Features of telemedicine focusing on predictive cancer diagnosis

Klaus Kayser, Stephan Borkenfeld, Amina Djenouni, Bathuyag Sereejav, Gian Kayser

Tissue – based diagnosis

Definition & recent approaches

Present stage of telemedicine

Predictive Diagnosis

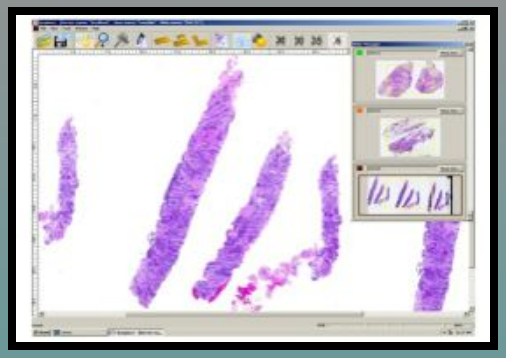
Definition & Algorithms

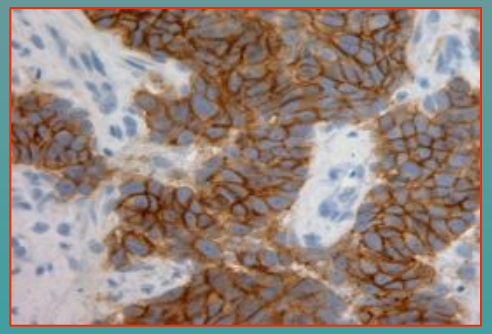
Applications in Cancer diagnosis

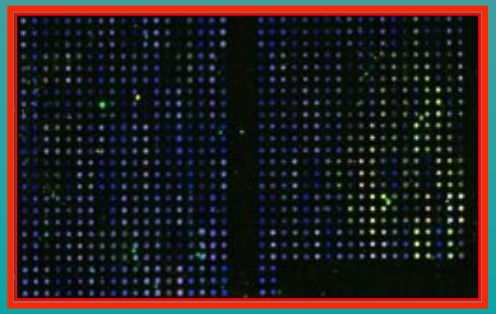
Perspectives

Definition of tissue based diagnosis

- **Tissue based diagnosis is the interpretation of images obtained from the human body at light microscopy and higher magnification in combination with clinical data.**
- **It includes histology, cytology, molecular biology, cytogenetics, molecular genetics, electron microscopy, and biochemistry images.**



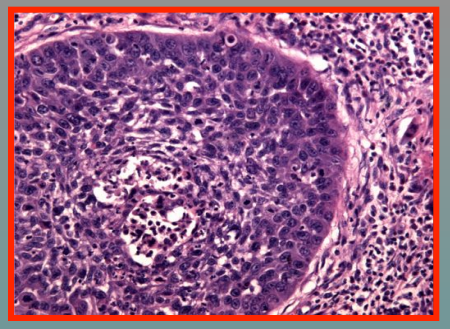


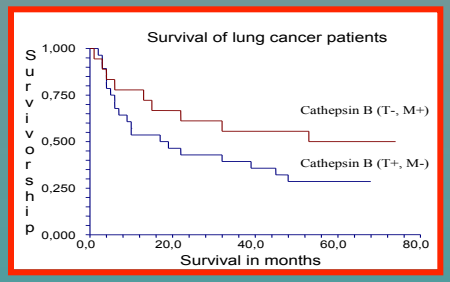


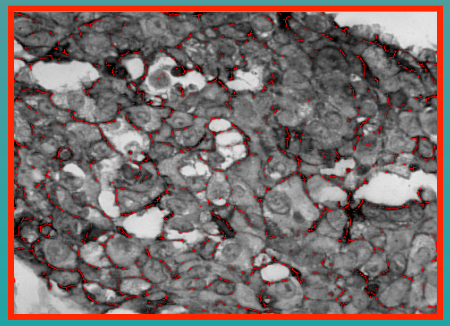
Medical Diagnosis is mainly derived from Visual Information

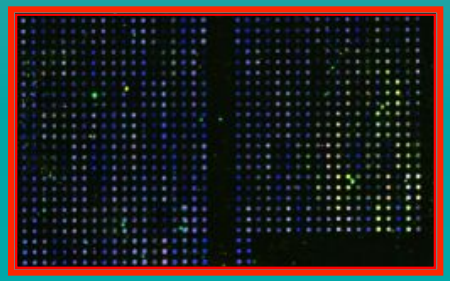
Tissue – based diagnosis types

- Classic diagnosis: H&E, PAS, cytoskeleton, organ origin markers
- Prognosis estimation: quantitative immune/ligand histochemistry
- Therapy advises (predictive): gene analysis & receptors.
- Risk estimation (array technique): gene analysis









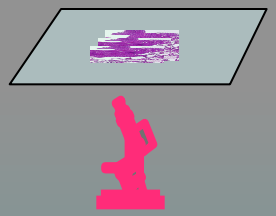
Definition / Background

Telepathology is tissue based diagnosis at a distance, part of telemedicine.

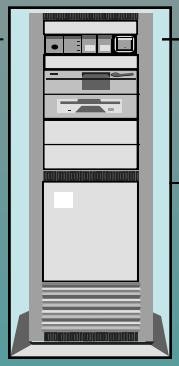
Telepathology can serve for

- **Medical diagnosis assistance independent on distance, date, language: frame of laboratory data;**
- **Use in daily routine, science, education, training;**
- **Direct transfer of diagnosis to centers of treatment and patients' care.**
- **Technology: According to social forums (php).**

Workflow of a TMCC tuned for developing countries Forum (MECES, www.diagnomx.eu)



Upload image



Email, SMS; phone

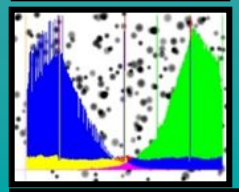
Client

External Information

Language Translation
Access Library NIH

Measurements

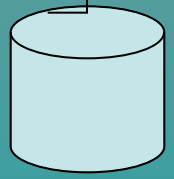
ROI Low Magnification



Quality Control

Confirmed Report (pdf)

Teaching Tools,
Tests



Relational
Database

Experts on duty

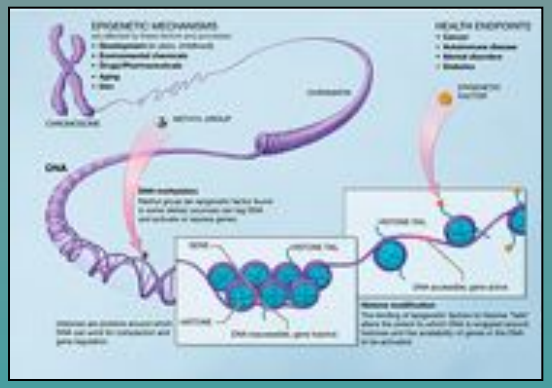
Diagnosis Assistants

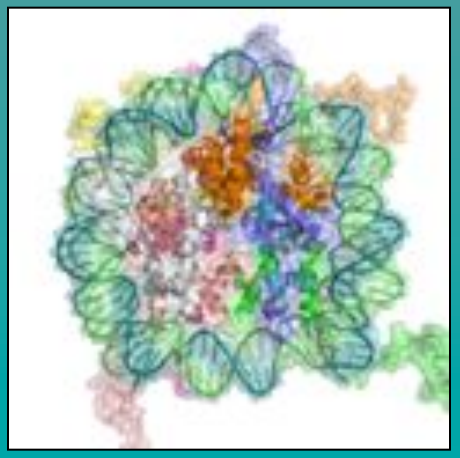
Client Expert Communication

Off line: email, SMS, Facebook, Twitter
On line: Skype, Chat,
Videoconferencing

Tumor cell sociology

- Definition (analoguous to epigenetics)
- Epigenetics involves modifications of the activation of certain genes, but not the basic structure of DNA.
- Cancer cell neighbors involve the behaviour of the involved cancer cell but not its basic features.
- Properties of nearest neighbor:
  - Cell type (cancer cell – macrophage)
  - Membrane receptors
  - Proliferation stage (cell cycle)
  - Structural differences
- How to measure?





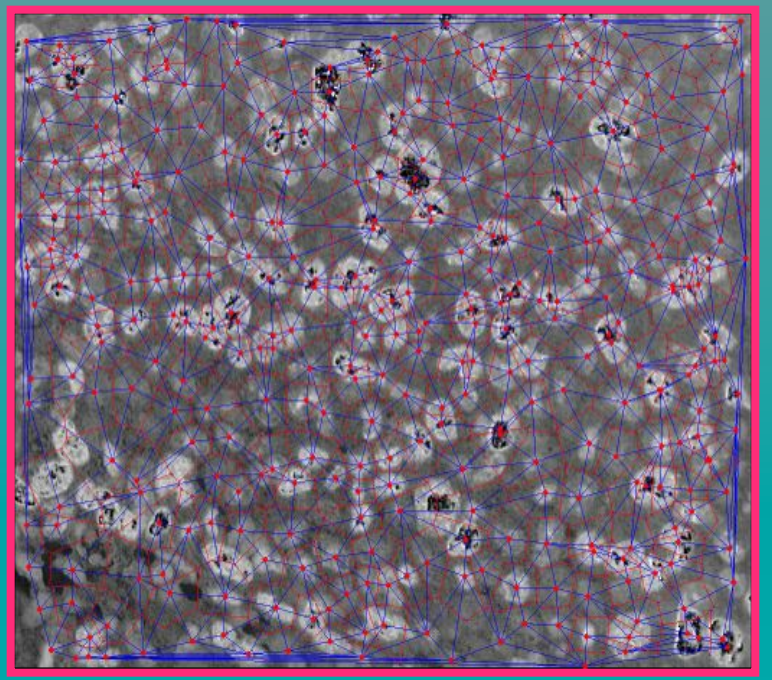
http://en.wikipedia.org/wiki/Epigenetics

Tumor cell sociology and syntactic structure analysis

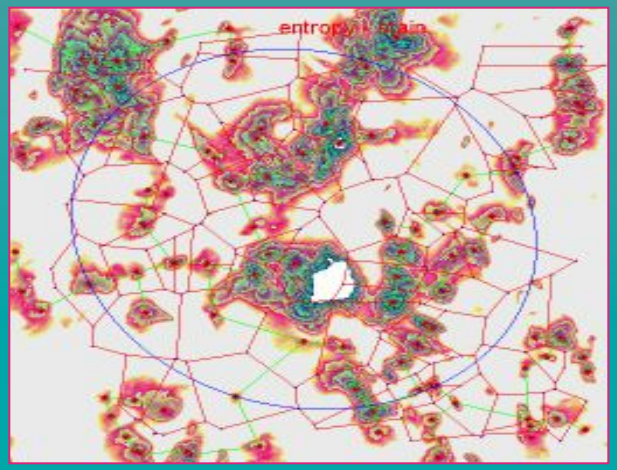
Definition

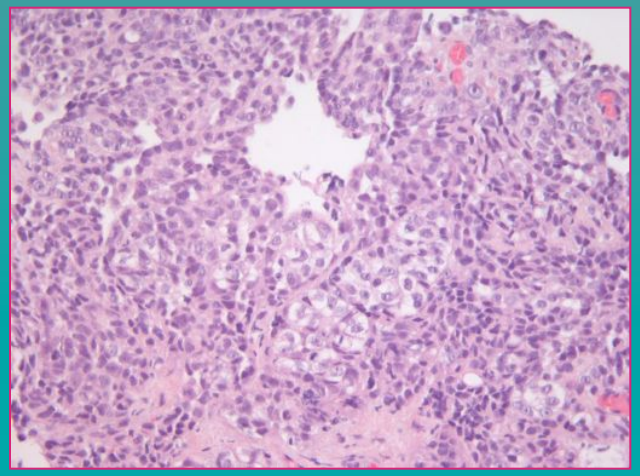
Syntactic structure analysis is the measure of any structure by ”decomposition” into its basic units.

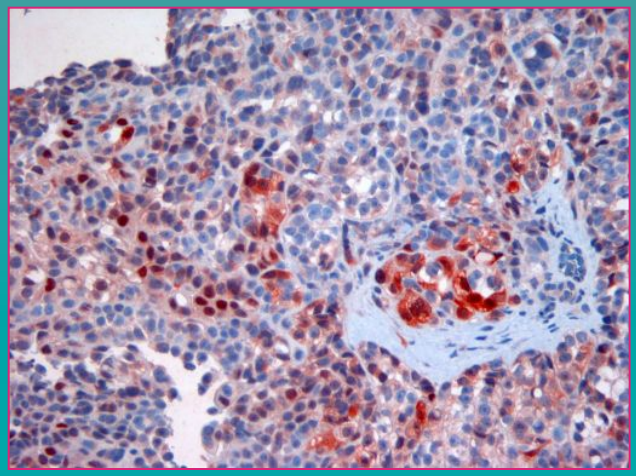
- The aim is to figure out how the texture of any image is generated.
- Measure: <structural entropy>.



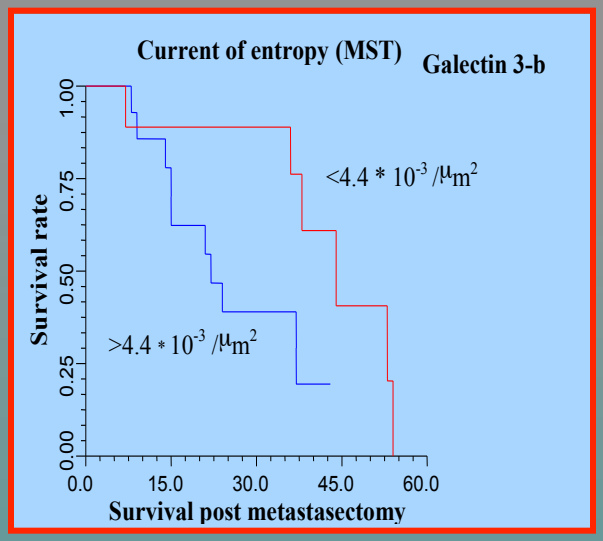
Entropy calculation	H & E	Calretinin
Shannon‘s entropy:	2.84	4.36
Texture entropy :	6.58	6.79
No of clusters:	23	51
Total entropy (cluster)	14.35	19.94
Entropy Primitives	0.51	0.79
Structure entropy	0.58	0.83







Example protein - carbohydrate recognition



It is probably a “high order” biological steering mechanism, and important for cell to cell and cell to matrix interactions, thus for

- growth regulation (apoptosis)
- cellular maturation
- organ development
- organ - environment behavior

Predictive Pathology in human Cancer

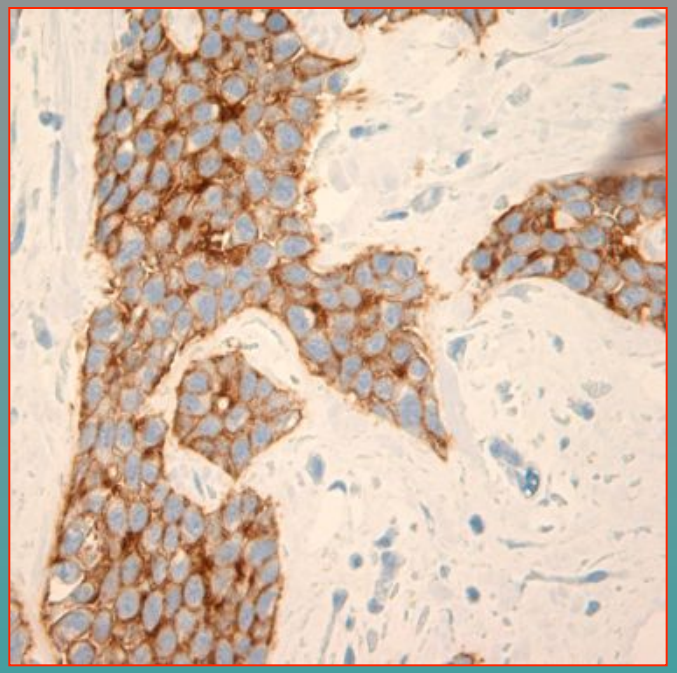
- Aim: to analyze extra- and intracellular pathways of cellular proliferation
- Provides information on membrane proteins in combination with intracellular pathways (gene expression)
- Specifies the potential therapy (by adding specific antibodies to cytostatic therapy)
- Guides the oncologist
- Examples: Her2_neu breast carcinoma, EGFR lung cancer

Algorithms of predictive diagnosis

Surgery, Radiology H&E, IHC	Conventional diagnosis	Tumor extension
IHC, FISH	Membrane receptors (*)	Cellular communication
IHC, PCR, FISH, TMA	Proteins, RNA, miRNA (**)	Intracellular pathways
PCR, RNA, DNA assays	Cancer-related target genes (***)	Gene anomalities

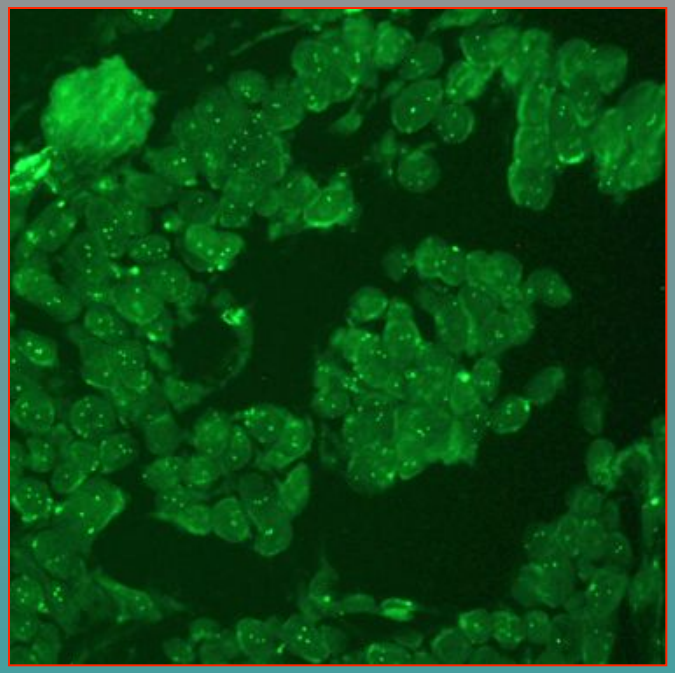
(*) EGFR, VGFR, etc.; (**) (*BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A*); (***) raf, myc, EML4,…

Her2_neu breast carcinoma / entropy



Score 2+
Trastuzumab
therapy ?

FISH
amplification:
Her2/neu gene

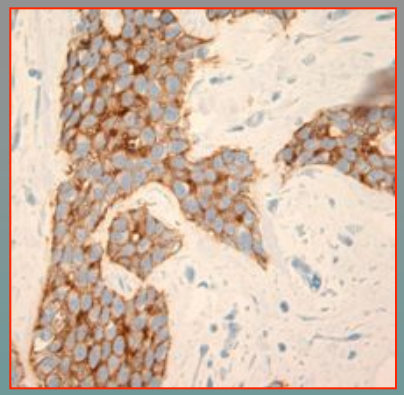


Microstages: tumor cells
IHC macrostages:
Tumor cells {3+, 2+, 1+, 0}
Connecting membranes
{n,M+}, (n=1-4, M = 0 - 3)
Σ = 16

Microstages: tumor cells
FISH macrostages:
Nuclear signals {n, F+}
n number of neighbors
(n=1- 4, F = 0 – 3)
Σ = 16

Results: IHC

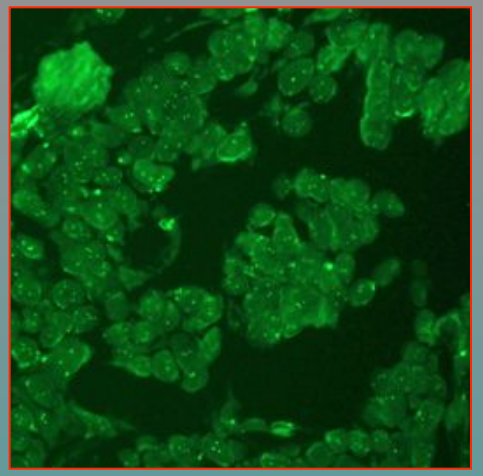
Microstages: Σ tumor cells: 320
M(0+) = 22, M(1+)=66, M(2+)=214,
M(3+)=38, N = No neighbors
Entropy: 1.03 Macrostages: 16



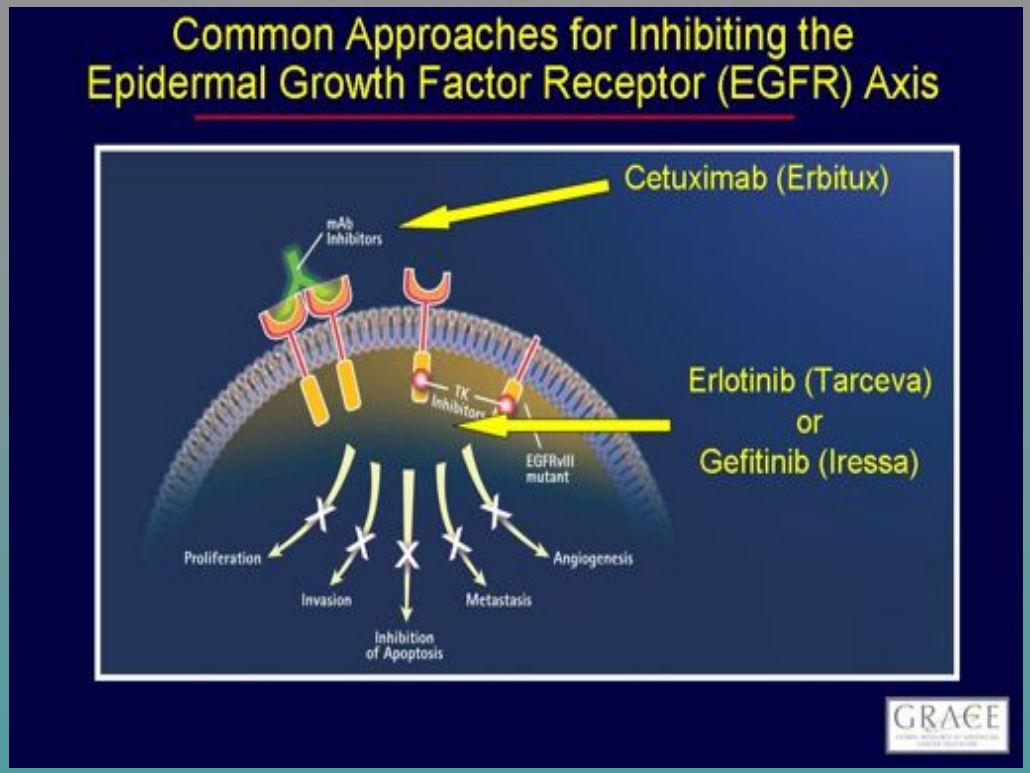
	N	1	2	3	4	Entropy
M	*0*	9	13	0	0	0.58
M	*1*	28	20	8	10	1.19
M	*2*	16	68	82	47	1.19
M	*3*	19	16	3	0	1.09

Results: FISH

Microstages: Σ tumor cells: 120
FISH(0+)= 8, FISH(1+)=16,
FISH(2+)=46, FISH(3+)=50
Entropy: 1.18 Macrostages: 16



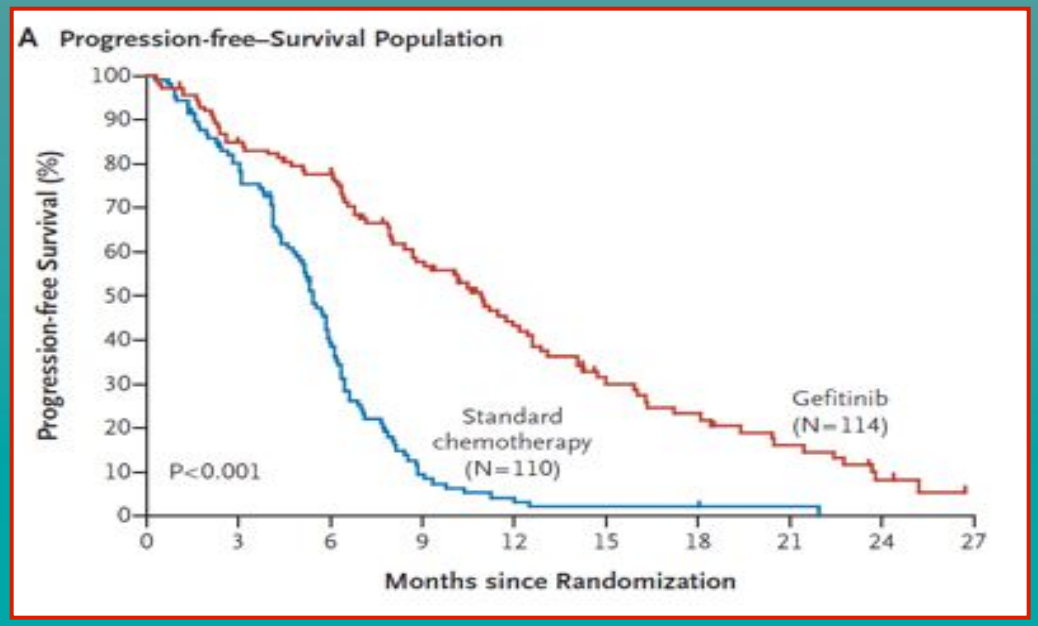
	N	1	2	3	4	Entropy
FISH	*0*	5	3	0	0	0.35
FISH	*1*	6	4	6	0	1.66
FISH	*2*	6	9	17	14	1.13
FISH	*3*	9	23	13	5	1.23



Molecular markers – potential EGFR inhibition

Extracellular: Erbitux

Intracellular: Erlotinib Gefitinib.



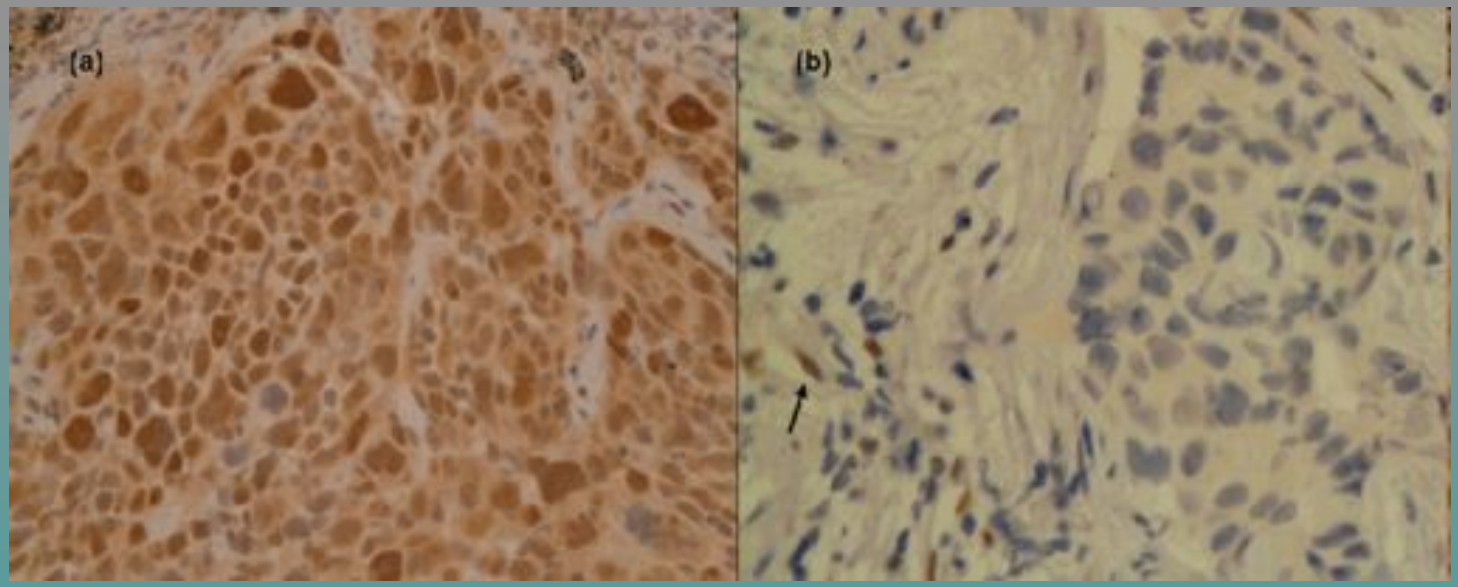
230 Patients with therapy relevant mutation in EGFR-Gene
Standard-Chemotherapy: Carboplatin + Paclitaxel

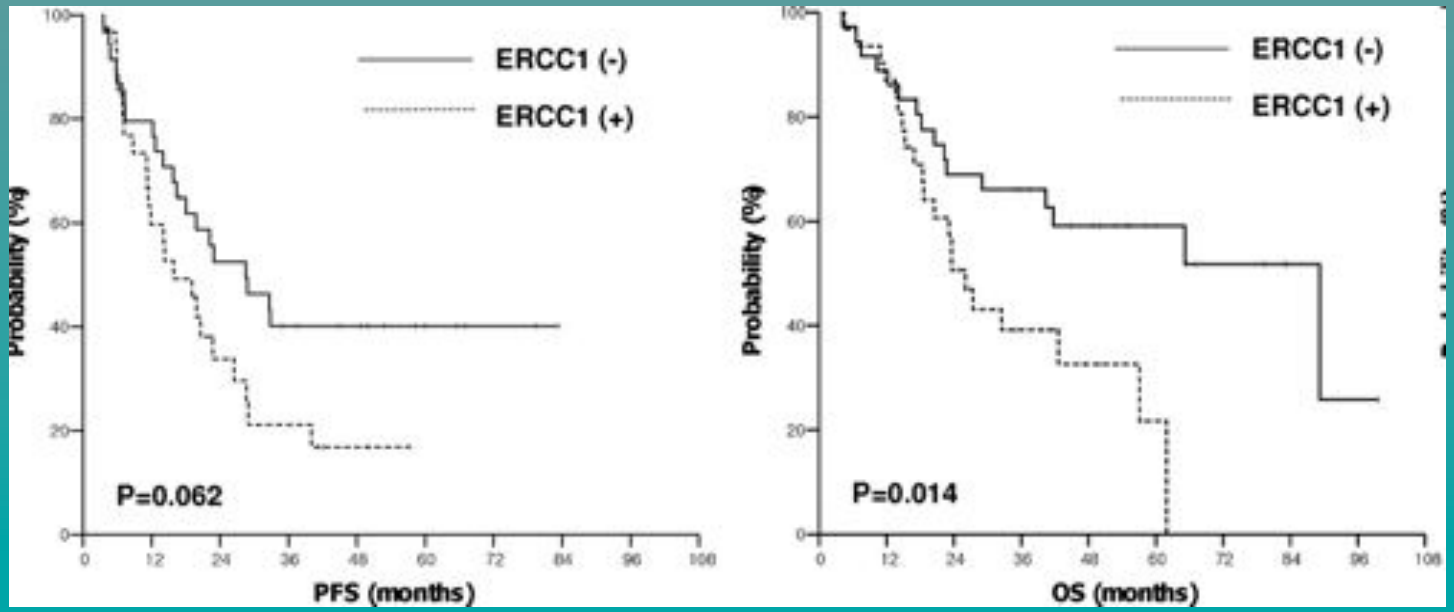
Maemondo et al. NEJM 2010 362:2380-2388

Molecular markers that add to EGFR therapy

- ERCC1 gene product functions in the nucleotide excision repair pathway involved in recombinational DNA repair and in the repair of inter-strand crosslinks, and is required for the repair of DNA
- RRM1 gene encodes one of two non-identical subunits which constitute ribonucleoside-diphosphate reductase that produces deoxyribonucleotides prior to DNA synthesis in dividing cells.

Molecular marker – ERCC1



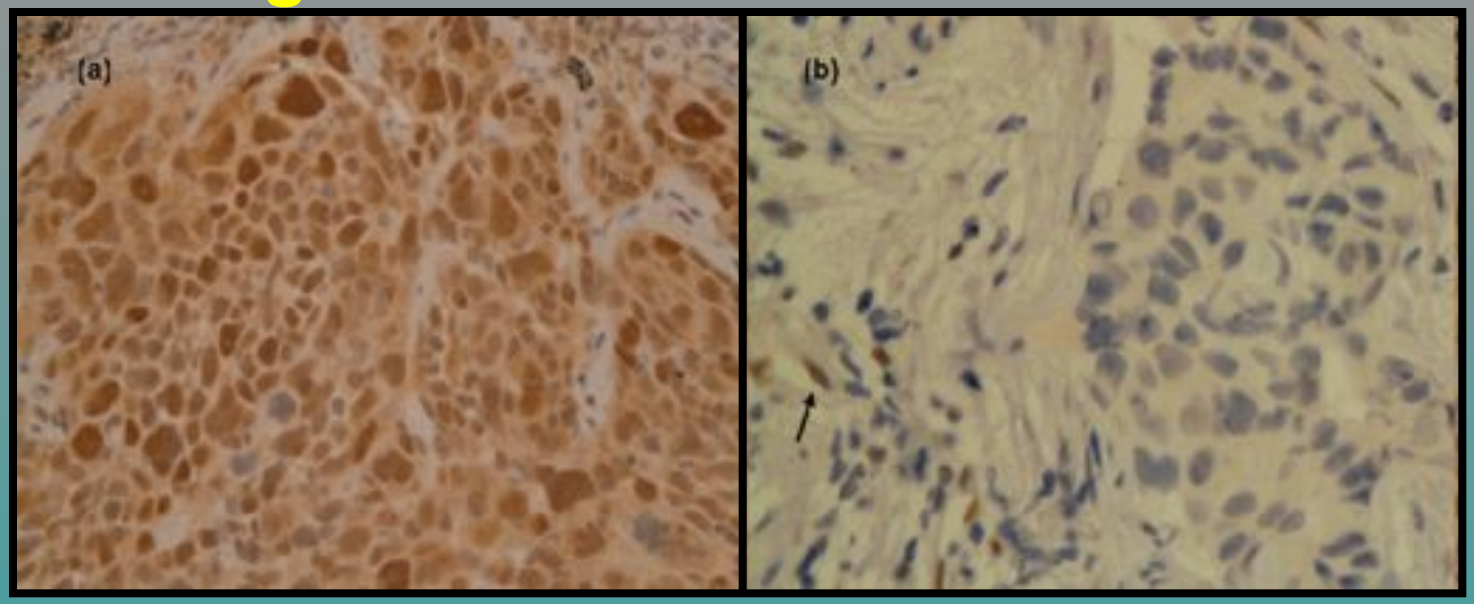


83 Patients with N2-stage confirmed by mediastinoscopy

Hwang Cancer 2008 113:1379-1386

Molecular marker – ERCC1, entropy micro- and macrostages

Hwang Cancer 2008 113:1379-1386

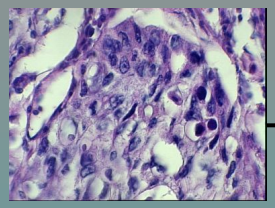


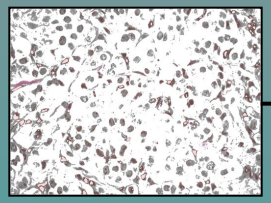
320	Σ No cells	160
{0, 30, 210, 80}	{0, 1+, 2+, 3+}	{148, 12, 0, 0}
0.84	Entropy	0.28
1.67 ± 0.3	MST Entropy	1.43 ± 0.2
2.43	Σ Entropy macrostages	0.92

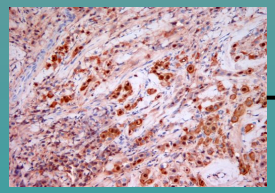
Workflow of a TMCC tuned for predictive diagnosis

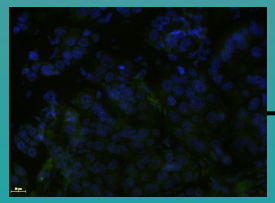
Forum (MECES, www.diagnomx.eu)

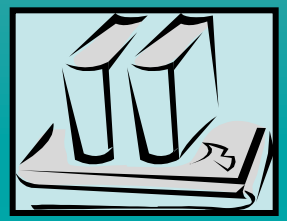
Upload images





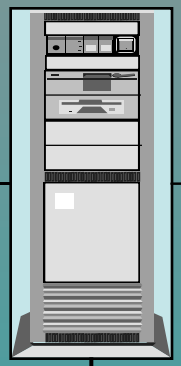






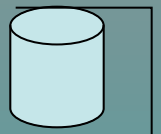
External Information

Clients

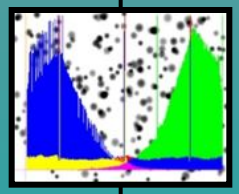


Relational Database

Email, SMS; phone
Video conference

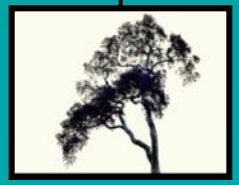


Experts on duty

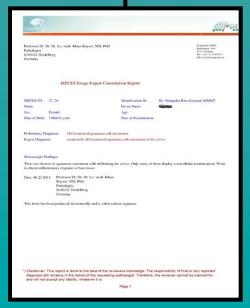


Quality Control

Measurements

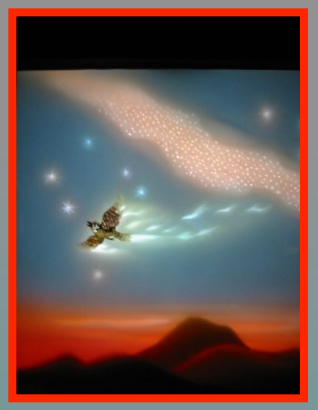


Teaching Tools
Tests



Confirmed Report

Organizing experts: Virtual International Pathology Institute



Pathologists agreed to found a virtual international pathology institute **(VIPI)** to

- organize themselves under the umbrella of the European Society of Pathology (ESP)
- perform consultation & definite diagnosis
- work in an institute – like organization
- Advice for additional tissue examinations
- organize continent – based virtual slide centers in collaboration with industry.

Conclusions

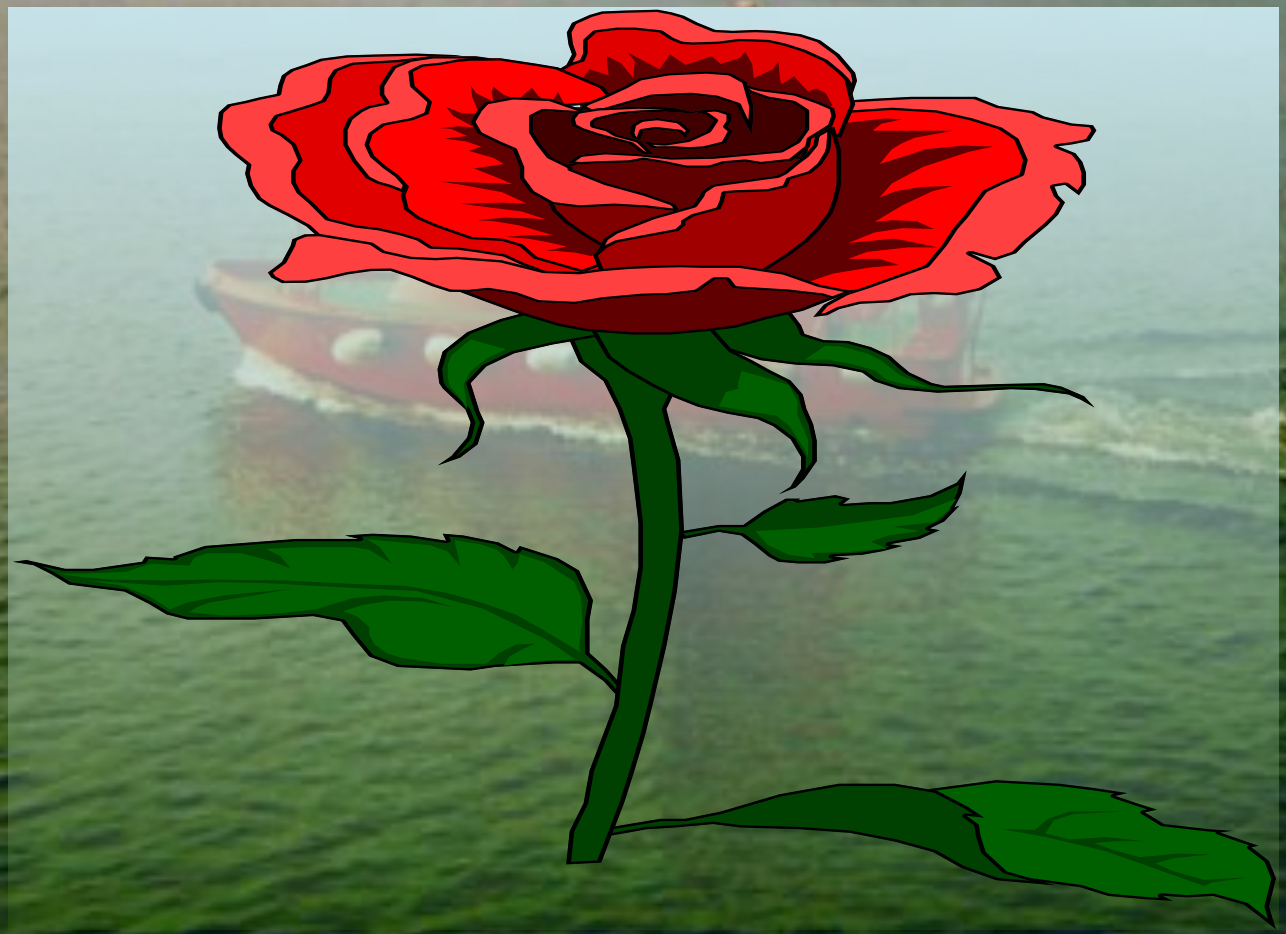
IT on tissue – based diagnosis starts with conventional morphology & image standards -> diagnosis

& MST entropy (flow) -> survival

Identification of molecular subtypes involved in cellular proliferation (EGFR), etc.. -> therapy advices

Quantitative analysis of cellular communication opens new perspectives for „targeted cancer therapy“.

Open Forums (MECES) can steer diagnostic information at different levels between different pathologists and laboratories

Predictive and Communicative Pathology acts as Pilot in Cancer Therapy

thank you very much for your attention