three, Dark Daily also predicts that these changes in histology will end the reign of "batch" processing of specimens, often using overnight processing methods. Instead, histology laboratories will be organized around single-piece work flow, using rapid processing methods.

- The lines between AP and CP are blurring
- Integration between AP, CP and other systems appears as a key issue for future development
- The LIS needs to acknowledge this fact and move towards the integration of all "diagnostics"
- Need to build solutions for the XXI century practice of pathology (i.e. genomics, proteomics and other 'omics')

Hot off the press!

Family History "Remains Most Valuable Genetic Test"

March 18, 2009

Pathologists Discuss State of Genetic Testing at World Congress of Pathology

Dateline: Sydney, Australia—New-fangled technology is making genetic testing and molecular diagnostics ever more precise tools to aid clinicians, but at least two internationally-respected experts in genetics still consider family history to be a primary—if not the most useful—source of knowledge about a patient's genetic risk factors. Both experts were in Sydney, Australia, to speak at the XXV World Congress of Pathology which took place on March 13-15, 2009.

"Family history remains the most valuable genetic test available to us today," declared Michael S. Watson, Ph.D., Executive Director of the American College of Medical Genetics in Rockville, Maryland, in his presentation titled "Translation of Genetic Information into Healthcare Use." He discussed the importance of building a multi-dimensional health record that included family history and would follow the patient from cradle to grave.

- Acknowledgements
  - Jill Hagenkord MD (Creighton)
  - Alexis Carter MD (Emory)
  - Mike Becich MD / Jeffrey Kant MD (UPMC)

Questions?