ΜΑΘΗΜΑ :ΚΛΙΝΙΚΗ ΧΗΜΕΙΑ

Molecular Oncology
A: introduction

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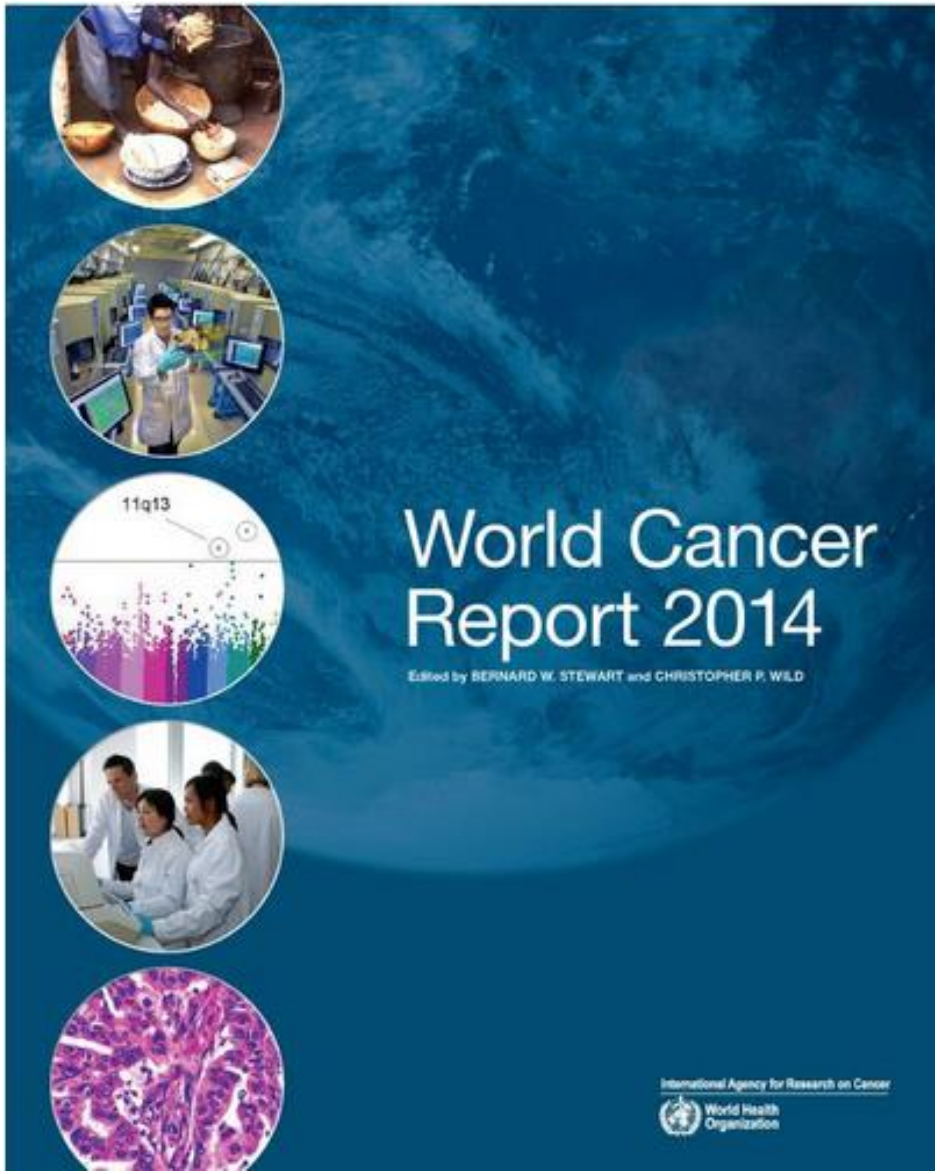
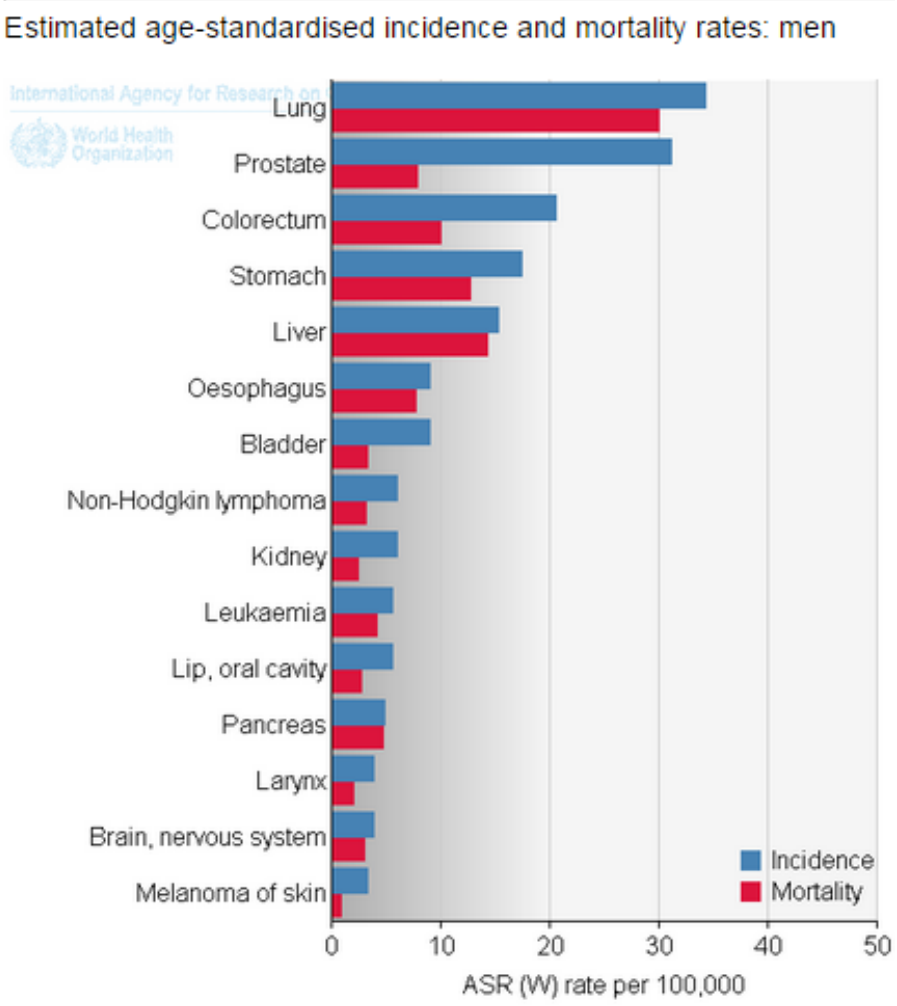
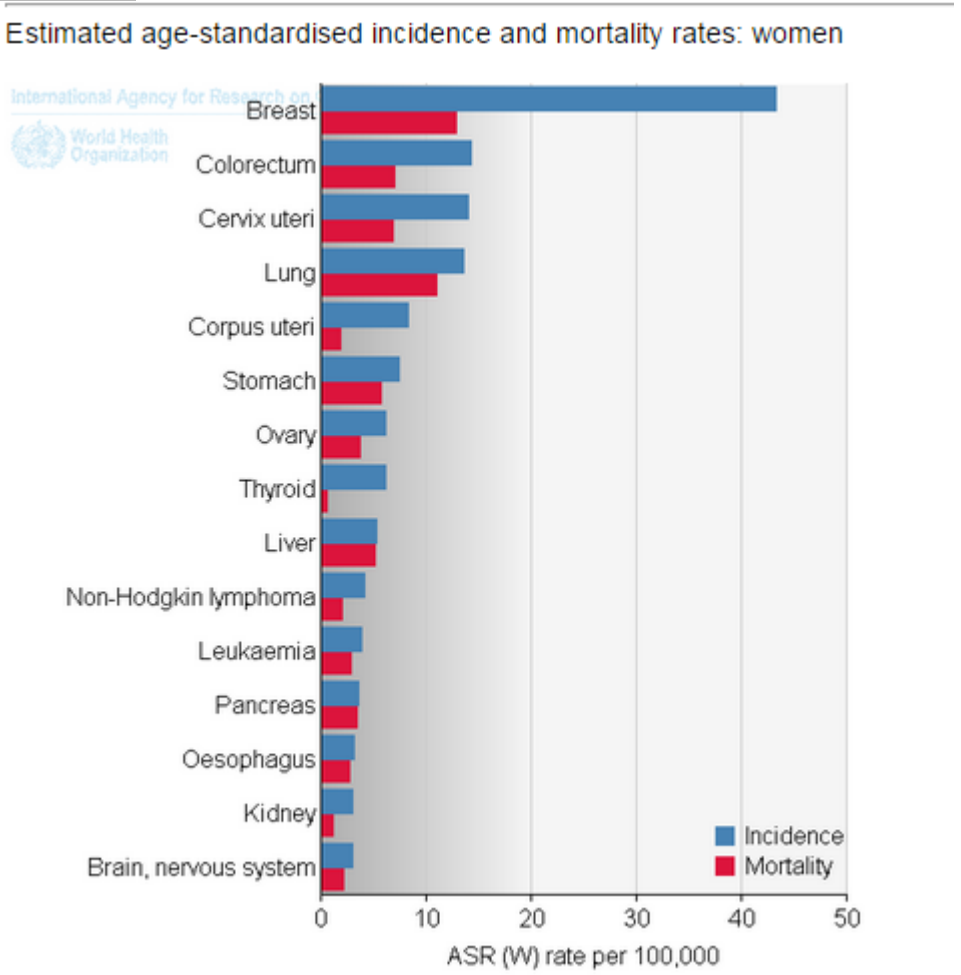


International Agency for Research on Cancer (IACR)

http://www.iarc.fr/en/publications/books/wcr/index.php

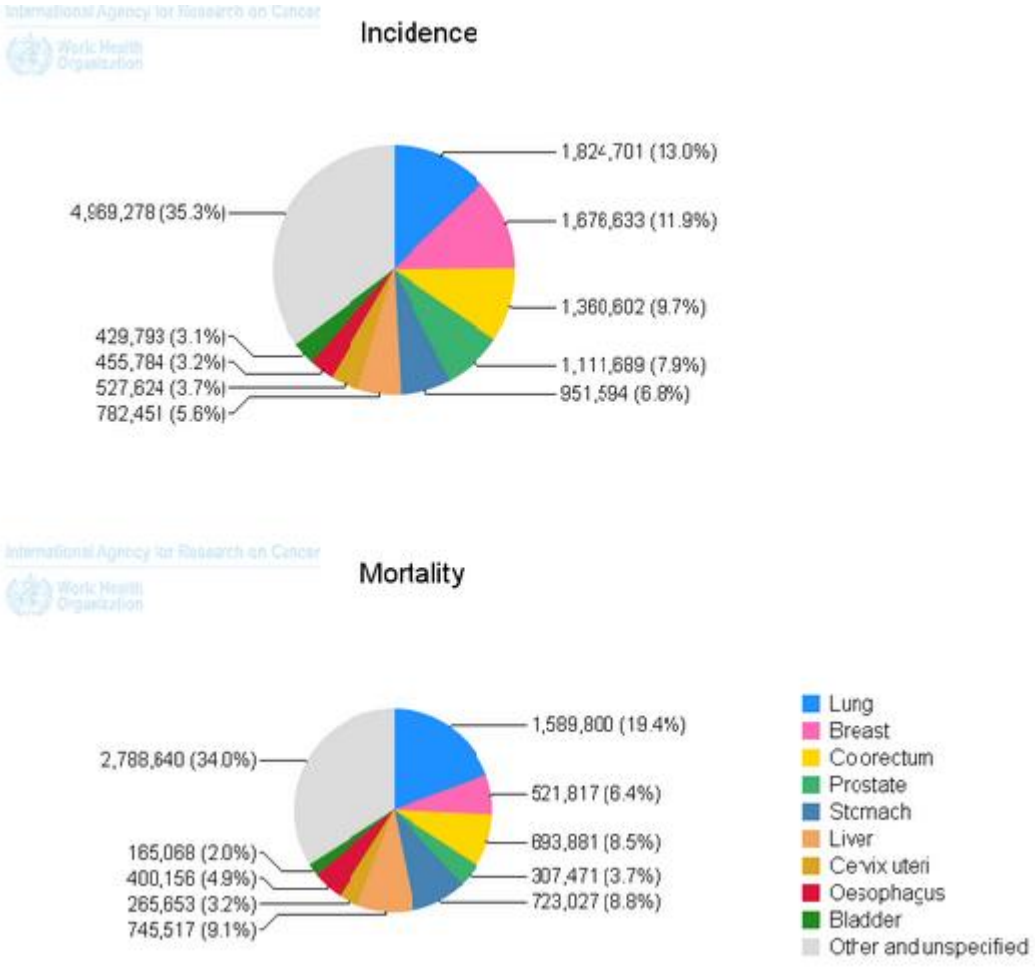
Estimated cancer incidence, mortality and Prevalence worldwide, in 2012, source: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx





Estimated cancer incidence, mortality and Prevalence worldwide, in 2012, source: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx

Both sexes



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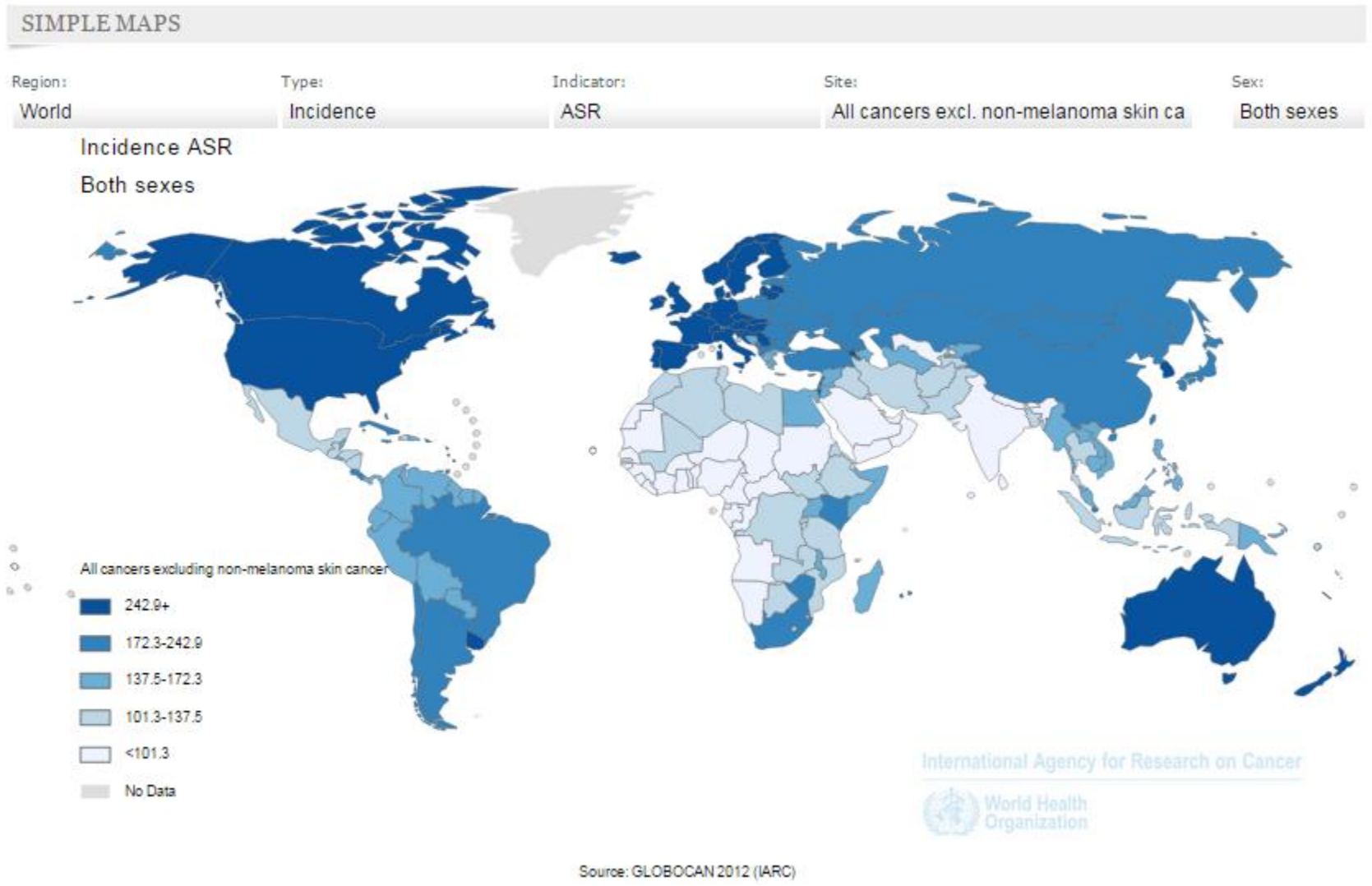
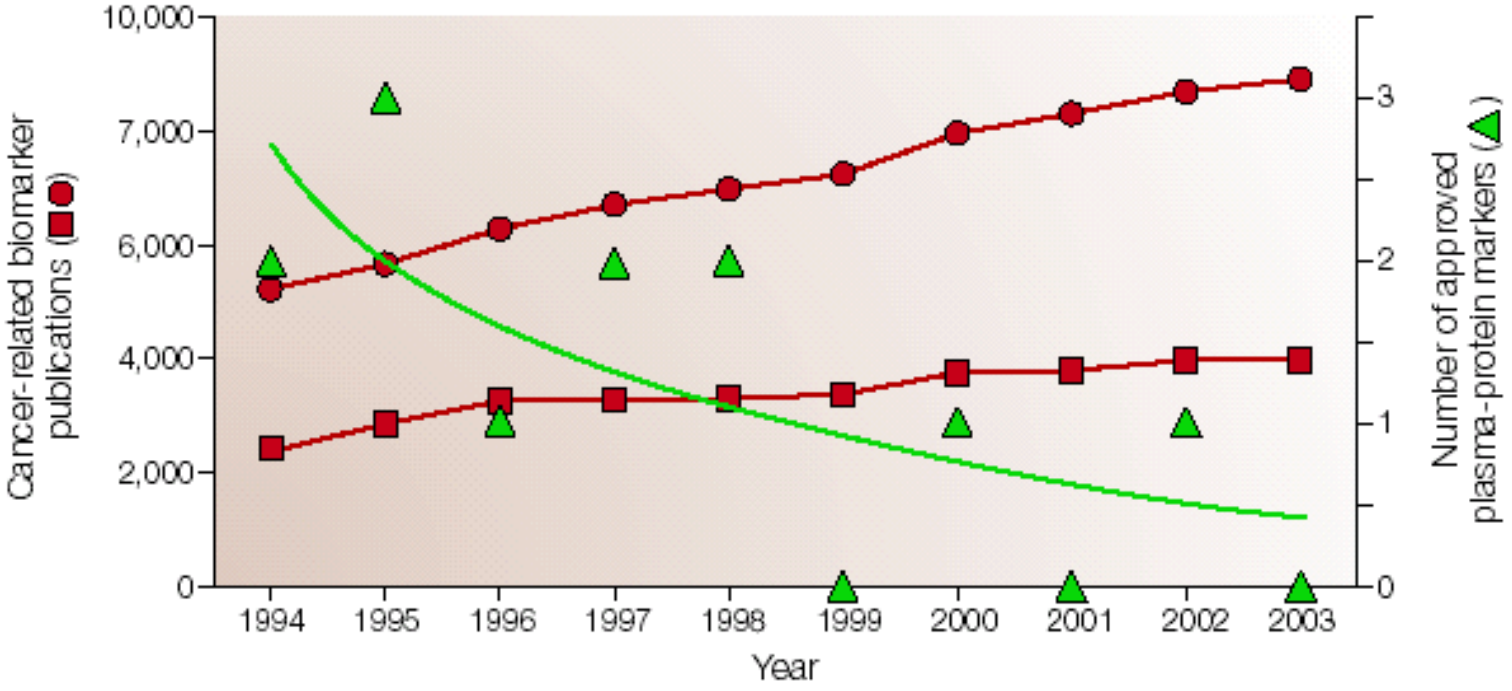


Tumor biomarkers – FDA approved



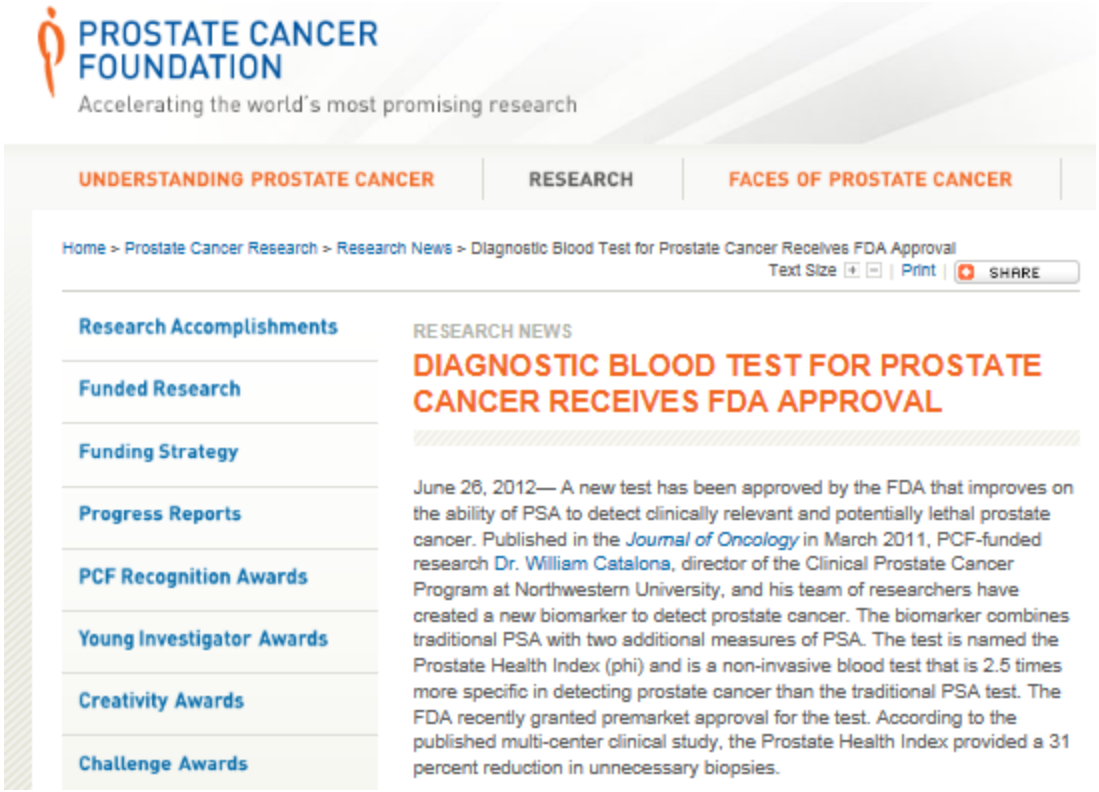
Ludwig and Weinstein, Nature Rev Cancer, Nov 2005, pg 845-856

FDA approved tumor biomarkers

Table 1 | **US Food and Drug Administration-approved cancer biomarkers**

Biomarker	Type	Source	Cancer type	Clinical use
α-Fetoprotein	Glycoprotein	Serum	Nonseminomatous testicular	Staging
Human chorionic gonadotropin-β	Glycoprotein	Serum	Testicular	Staging
CA19-9	Carbohydrate	Serum	Pancreatic	Monitoring
CA125	Glycoprotein	Serum	Ovarian	Monitoring
Pap smear	Cervical smear	Cervix	Cervical	Screening
CEA	Protein	Serum	Colon	Monitoring
Epidermal growth factor receptor	Protein	Colon	Colon	Selection of therapy
KIT	Protein (IHC)	Gastrointestinal tumour	GIST	Diagnosis and selection of therapy
Thyroglobulin	Protein	Serum	Thyroid	Monitoring
PSA (total)	Protein	Serum	Prostate	Screening and monitoring
PSA (complex)	Protein	Serum	Prostate	Screening and monitoring
PSA (free PSA %)	Protein	Serum	Prostate	Benign prostatic hyperplasia versus cancer diagnosis
CA15-3	Glycoprotein	Serum	Breast	Monitoring
CA27-29	Glycoprotein	Serum	Breast	Monitoring
Cytokeratins	Protein (IHC)	Breast tumour	Breast	Prognosis
Oestrogen receptor and progesterone receptor	Protein (IHC)	Breast tumour	Breast	Selection for hormonal therapy
HER2/NEU	Protein (IHC)	Breast tumour	Breast	Prognosis and selection of therapy
HER2/NEU	Protein	Serum	Breast	Monitoring
HER2/NEU	DNA (FISH)	Breast tumour	Breast	Prognosis and selection of therapy
Chromosomes 3, 7, 9 and 17	DNA (FISH)	Urine	Bladder	Screening and monitoring
NMP22	Protein	Urine	Bladder	Screening and monitoring
Fibrin/FDP	Protein	Urine	Bladder	Monitoring
BTA	Protein	Urine	Bladder	Monitoring
High molecular weight CEA and mucin	Protein (Immunofluorescence)	Urine	Bladder	Monitoring

Prostate cancer: novel PSA assay, FDA cleared 2012



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Home > Prostate Cancer Research > Research News > Diagnostic Blood Test for Prostate Cancer Receives FDA Approval

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- Progress Reports
- PCF Recognition Awards
- Young Investigator Awards
- Creativity Awards
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RESEARCH NEWS

DIAGNOSTIC BLOOD TEST FOR PROSTATE CANCER RECEIVES FDA APPROVAL

June 26, 2012— A new test has been approved by the FDA that improves on the ability of PSA to detect clinically relevant and potentially lethal prostate cancer. Published in the *Journal of Oncology* in March 2011, PCF-funded research Dr. William Catalona, director of the Clinical Prostate Cancer Program at Northwestern University, and his team of researchers have created a new biomarker to detect prostate cancer. The biomarker combines traditional PSA with two additional measures of PSA. The test is named the Prostate Health Index (phi) and is a non-invasive blood test that is 2.5 times more specific in detecting prostate cancer than the traditional PSA test. The FDA recently granted premarket approval for the test. According to the published multi-center clinical study, the Prostate Health Index provided a 31 percent reduction in unnecessary biopsies.

Prostate cancer: novel PAC3 assay, FDA cleared 2012

GEN-PROBE **Gen-Probe**
www.gen-probe.com

Gen-Probe Incorporated (Gen-Probe) is engaged in the development, manufacture and marketing of nucleic acid tests (NATs) used to diagnose human diseases and screening donated human blood. It also markets a range of products to detect infectious microorganisms, including those causing sexually transmitted diseases (STDs), tuberculosis, strep throat, and other infections. The Company categorizes its products into clinical diagnostic products and blood screening products.

Full Gen-Probe profile here

FDA approves Gen-Probe's prostate cancer diagnostic test

15th Feb 2012, 12:40 pm by **Brad Lemaire**

Gen-Probe (NASDAQ:GPRO) said Wednesday U.S. health regulators approved its diagnostic test Progensa PAC3 which is used to verify the need for repeat biopsies in men at risk of getting prostate cancer.

The company, founded in 1983 and with about 1,363 employees, makes molecular diagnostic products and services to diagnose diseases and screen donated blood.

Gen-Probe acquired worldwide diagnostics rights to the biomarker Prostate Cancer Antigen 3 (PAC3) gene from DiagnoCure (TSE:CUR) in 2003.

The FDA approval was backed by a clinical study launched in August 2009 and finished in May 2010. The study enrolled 495 men at 14 clinical sites. Gen-Probe submitted their premarket approval application to the FDA in August 2010.

In the clinical study, the PAC3 assay had a negative predictive value of 90 percent, meaning a negative PCA3 assay result predicted a negative prostate biopsy 90 percent of the time.

The PCA3 gene test – carried out through urine samples taken after a digital rectal examination – is highly over-expressed in more than 90 percent of prostate cancers. The test is the first urine-based molecular diagnostic test for prostate cancer.

Prostate cancer: Circulating Tumor Cells

FDA Clears Cellsearch™ Circulating Tumor Cell Test For Monitoring Metastatic Prostate Cancer Patients

Main Category: Prostate / Prostate Cancer
Also Included In: Regulatory Affairs / Drug Approvals; Medical Devices / Diagnostics
Article Date: 29 Feb 2008 - 0:00 PDT

FDA cleared novel tumor biomarkers

Simply Google:
FDA approved cancer diagnostic tests!!!!!!

But how are novel tumor biomarkers

Identified in our new genomics era???

Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

Review

Douglas Hanahan* and Robert A. Weinberg†
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evolve progressively from normalcy via a series of premalignant states into invasive cancers (Foulds, 1954).

These observations have been rendered more concrete by a large body of work indicating that the genomes of tumor cells are invariably altered at multiple sites, having suffered disruption through lesions as subtle as point mutations and as obvious as changes in chromosome complement (e.g., Kinzler and Vogelstein, 1996). Transformation of cultured cells is itself a

Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
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[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
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DOI 10.1016/j.cell.2011.02.013

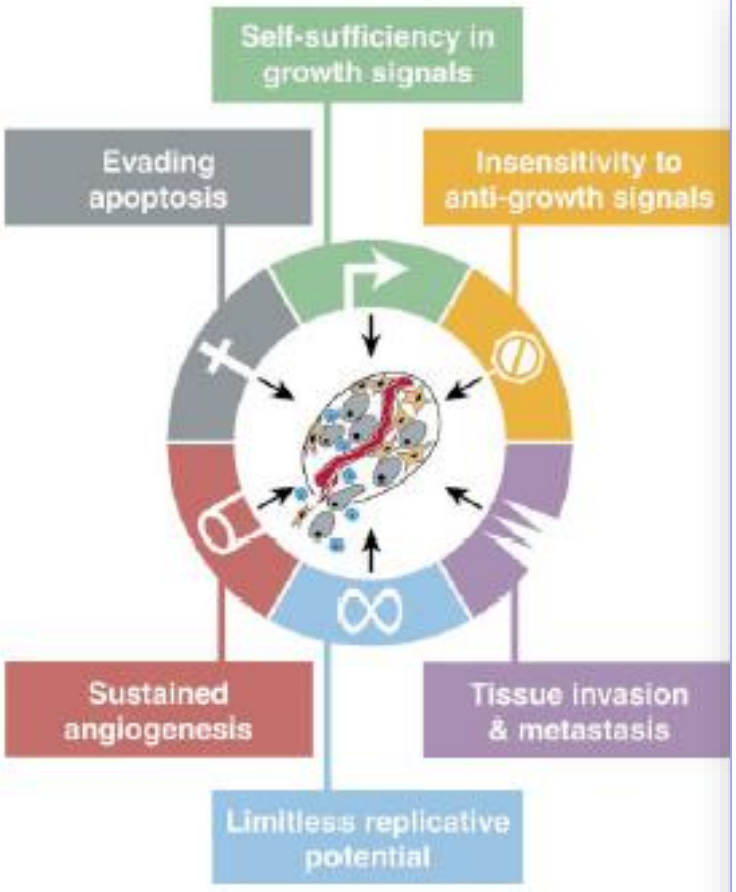
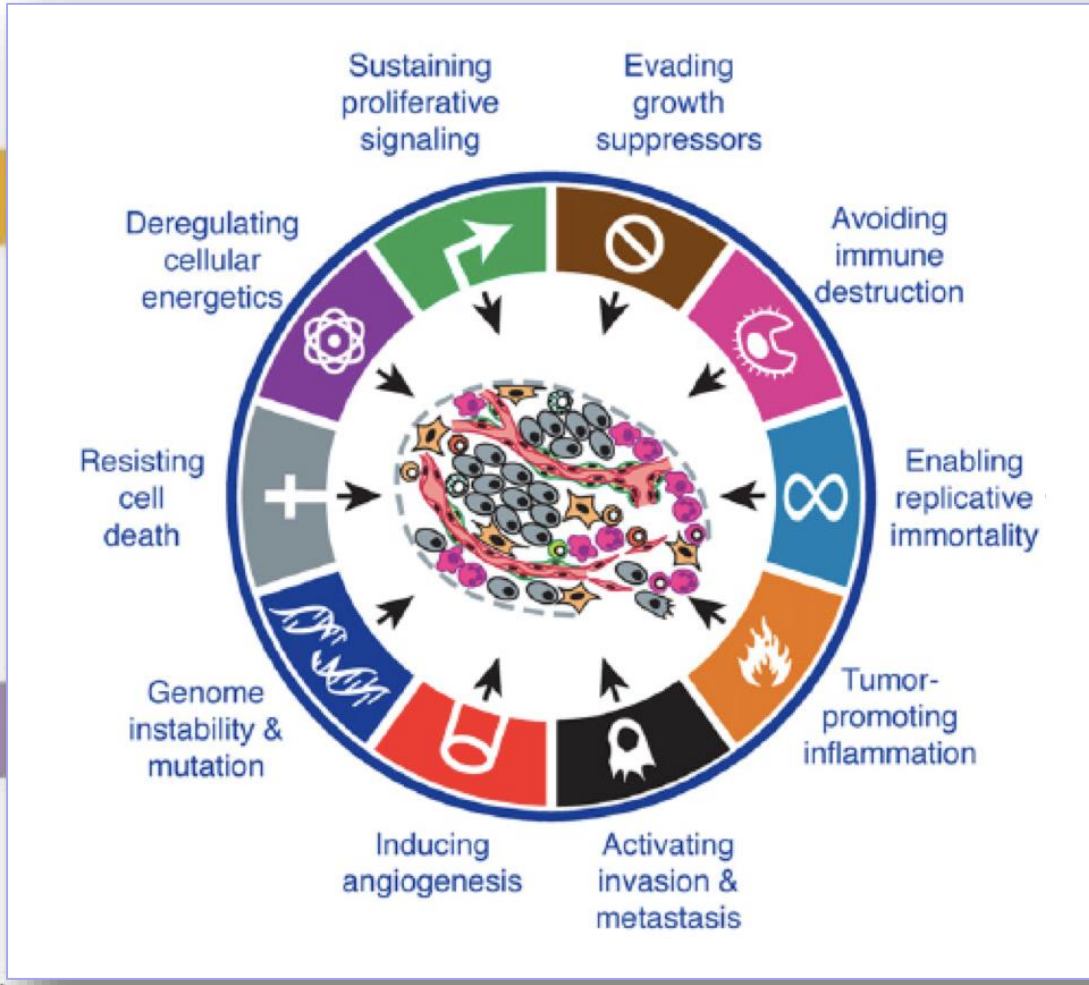


Figure 1. Acquired Capabilities of Cancer

We suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies.



The Hallmarks of Cancer,
D. Hanahan, Bob Weinberg,
Cell, 2000

The Hallmarks of Cancer,
D. Hanahan, Bob Weinberg,
Cell, 2011

The Hallmarks of Cancer, 10 years after!!!

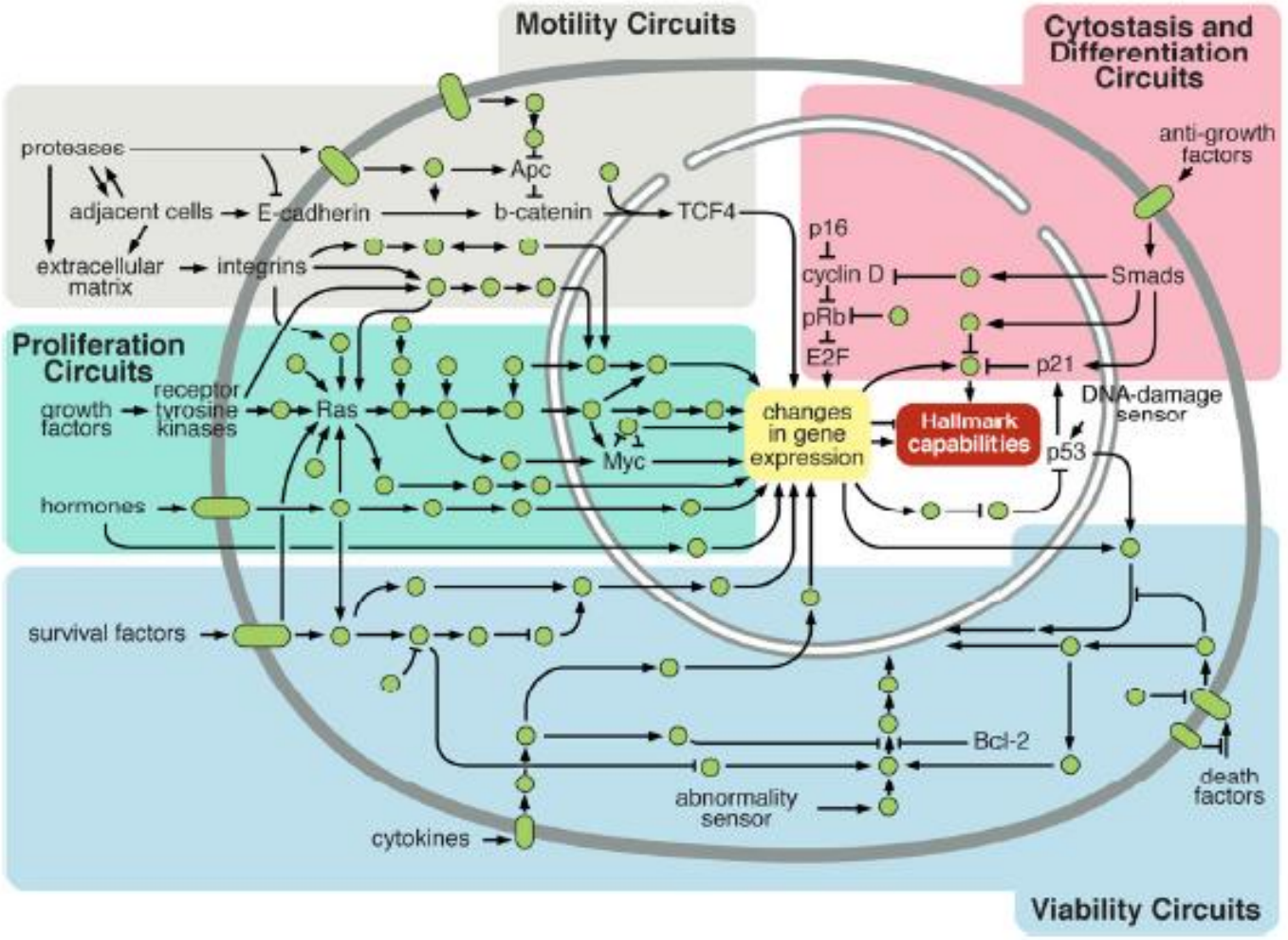


Figure 2. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell

An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate subcircuits, depicted here in differently colored fields, are specialized to orchestrate the various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such subcircuits. In addition, because each cancer cell is exposed to a complex mixture of signals from its microenvironment, each of these subcircuits is connected with signals originating from other cells in the tumor microenvironment, as outlined in Figure 5.

The Hallmarks of Cancer, 10 years after!!! What is new???

Cell

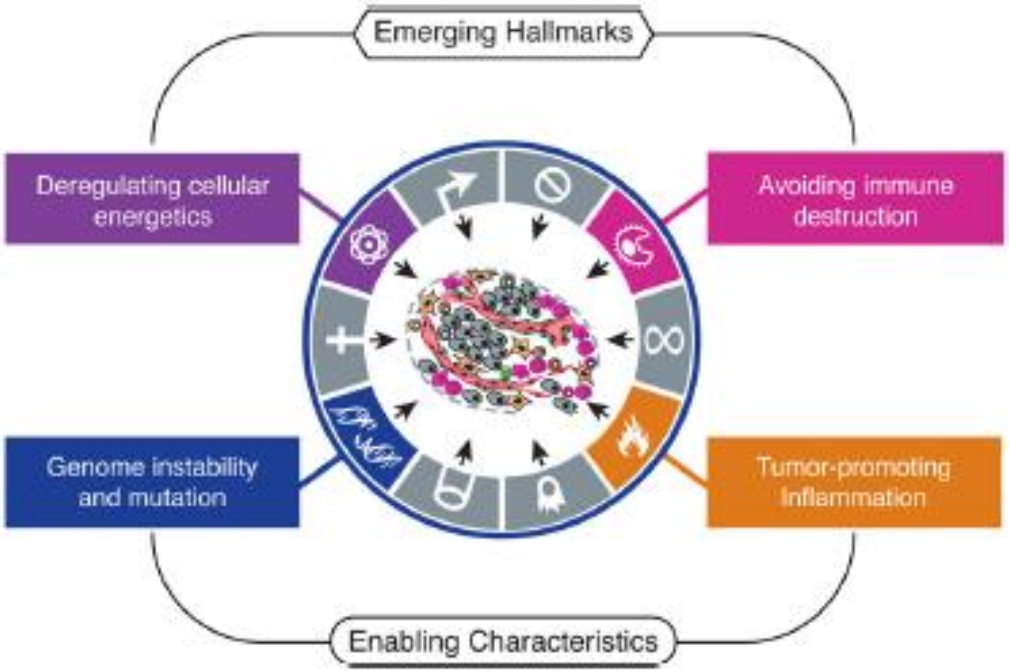
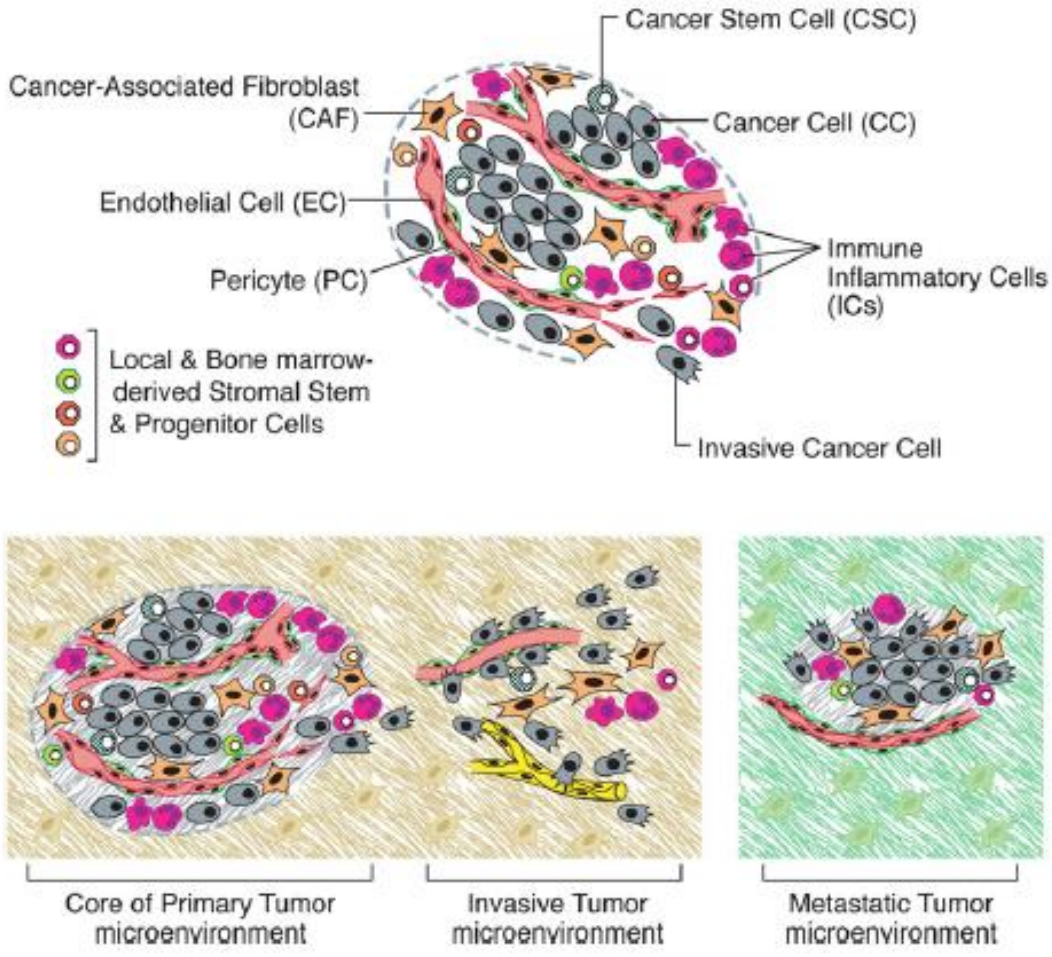


Figure 3. Emerging Hallmarks and Enabling Characteristics

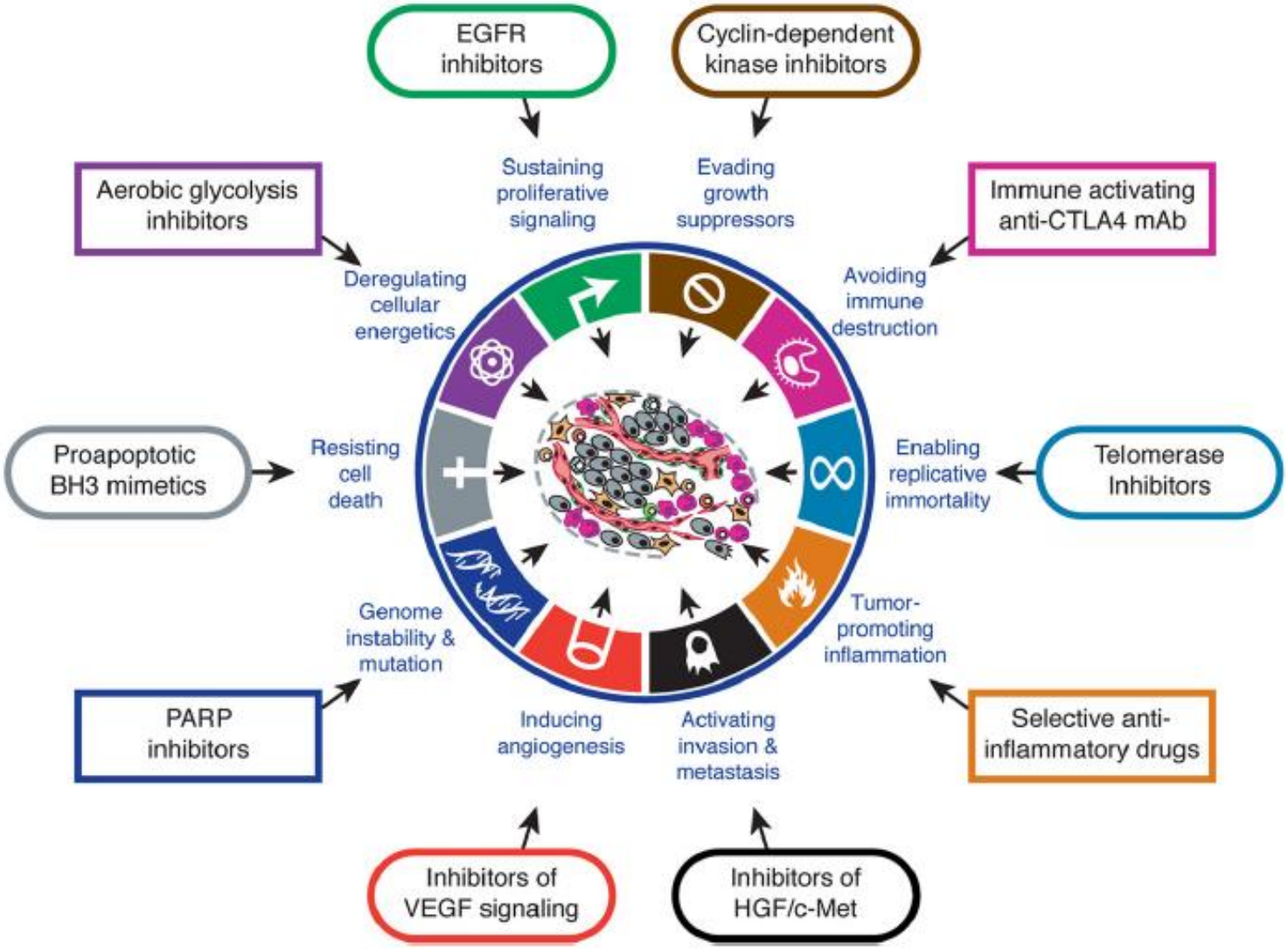
An increasing body of research suggests that two additional hallmarks of cancer are involved in the pathogenesis of some and perhaps all cancers. One involves the capability to modify, or reprogram, cellular metabolism in order to most effectively support neoplastic proliferation. The second allows cancer cells to evade immunological destruction, in particular by T and B lymphocytes, macrophages, and natural killer cells. Because neither capability is yet generalized and fully validated, they are labeled as emerging hallmarks. Additionally, two consequential characteristics of neoplasia facilitate acquisition of both core and emerging hallmarks. Genomic instability and thus mutability endow cancer cells with genetic alterations that drive tumor progression. Inflammation by innate immune cells designed to fight infections and heal wounds can instead result in their inadvertent support of multiple hallmark capabilities, thereby manifesting the now widely appreciated tumor-promoting consequences of inflammatory responses.

The Hallmarks of Cancer, 10 years after!!! What is new???

The emerging role of the cells of the tumor microenviroment



Therapeutic targeting of the hallmarks of Cancer



Molecular tumor biomarkers

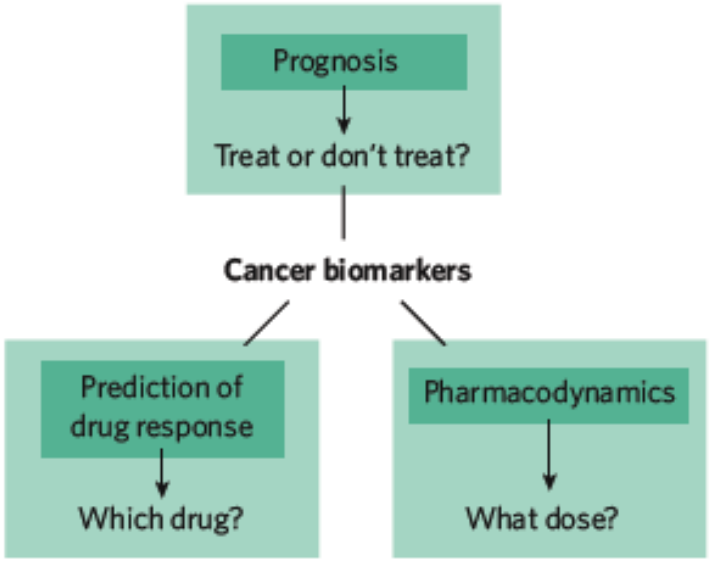


Figure 1 | Types of biomarker. Cancer biomarkers can be used for prognosis: to predict the natural course of a tumour, indicating whether the outcome for the patient is likely to be good or poor (prognosis). They can also help doctors to decide which patients are likely to respond to a given drug (prediction) and at what dose it might be most effective (pharmacodynamics).

Clinical Chemistry 59:1
147–157 (2013)

The Long Journey of Cancer Biomarkers from the Bench to the Clinic

Maria P. Pavlou,[1,2] Eleftherios P. Diamandis,[1,2,3] and Ivan M. Blasutig[2,3*]

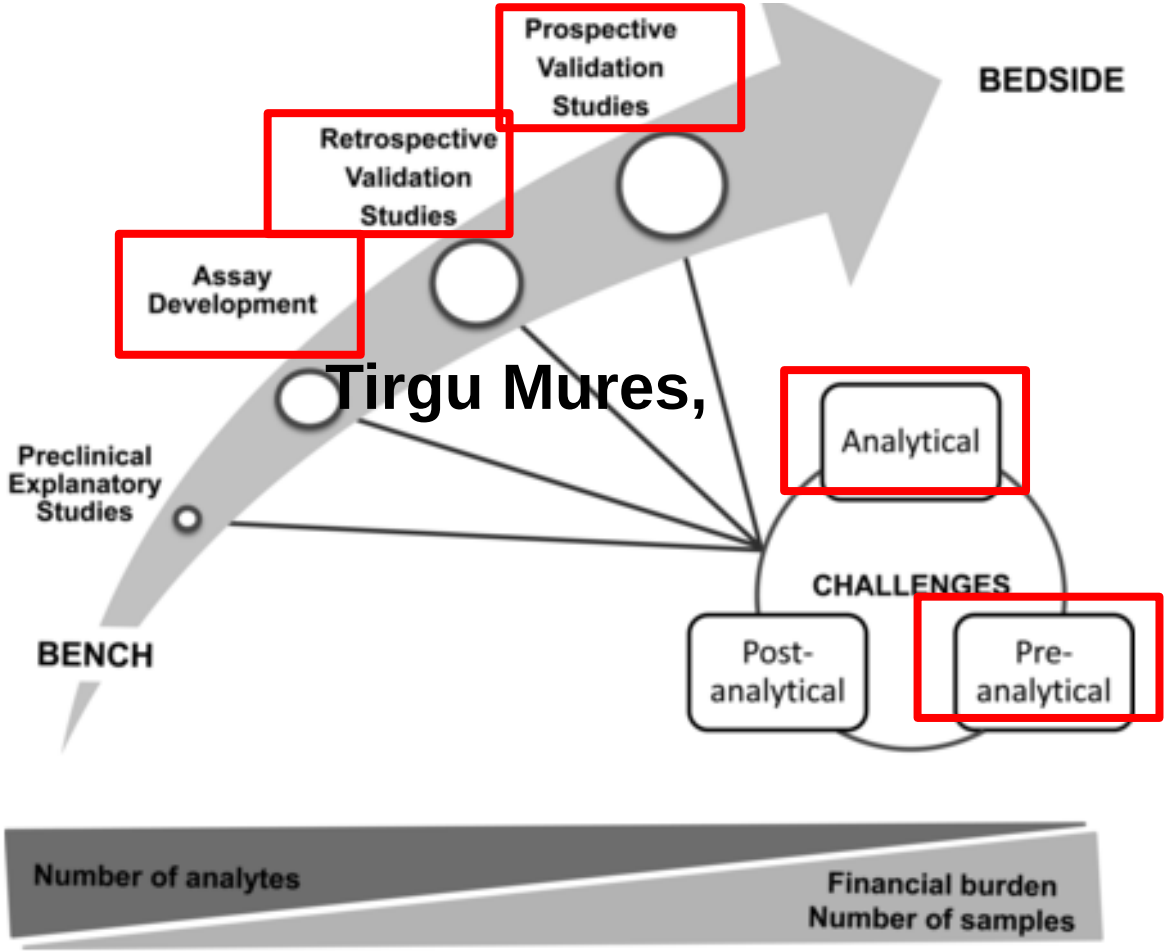


Table 1. FDA-cleared protein cancer biomarkers.

Biomarker	Official gene name[a]	Clinical use	Cancer type	Source type
α-fetoprotein (AFP)	*AFP*	Staging	Nonseminomatous testicular	Serum
Human chorionic gonadotropin (hGC)	*CGB*	Staging	Testicular	Serum
Carbohydrate antigen 19-9 (CA19-9)		Monitoring	Pancreatic	Serum
Carbohydrate antigen 125 (CA125)	*MUC16*	Monitoring	Ovarian	Serum
Carcinoembryonic antigen (CEA)	*PSG2*	Monitoring	Colorectal	Tissue
Epidermal growth factor receptor (EGFR)	*EGFR*	Prediction	Colorectal	Tissue
v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT)	*KIT*	Prediction	Gastrointestinal	Tissue
Thyroglobulin	*TG*	Monitoring	Thyroid	Serum
Prostate specific antigen (PSA)	*KLK3*	Screening and monitoring	Prostate	Serum
Carbohydrate antigen 15.3 (CA 15.3)	*MUC1*	Monitoring	Breast	Serum
Carbohydrate antigen 27.29 (CA27.29)	*MUC1*	Monitoring	Breast	Serum
Estrogen receptor (ER)	*ESR1*	Prognosis and prediction	Breast	Tissue
Progesterone receptor (PR)	*PGR*	Prognosis and prediction	Breast	Tissue
v-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (HER2-neu)	*ERBB2*	Prognosis and prediction	Breast	Tissue
Nuclear matrix protein 22 (NMP-22)		Screening and monitoring	Bladder	Urine
Fibrin/fibrinogen degradation products (FDP)		Monitoring	Bladder	Urine
Bladder tumor antigen (BTA)		Monitoring	Bladder	Urine
High molecular CEA and mucin		Monitoring	Bladder	Urine

[a] Human genes: *AFP*, alpha-fetoprotein; *CGB*, chorionic gonadotropin, beta polypeptide; *MUC16*, mucin 16, cell surface associated; *PSG2*, pregnancy specific beta-1-glycoprotein 2; *EGFR*, epidermal growth factor receptor; *KIT*, Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; *TG*, thyroglobulin; *KLK3*, kallikrein-related peptidase 3; *MUC1*, mucin 1, cell surface associated; *ESR1*, estrogen receptor 1; *PGR*, progesterone receptor; *ERBB2*, v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian).

Table 2. Reasons for biomarker failures.

Reason	Solutions	Frequency	Examples
Fraud		Low	Potti et al. *(79)*
Preanalytical factors • Patient selection bias • Sample collection, handling and storage	• Clearly define the clinical question to be addressed • Use samples collected under detailed SOPs • Use well annotated samples	High	Xu et al. *(80)* Villanueva et al. *(81)*
Analytical factors • Methodological artefacts • Poor analytical method	• Validate the analytical method • Use appropriate quality controls with all analyses	High	Leman et al. *(82)*
Statistics/Bioinformatics • Inappropriate statistical analysis • Data overfitting • Small sample size • Multiple hypothesis testing • Overlapping training and validation patient cohorts	• Seek and follow the expertise of an experienced biostatistician	High	Mor et al. *(83)* Petricoin et al. *(84)*
Clinical validation • Nonreproducible validation • Poor study design • No adequate clinical performance	• Clearly define the clinical question to be addressed prior to undertaking any study • Collaborate with an experienced biostatistician • Use appropriate specimens to avoid bias • Use validated analytical methods	Medium	Esrig et al. *(85)* Malats et al. *(86)* Kim et al. *(87)*
Commercialization • Intellectual property	• Apply for patents to obtain intellectual property rights as early as possible	Low	
FDA approval	• Seek FDA guidance early in development phases	Low	

Clinical Chemistry 61:6
809–820 (2015)

Review

Validation of New Cancer Biomarkers: A Position Statement from the European Group on Tumor Markers

Michael J. Duffy,[1*] Catharine M. Sturgeon,[2] György Sölétormos,[3] Vivian Barak,[4] Rafael Molina,[5] Daniel F. Hayes,[6] Eleftherios P. Diamandis,[7] and Patrick M.M. Bossuyt[8]

Table 1. Parameters used in the analytical validation of biomarkers measured by quantitative assays.[a]

Parameter	Definition
Accuracy[b]	How close a result is to the true result.
Precision/imprecision	Closeness of agreement between a series of measurement for the same sample established under specific conditions. Depends on repeatability and reproducibility of assay.
Repeatability	Describes measurements made under the same conditions.
Reproducibility	Describes measurements done under different conditions.
Analytical specificity	Ability of an assay to distinguish the analyte of interest from structurally similar molecules.
Analytical sensitivity	Ability of an assay to detect low quantities of an analyte.
Limit of detection[c]	Lowest amount of analyte that can be reliably distinguished from zero.
Interference (cross-reaction)[d]	Effect of a substance in a sample that alters the correct value of a result.
Carryover[c]	Occurs when a portion of a sample or reaction reagent are unintentionally transferred from one assay reaction into another.
Linearity	The ability of an assay to give concentrations that are directly proportional to the levels of the analyte following sample dilution.
Robustness	Precision of an assay following changes in assay conditions, e.g., variation in ambient temperature, storage condition of reagents.

[a] Adapted from Jennings et al. *(23)*.

[b] For qualitative assays, accuracy has been defined as the amount agreement between the information in the assay undergoing evaluation and that obtained from the best available method for determining the presence or absence of that analyte *(23)*.

[c] Particularly relevant for quantitative assays carried on blood.

[d] May be due to chemically related molecules or heterophilic or human anti-mouse antibodies.

Table 2. Parameters used in evaluating clinical validity of a biomarker.

Parameter	Definition
Clinical sensitivity	True positive rate, how good is the test in detecting individuals who have the condition of interest.
Clinical specificity	True negative rate, how good is the test in correctly excluding individuals without the condition of interest.
PPV[a,b]	Proportion of positive tests that are correct.
NPV[b]	Proportion of negative tests that are correct.
Positive likelihood ratio	How much more likely is a positive test to be found in an individual with the relevant condition than in a person without it.
Negative likelihood ratio	How much more likely is a negative test to be found in an individual without the relevant condition than in a person with it.
AUC	Area under ROC curve. AUC is used to compare different tests, i.e., an AUC value close to 1 indicates good discrimination, whereas an AUC of 0.5 provides no useful diagnostic information.
ROC analysis	A graphical approach for showing accuracy across the entire range of biomarker concentrations.
Hazard ratio	Chance of an event (e.g., disease recurrence, death) occurring in the treatment arm divided by the chance of the event occurring in the control arm, or vice versa.
Relative risk	Ratio of the probability of an event (e.g., disease recurrence, death) occurring in treated group to the probability of the event occurring in the control group.

[a] PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve.
[b] With PPV and NPV, it is necessary to define the population to which it applies.

Table 3. Cancer biomarkers that have undergone/or are undergoing validation in level I evidence (LOE I) studies.

Biomarker	Clinical use	Type of validation
FOBT [a]	Screening for colorectal cancer	PRCT
PSA	Screening for prostate cancer[b]	PRCT
CA 125	Screening for ovarian cancer[b]	PRCT
uPA/PAI-1	Determining prognosis in breast cancer	PRCT, pooled analysis
Estrogen receptor	Predicting response to hormone therapy in breast cancer	PRCT, metaanalysis
HER2	Predicting response to anti-HER2 therapy in breast cancer	PRCT
Oncotype DX[b]	Determining prognosis in ER-positive lymph node–negative breast cancer	PRT
MammaPrint[b]	Determining prognosis in lymph node–negative breast cancer	PRT
BRAF mutation	Predicting response to anti-BRAF therapy in melanoma	PRCT
KRAS mutations	Predicting response to anti-EGFR antibodies in colorectal cancer	PRT
EGFR mutations	Predicting response to anti-EGFR kinase inhibitors in non–small cell lung cancer	PRT
CEA	Postoperative surveillance after curative surgery in colorectal cancer	PRT, metaanalyses

[a] FOBT, fecal occult blood testing; PRCT, prospective randomized clinical trial; PRT, prospective retrospective trial; ER, estrogen receptor; CEA, carcinoembryonic antigen.

[b] PRCT in progress. The fact that a biomarker has undergone validation in a LOE I evidence study does not necessarily qualify that biomarker for clinical use. Thus, CA 125 is not currently recommended for screening asymptomatic women for ovarian cancer although it was evaluated in a prospective randomized trial (which showed that screening with CA 125 and ultrasound failed to reduce mortality from ovarian cancer).

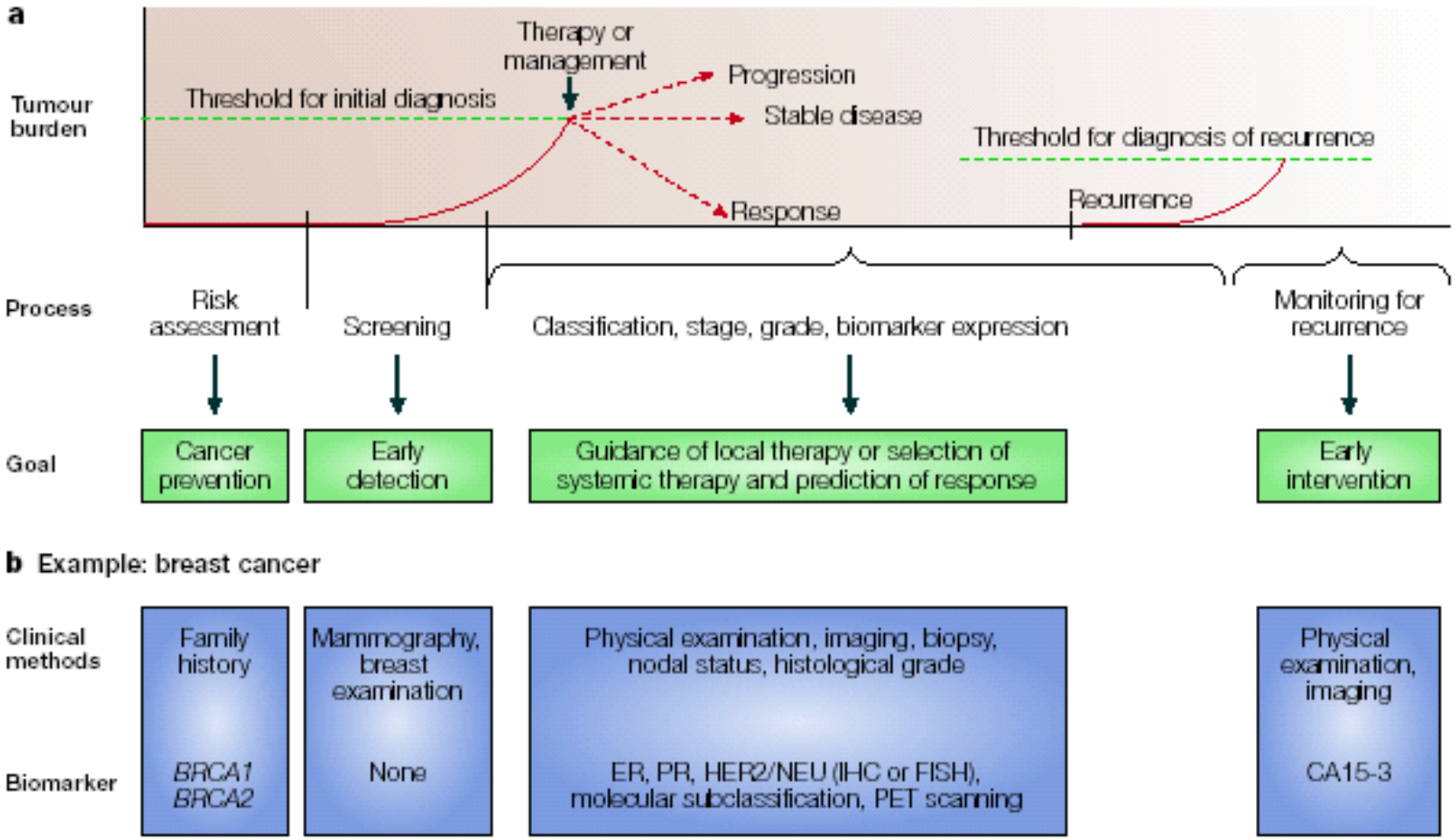
Table 4. Guidelines for reporting biomarker studies.

Application	Aims	Guideline	Reference
Biospecimen handling and processing	How to collect, process and store human tissue in a standardized manner	BRISQ[a]	Moore et al. *(67)*
Diagnostic accuracy	To improve the accuracy and completeness of reporting of studies of diagnostic accuracy and to allow assessment of the potential for bias as well as evaluate its generalizability	STARD	Bossuyt et al. *(68, 69)*
Prognostic biomarkers[b]	Recommendations for reporting biomarker prognostic studies	REMARK	McShane et al. *(70)*; Altman et al. *(71)*
Monitoring biomarkers	Recommendations for performing biomarker monitoring studies	MONITOR	Sölétormos et al. *(72)*
Biomarkers in clinical trials	Describes a risk-management approach for use of biomarkers in clinical trials		Hall et al. *(73)*
Omics in clinical trials	To establish the readiness of omics-based assays for use in clinical trials		McShane et al. *(74)*; McShane et al. *(75)*
Immunohistochemistry and in situ hybridization studies	Reporting immunohistochemistry and in situ hybridization	MISFISHIE	Deutsch et al. *(76)*
Preparing systematic reviews	Evaluating quality of individual studies	QUADAS	Whiting et al. *(52)*; Moher et al. *(77)*

[a] BRISQ, Biospecimen Reporting for Improved Study Quality; STARD, STAndards for the Reporting of Diagnostic accuracy studies; REMARK, REporting recommendations for tumour MARKer prognostic studies; MISFISHIE, Minimum Information Specification For In Situ Hybridization and Immunohistochemistry Experiments; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

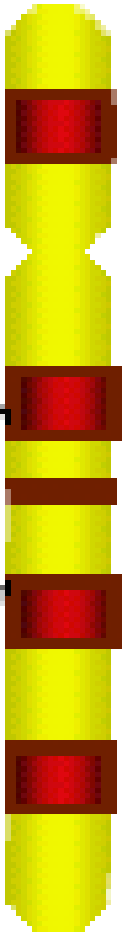
[b] Although primarily designed for prognostic biomarkers, these guidelines may also be used for predictive biomarkers.

Clinical applications of molecular tumor biomarkers: breast cancer



Ludwig and Weinstein, Nature Rev Cancer, Nov 2005, pg 845-856

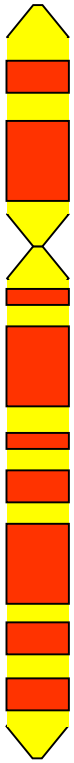
BRCA1



- *Discovered in 1990 (Hall J M, et al)*
- *Cloned and sequenced in 1994 (Miki, et al)*

17q21-q17 (Narod SA, et al 1991)

BRCA2

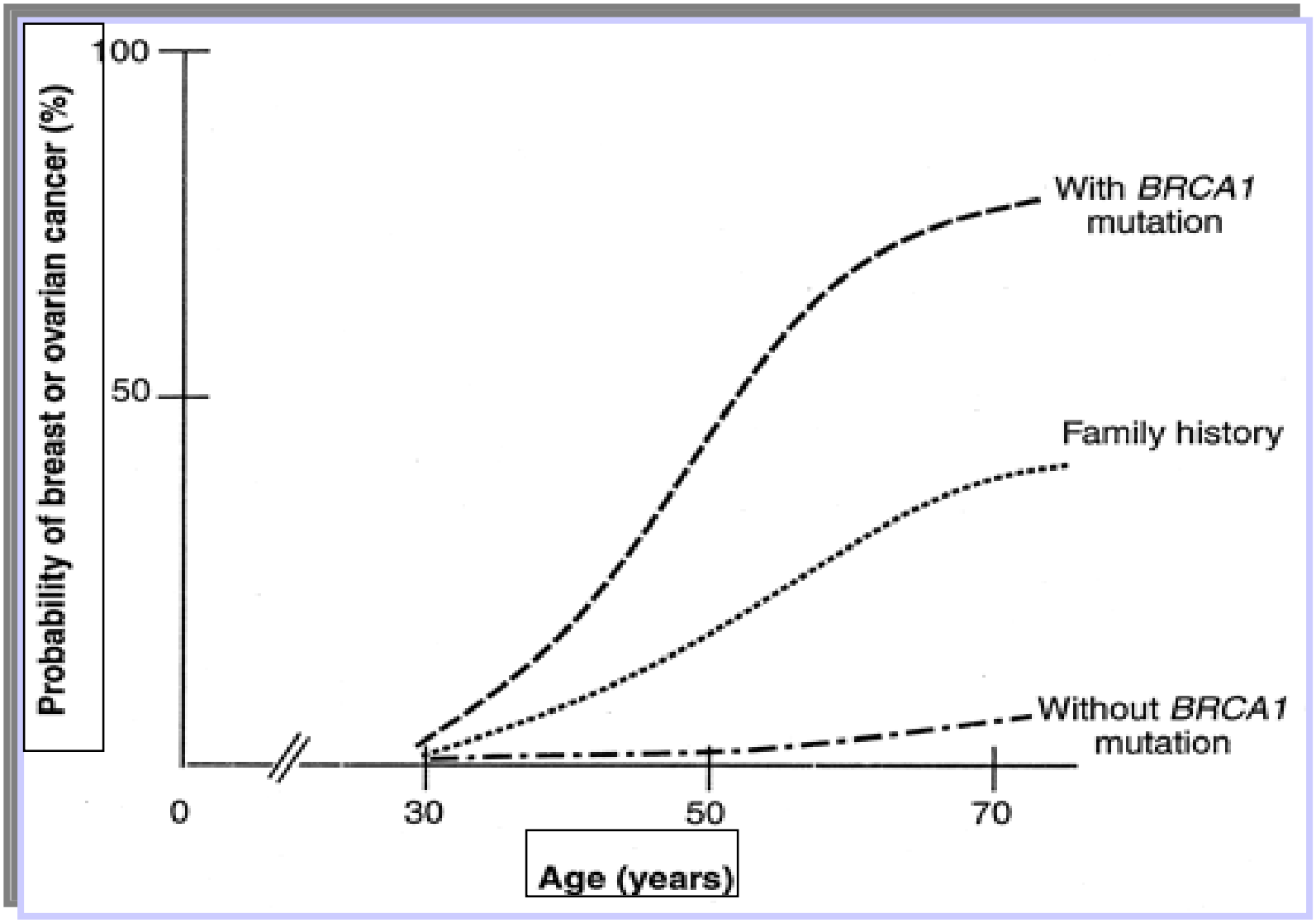


- *Discovered in 1995 (Wooster R, et al)*

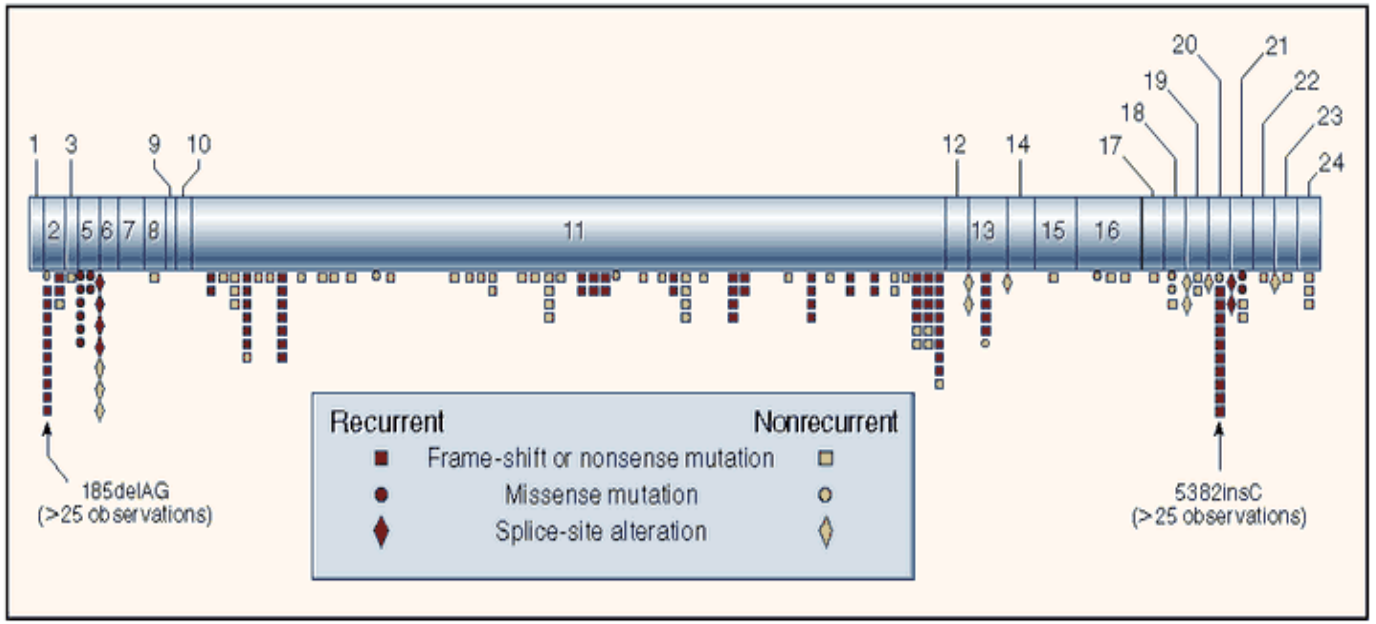
Cloned and sequenced in 1996 (Wooster R, et al)

13q12-q13 (Wooster R, et al)

BRCA1 mutations
breast and ovarian cancer



BRCA1 mutations
breast and ovarian cancer



most recent Case of „personalized Medicine“

A) regular Diagnosis for Carriers of a hereditary Breast Cancer Risk
B) stratified Therapy on a Knowledge Basis

Breast Cancer RESEARCH

RESEARCH ARTICLE Open Access

The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services

Table 1 National Health Service Regional Genetics Centres and family history clinics, their potential catchment area and referrals in 2012/2013

Centre	Type	Population coverage	Number referred 2012	Number referred 2013
Guys Hospital, SW Thames, London	Regional Genetics Centre	4.9 million	1,762	2,727
Birmingham	Regional Genetics Centre	5.5 million	1,993	3,421
Southampton	Regional Genetics Centre	Approximately 3 million	735	1,032
Leicester	Regional Genetics Centre	Approximately 2 million	331	443
Aberdeen, Scotland	Regional Genetics Centre	Approximately 1 million	387	742
Bristol	Regional Genetics Centre	2.46 million	919	1,462
All Wales Genetics Service	National Genetics Centre	3.1 million	1,462	2,727
Nottingham	Regional Genetics Centre	2.2 million	1,015	1,252
Northwick Park, London	Regional Genetics Centre	3.6 million	760	1,902
Genesis Prevention Centre, Manchester	Family history clinic	4.5 million (for high risk)	367	678
Royal Marsden, London	Family history clinic	<1 million	255	320
Nottingham	Family history clinic	~1 million	554	739
Bath	Family history clinic	<1 million	166	278
St Bartholomew's, London	Family history clinic	<1 million	538	627
Royal Derby Hospital	Family history clinic	<1 million	285	511
United Lincolnshire Hospitals NHS Trust	Family history clinic	<0.5 million	33	53
Sandwell Hospital, Birmingham	Family history clinic	<1 million	78	48
Edinburgh, Scotland	Family history clinic	<1 million	73	160
Leighton Hospital, Crewe	Family history clinic	<1 million	121	172
Coventry	Family history clinic	<0.5 million	178	192
Altnagelvin Hospital, N Ireland	Family history clinic	<1 million	130	202

Causes of Hereditary Susceptibility to Breast Cancer

Gene	Contribution to Hereditary Breast Cancer
BRCA1	**20-40%**
BRCA2	**10-30%**
TP53	**<1%**
PTEN	**<1%**
Undiscovered genes ????	**30-70%**

BUT!!! new genes are discovered!

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 7, 2014 VOL. 371 NO. 6

Breast-Cancer Risk in Families with Mutations in *PALB2*

A.C. Antoniou, S. Casadei, T. Heikkinen, D. Barrowdale, K. Pylkäs, J. Roberts, A. Lee, D. Subramanian, K. De Leeneer, F. Fostira, E. Tomiak, S.L. Neuhausen, Z.L. Teo, S. Khan, K. Aittomäki, J.S. Moilanen, C. Turnbull, S. Seal, A. Mannermaa, A. Kallioniemi, G.J. Lindeman, S.S. Buys, I.L. Andrulis, P. Radice, C. Tondini, S. Manoukian, A.E. Toland, P. Miron, J.N. Weitzel, S.M. Domchek, B. Poppe, K.B.M. Claes, D. Yannoukakos, P. Concannon, J.L. Bernstein, P.A. James, D.F. Easton, D.E. Goldgar, J.L. Hopper, N. Rahman, P. Peterlongo, H. Nevanlinna, M.-C. King, F.J. Couch, M.C. Southey, R. Winqvist, W.D. Foulkes, and M. Tischkowitz

Causes of Hereditary Susceptibility to Breast Cancer- new genes discovered!

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Breast and Ovarian Cancer among Female *PALB2* Mutation Carriers and Noncarriers and Untested Females, According to Age at Diagnosis or Data Censoring.

Age Group	*PALB2* Mutation Carriers			Tested Noncarriers			Untested		
	Unaffected	Breast Cancer	Ovarian Cancer*	Unaffected	Breast Cancer	Ovarian Cancer*	Unaffected	Breast Cancer	Ovarian Cancer*
	number of women								
<20 yr	1	0	0	1	0	0	172	0	0
20–29 yr	4	7	0	6	0	0	170	8	0
30–39 yr	2	50	0	24	5	0	218	32	1
40–49 yr	15	84	1	22	10	3	235	81	3
50–59 yr	23	55	4	30	10	3	321	62	8
60–69 yr	14	24	1	18	6	0	364	61	6
70–79 yr	12	7	2	11	1	0	315	34	7
≥80 yr	11	2	0	13	0	0	436	3	0
Total	82	229	8	125	32	6	2231	281	25

* This category includes all diagnosed cases of ovarian cancer (including those diagnosed after a breast-cancer diagnosis).

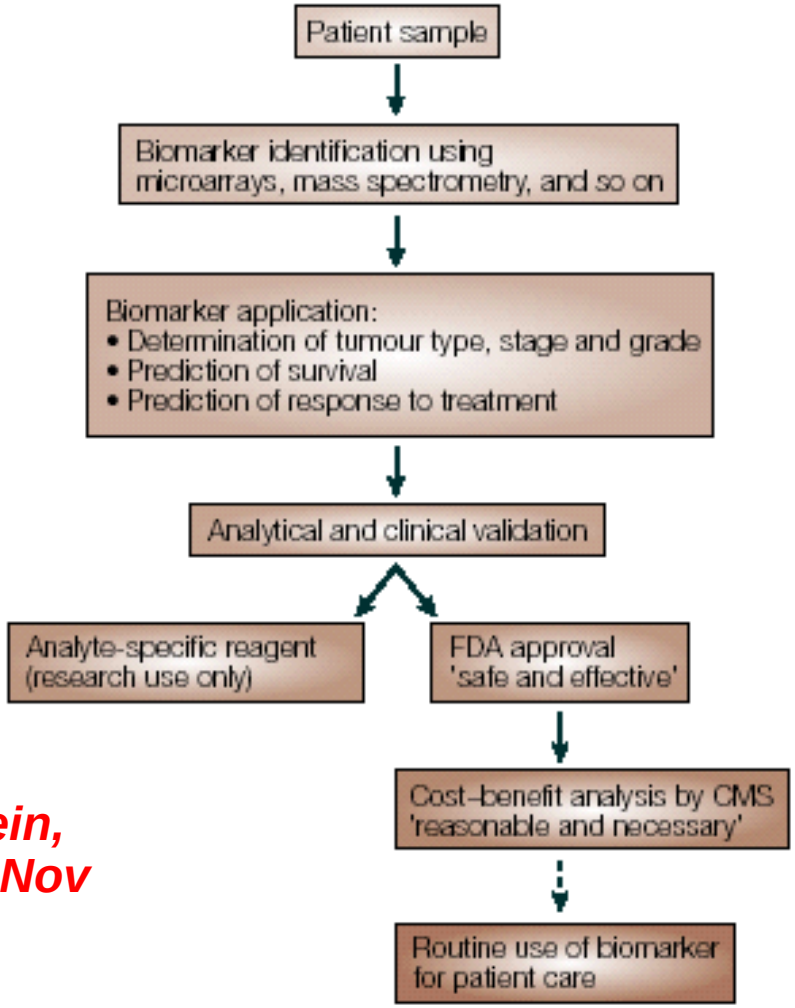
The new era in tumor biomarkers

- **From one gene to thousands**

- **DNA microarrays technology**
- **Next Generation Sequencing (NGS) technologies**
- **Molecular targeted therapy - Companion Diagnostics**

New FDA cleared tumor biomarker assays

Main steps towards tumor biomarker discoveries



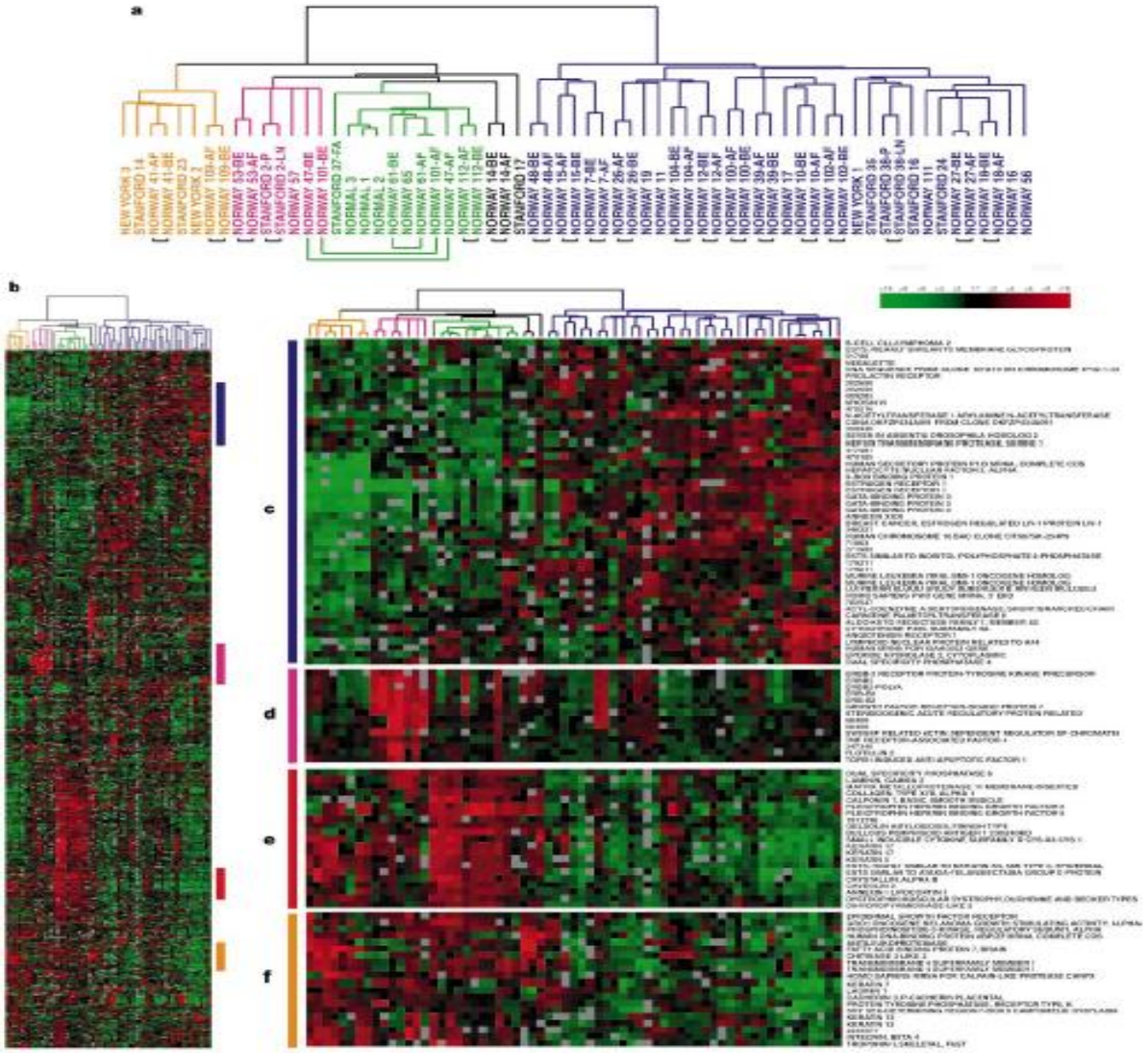
Ludwig and Weinstein, Nature Rev Cancer, Nov 2005, pg 845-856

Molecular portraits of human breast tumours

Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein***

* *Department of Genetics, Stanford University School of Medicine, Stanford, California 94305, USA*

Nature, 406, 747-752, 2000

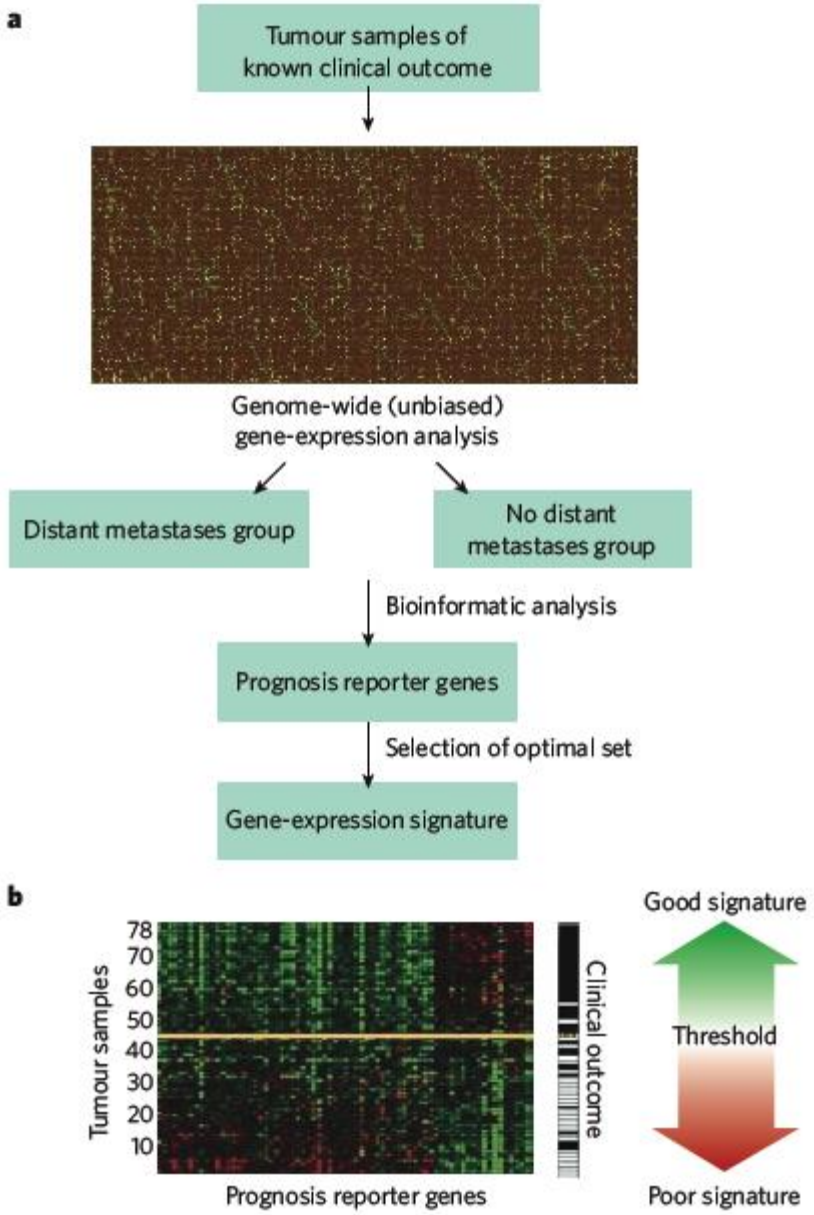


luminal/ER

Erb-B2 overexpression cluster

basal cluster

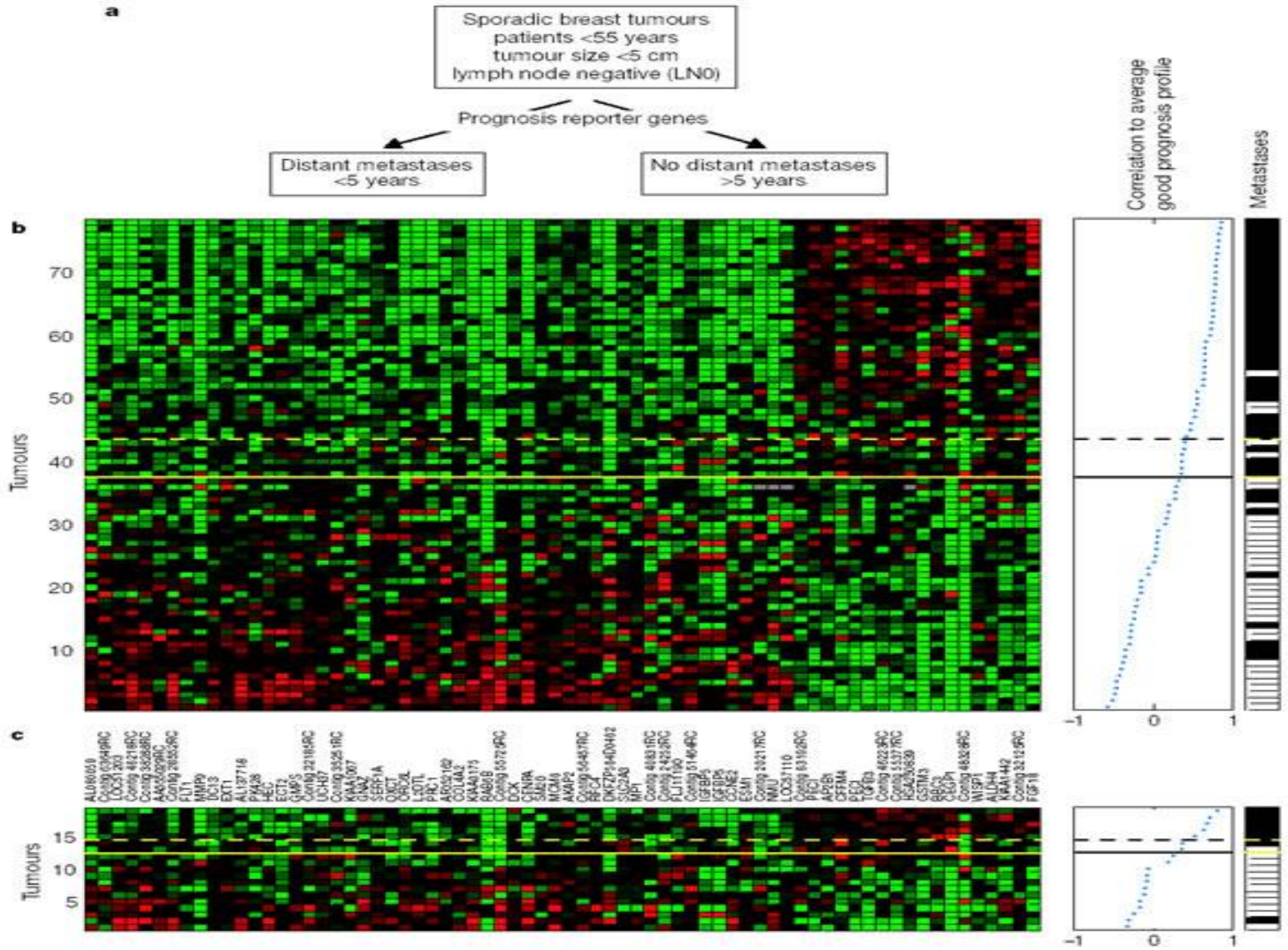
basal cluster



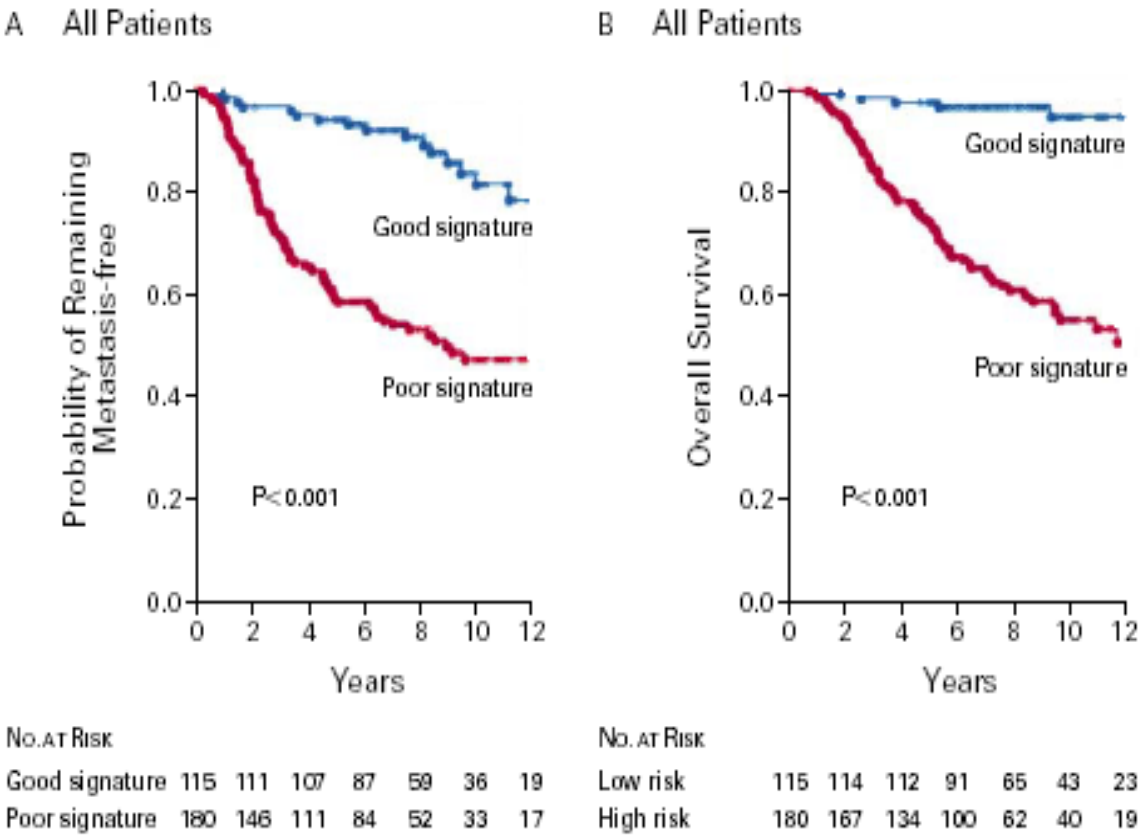
Predicting disease outcome by using complex gene expression tests

L. Vant Veer et al, NATURE, Vol 452, 3 April 2008|

Gene expression profiling predicts clinical outcome of breast cancer
L. Van't Veer et al, Nature, 415, 530, 2002.



A gene expression signature as a predictor of survival in breast cancer.
M. Van de Vliver, L. Van't Veer et al, NEJM, 347, 1999-2009, 2002.



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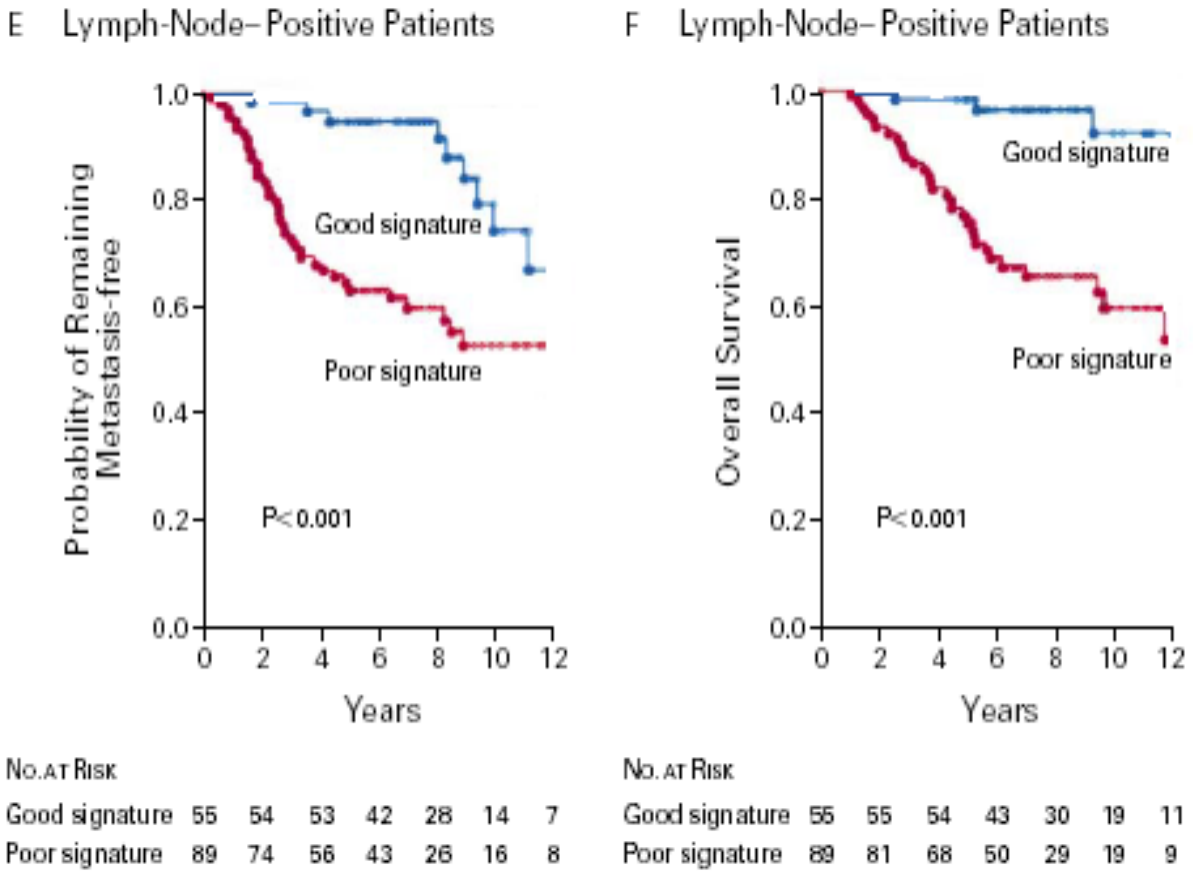

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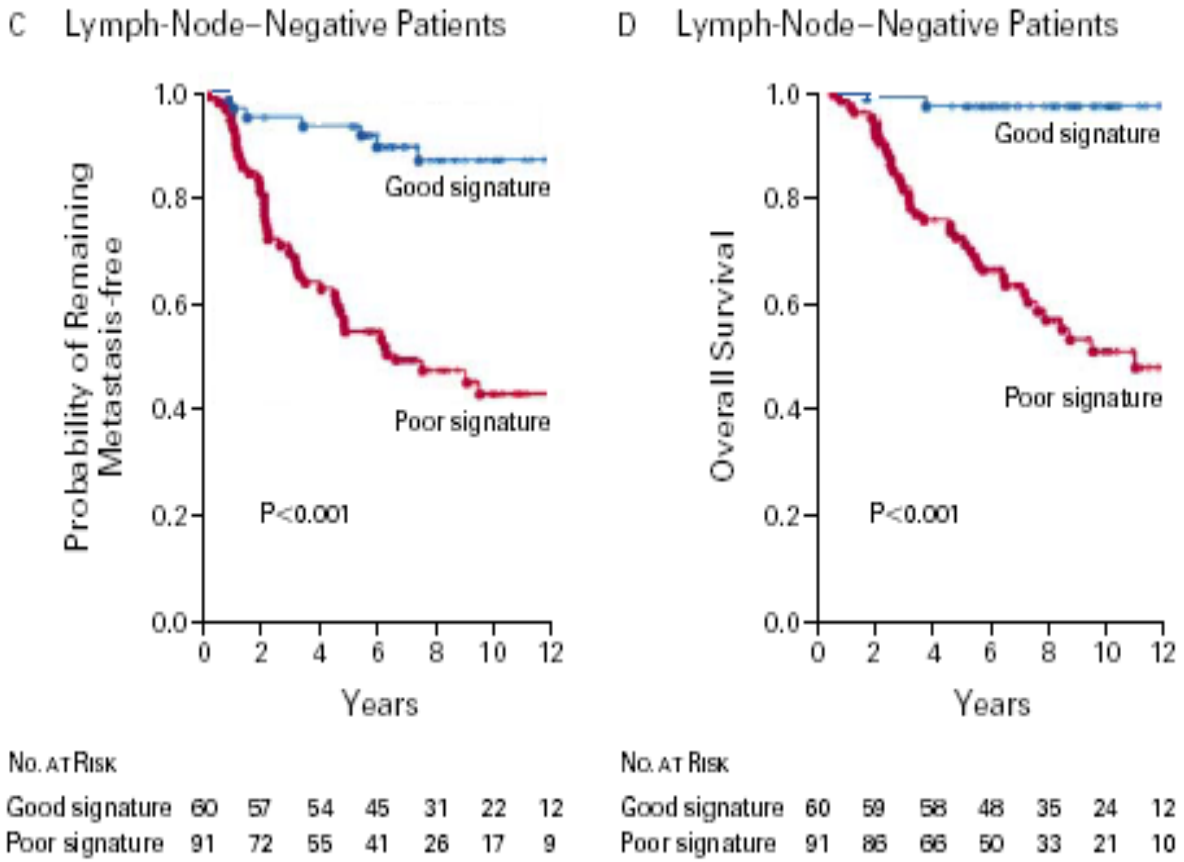
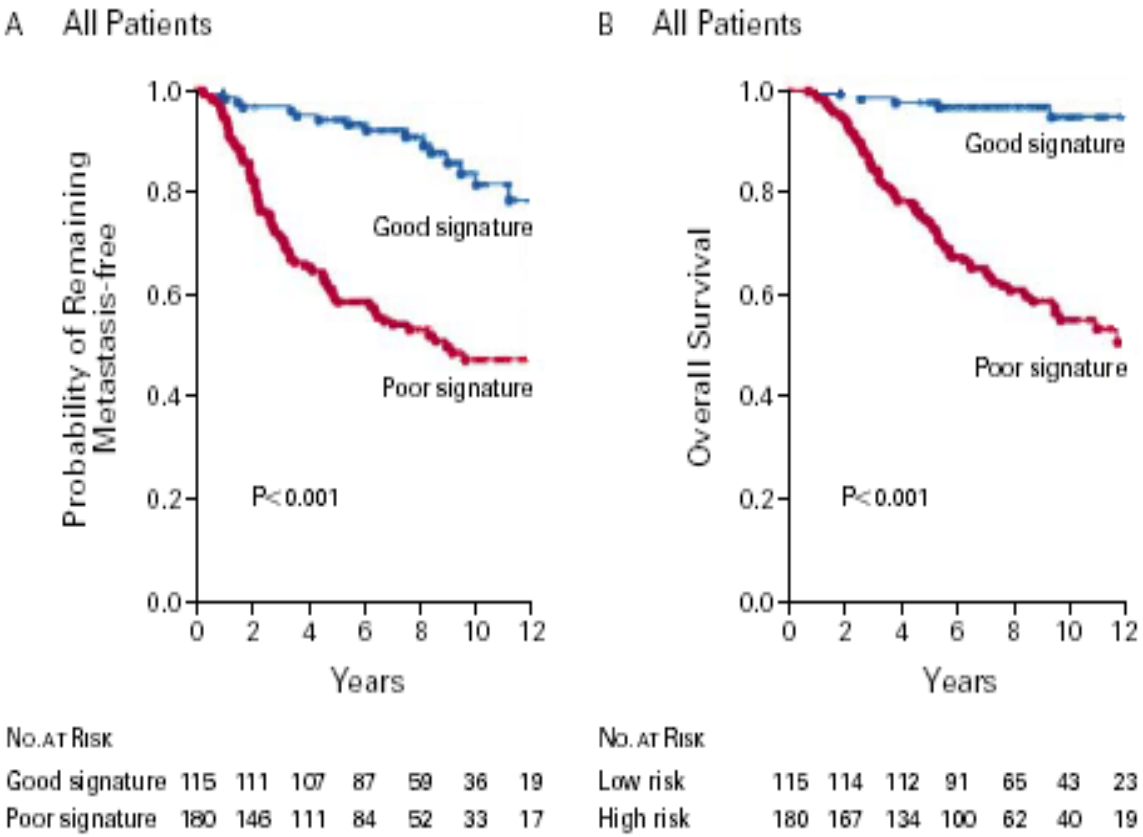
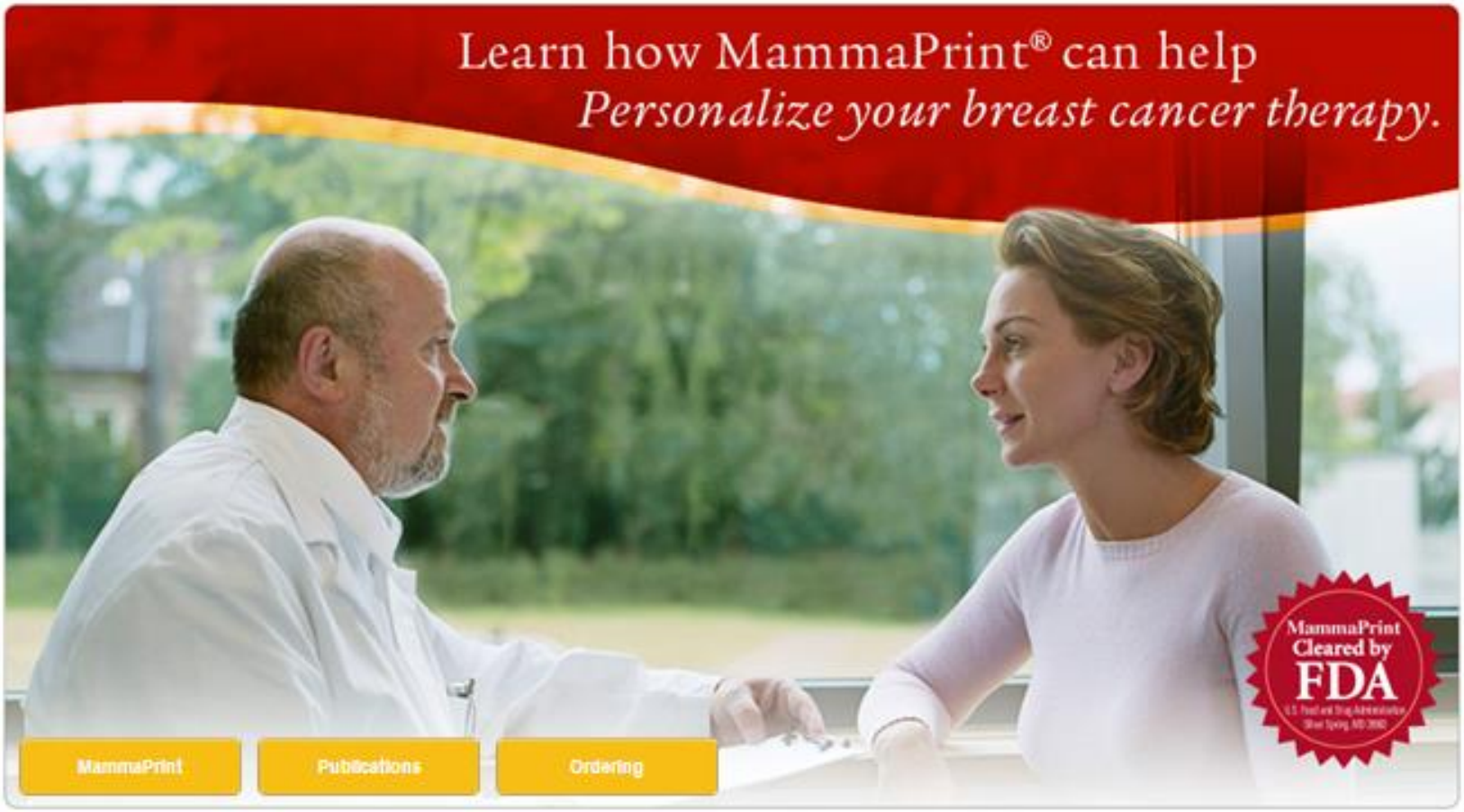


FDA approved: Mammaprint assay



Mammaprint assay, FDA cleared



MammaPrint's FDA IVDMIA Clearance Confers Confidence in its Safety and Efficacy for Breast Cancer Patients

The First and *Only* Breast Cancer Recurrence Test with FDA IVDMIA Clearance

MammaPrint is the first and only in vitro diagnostic multivariate index assay (IVDMIA) to be cleared by the FDA. Prior to its clearance, the FDA reviewed evidence that the test had been properly validated for its use.[1]

When MammaPrint was cleared in February of 2007, The Director of the Office of In Vitro Diagnostic Evaluation stated, "There have been rapid advances in microarrays and other pioneering diagnostics, and a corresponding increase in the use and impact of these complex devices. This has prompted FDA to take a closer look at the potential risks as well as the benefits associated with such tests when they are developed and used in laboratories. This test clearance takes into account the development of these innovative technologies and ensures public health by carefully evaluating their performance."

"Clearance of the MammaPrint test marks a step forward in the initiative to bring molecular-based medicine into current practice. MammaPrint results will provide patients and physicians with more information about the prospects for the outcome of the disease. This information will support treatment decisions."

—Andrew C. von Eschenbach, M.D., *Former Commissioner of Food and Drug Administration*

Oncotype assay, based on multiplex PCR from FFPEs tissues
Breast cancer, colorectal cancer

oncotype DX®

The Oncotype DX Breast Cancer Assay and the Oncotype DX Colon Cancer Assay are unique diagnostic tests that can help patients and their doctors make informed, individualized treatment decisions.

Breast Cancer Assay	Colon Cancer Assay	Worldwide Users
oncotype DX Breast Cancer Assay	oncotype DX Colon Cancer Assay	oncotype DX Breast Cancer Assay

ARTICLE

doi:10.1038/nature12477

Signatures of mutational processes in human cancer

A list of authors and their affiliations appears at the end of the paper

All cancers are caused by somatic mutations; however, understanding of the biological processes generating these mutations is limited. The catalogue of somatic mutations from a cancer genome bears the signatures of the mutational processes that have been operative. Here we analysed 4,938,362 mutations from 7,042 cancers and extracted more than 20 distinct mutational signatures. Some are present in many cancer types, notably a signature attributed to the APOBEC family of cytidine deaminases, whereas others are confined to a single cancer class. Certain signatures are associated with age of the patient at cancer diagnosis, known mutagenic exposures or defects in DNA maintenance, but many are of cryptic origin. In addition to these genome-wide mutational signatures, hypermutation localized to small genomic regions, 'kataegis', is found in many cancer types. The results reveal the diversity of mutational processes underlying the development of cancer, with potential implications for understanding of cancer aetiology, prevention and therapy.

Nature. Aug 22, 2013; 500(7463): 415–421

The new era in tumor biomarkers: Signatures of mutational processes in human cancers

- **All cancers are caused by somatic mutations**
- **Understanding of the biological processes generating these mutations is limited.**
- **The catalogue of somatic mutations from a cancer genome bears the signatures of the mutational processes that have been operative.**
- **M. Stratton's group analyzed 4,938,362 mutations from 7,042 cancers and extracted more than 20 distinct mutational signatures.**
- **Some are present in many cancer types, notably a signature attributed to the APOBEC family of cytidine deaminases, whereas others are confined to a single class.**
- **Certain signatures are associated with age of the patient at cancer diagnosis, known mutagenic exposures or defects in DNA maintenance, but many are of cryptic origin.**

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The new era in tumor biomarkers: Signatures of mutational processes in human cancers

- **In addition to these genome-wide mutational signatures, hypermutation localized to small genomic regions, "kataegis"(in Greek means: storm!!) is found in many cancer types.**
- **The results reveal the diversity of mutational processes underlying the development of cancer with potential implications for understanding of cancer etiology, prevention and therapy.**

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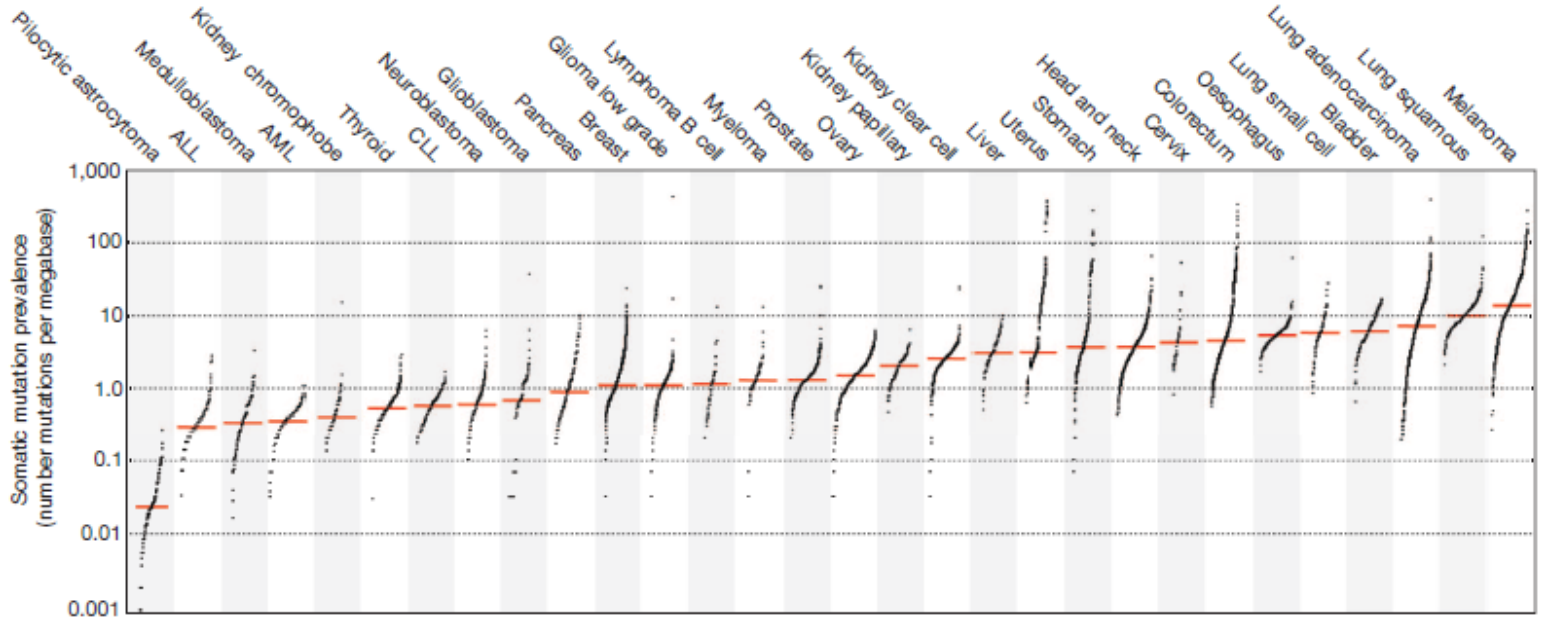


Figure 1 | The prevalence of somatic mutations across human cancer types. Every dot represents a sample whereas the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase whereas the different cancer types are ordered on the horizontal axis based on their median numbers of somatic mutations. We thank G. Getz and colleagues for the design of this figure[26]. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

11 different signatures of mutational processes in human cancers

Nature. Aug 22, 2013; 500(7463): 415–421

The new era in tumor biomarkers

Nature. Aug 22, 2013; 500(7463): 415–421

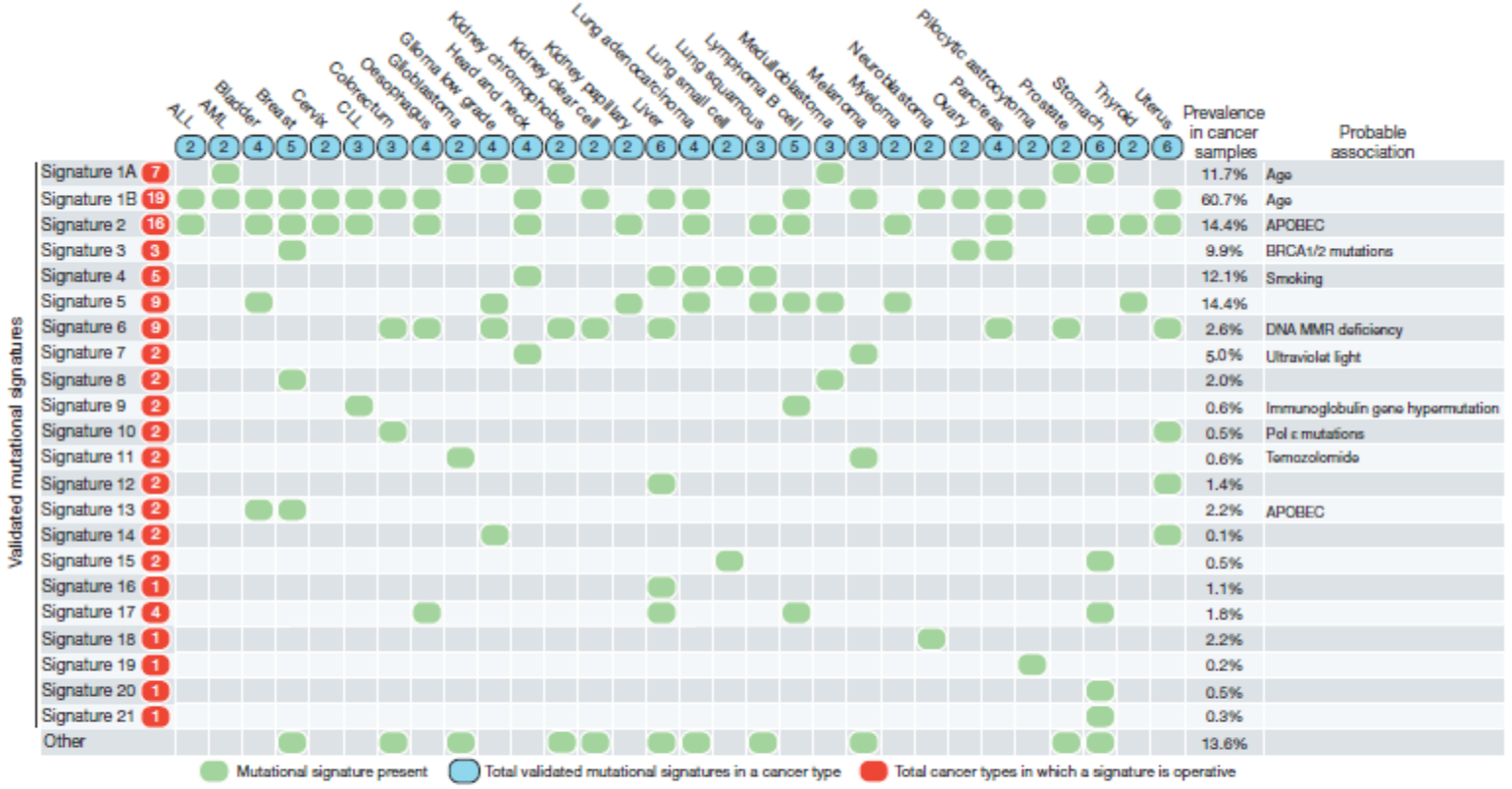


Figure 3 | The presence of mutational signatures across human cancer types. Cancer types are ordered alphabetically as columns whereas mutational signatures are displayed as rows. 'Other' indicates mutational signatures for which we were not able to perform validation or for which validation failed (Supplementary Figs 24–28). Prevalence in cancer samples indicates the percentage of samples from our data set of 7,042 cancers in which the signature contributed significant number of somatic mutations. For most signatures, significant number of mutations in a sample is defined as more than 100 substitutions or more than 25% of all mutations in that sample. MMR, mismatch repair.

The new era in tumor biomarkers

ARTICLE

OPEN

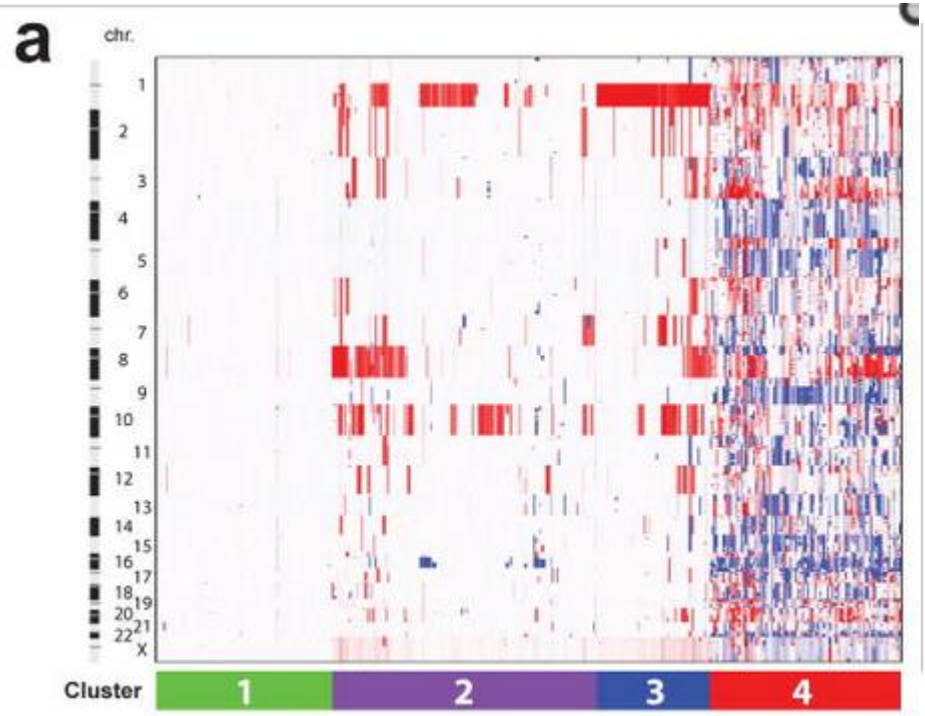
doi:10.1038/nature12113

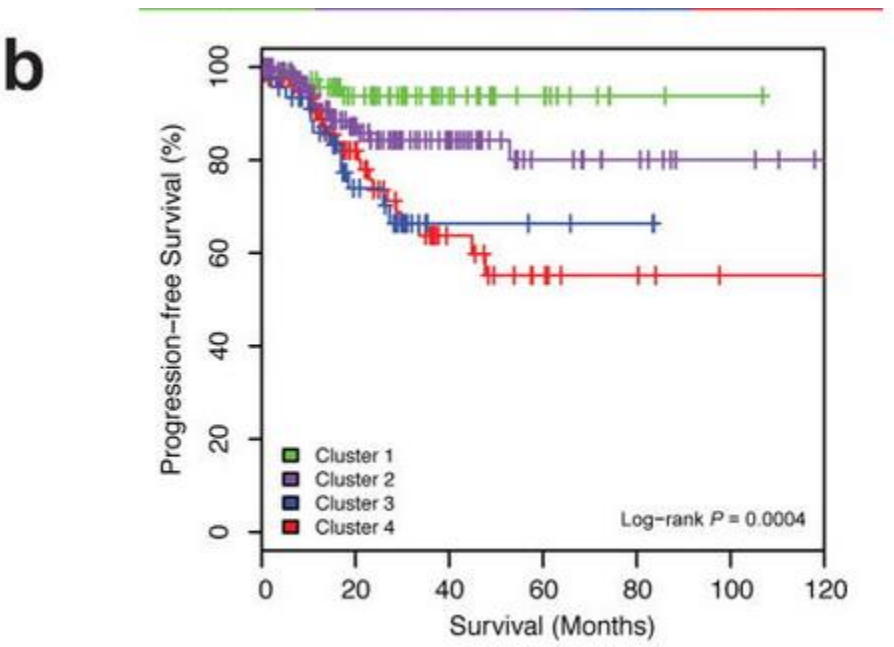
Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

Nature. 2013 May 2; 497(7447): 67–73

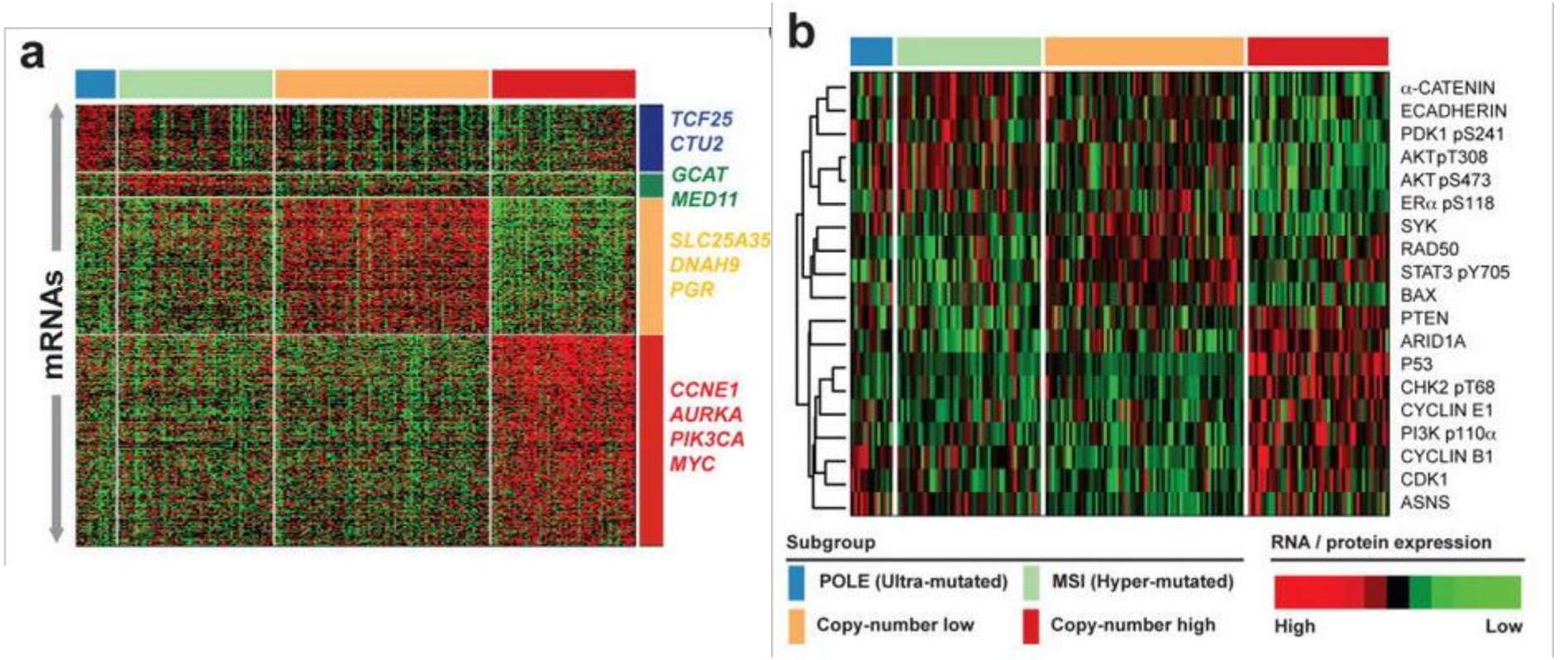
somatic copy alterations in endometrial carcinomas





Nature. 2013 May 2; 497(7447): 67–73

mRNA and protein expression heat maps in endometrial carcinomas



Nature. 2013 May 2; 497(7447): 67–73

pathway alterations in endometrial carcinomas

ARTICLE RESEARCH

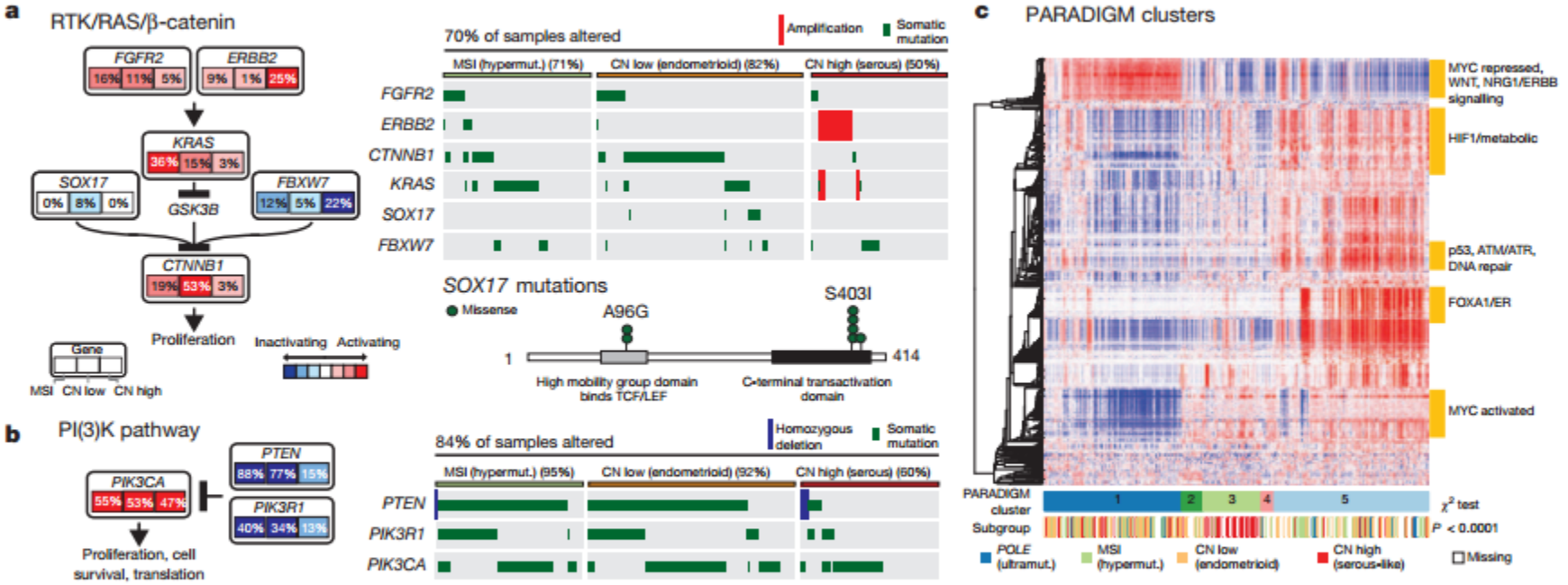


Figure 4 | Pathway alterations in endometrial carcinomas. **a**, The RTK/RAS/β-catenin pathway is altered through several mechanisms that exhibit mutually exclusive patterns. Alteration frequencies are expressed as a percentage of all cases. The right panel shows patterns of occurrence. **b**, The PI(3)K pathway has mutually exclusive *PIK3CA* and *PIK3R1* alterations that frequently co-occur with *PTEN* alterations in the MSI and copy-number low subgroups. **c**, Heat map display of top 1,000 varying pathway features within PARADIGM consensus clusters. Samples were arranged in order of their consensus cluster membership. The genomic subtype for each sample is displayed below the consensus clusters.

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the cancer genome atlas!!!
http://cancergenome.nih.gov/

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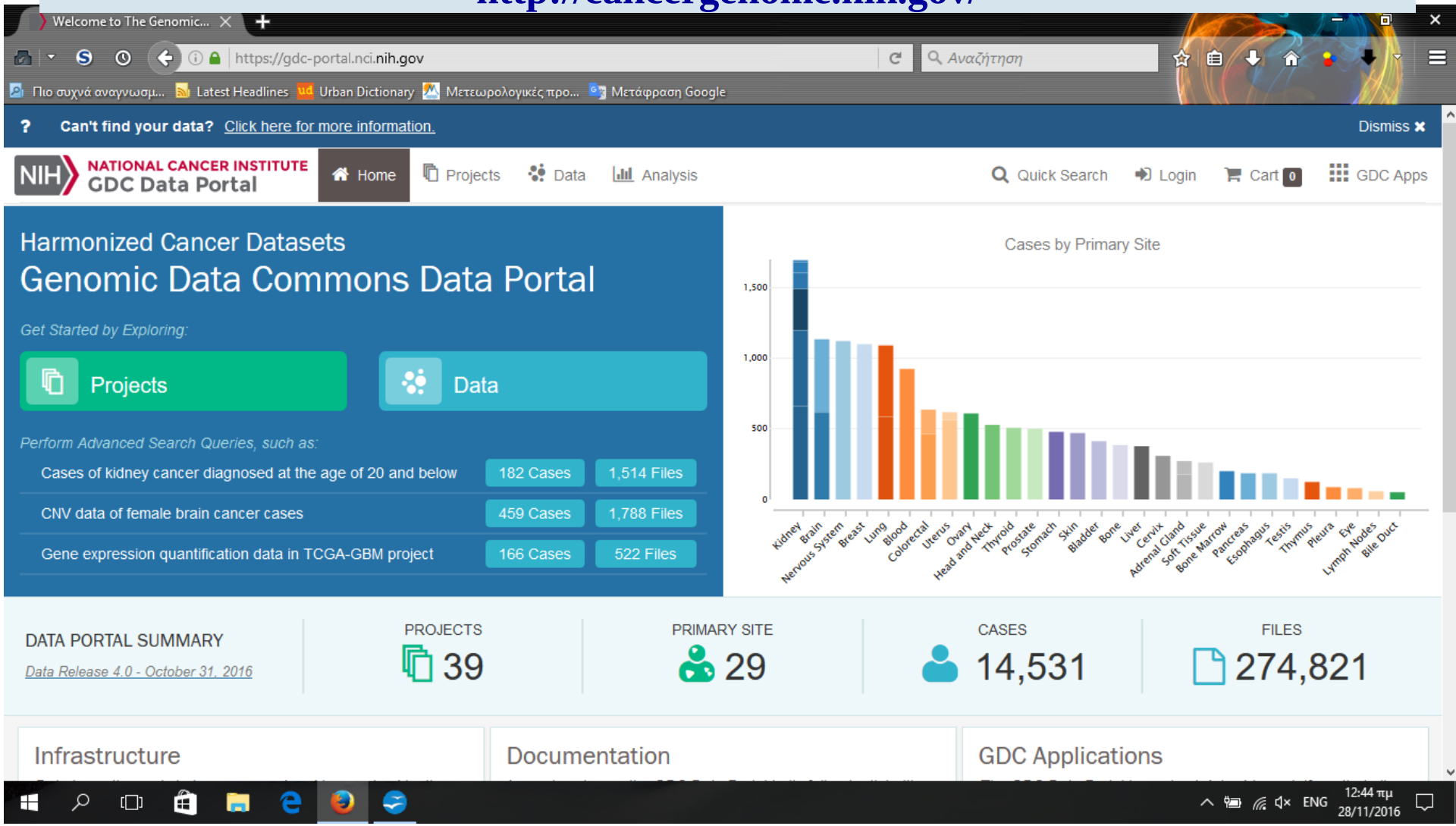

Tirgu Mures, Evi Lianidou

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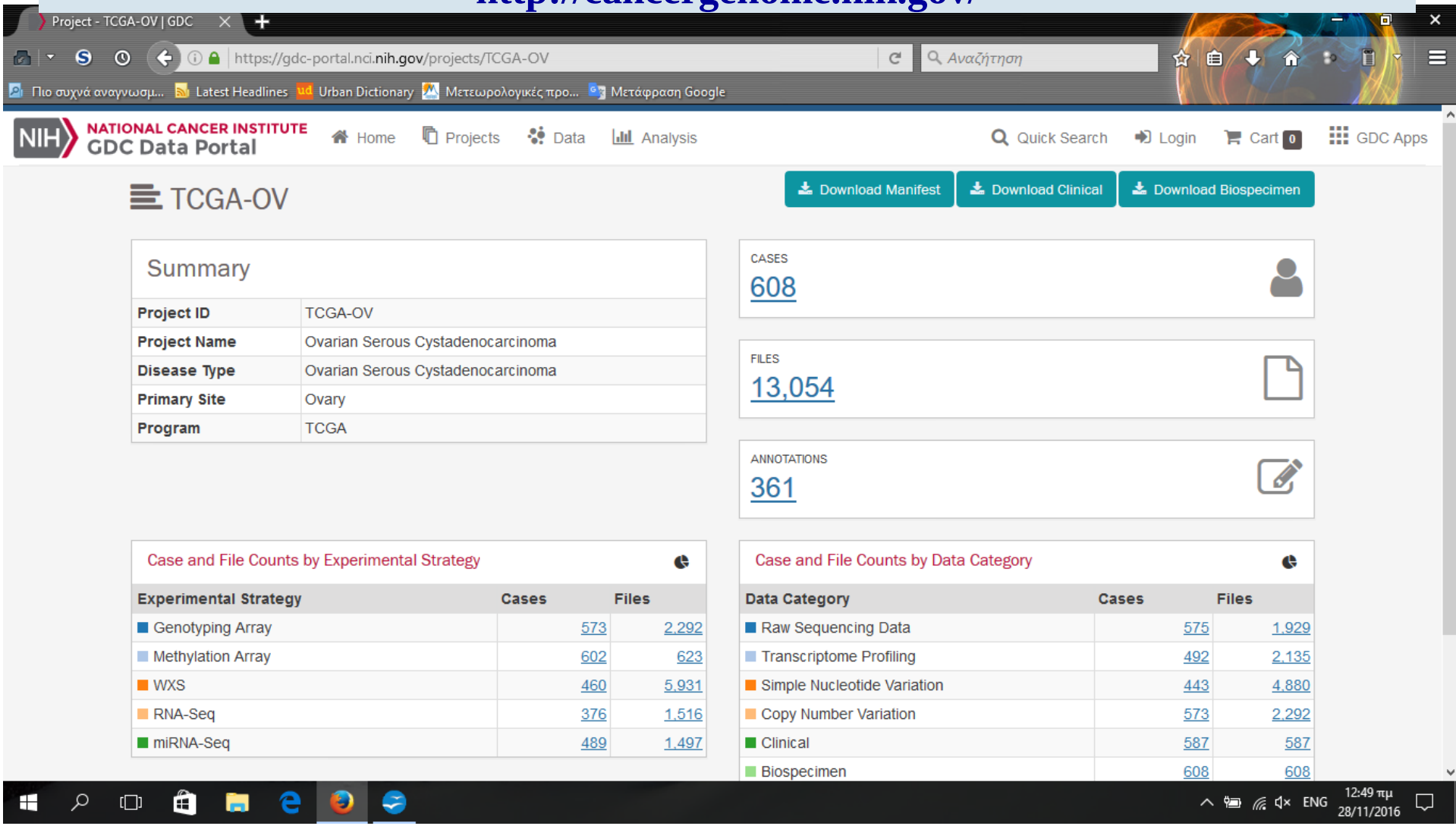

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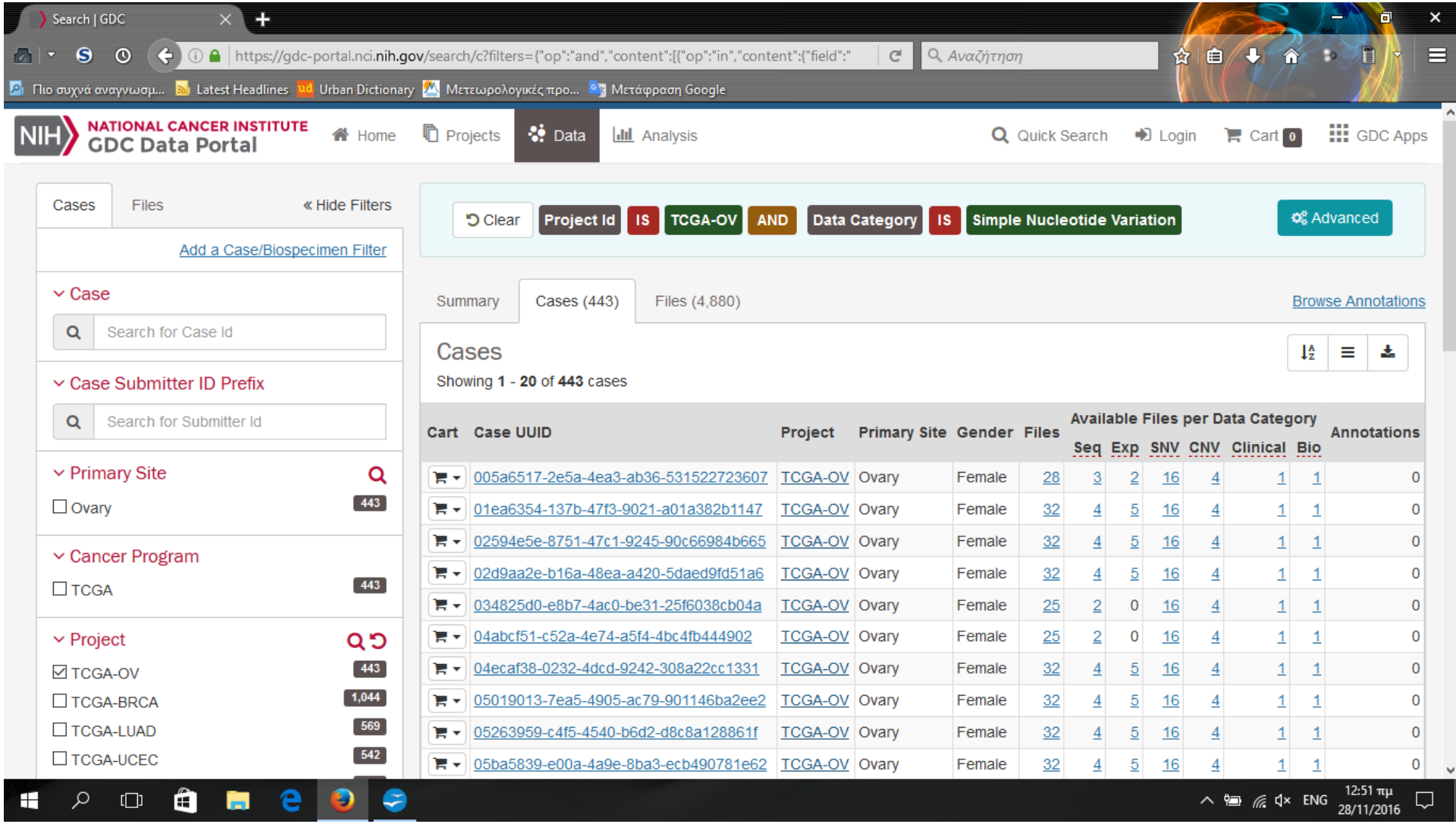

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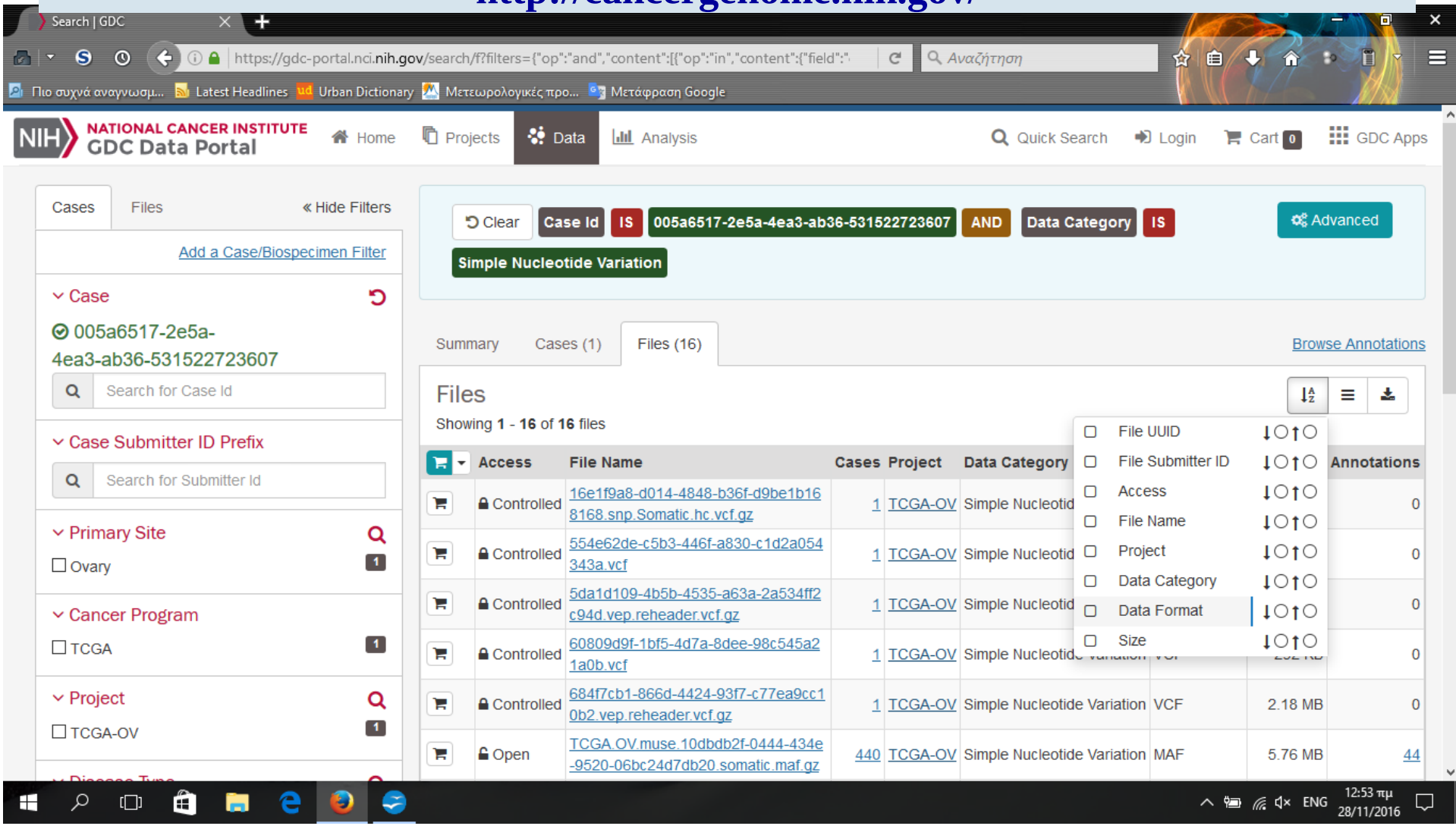

Tirgu Mures, Evi Lianidou

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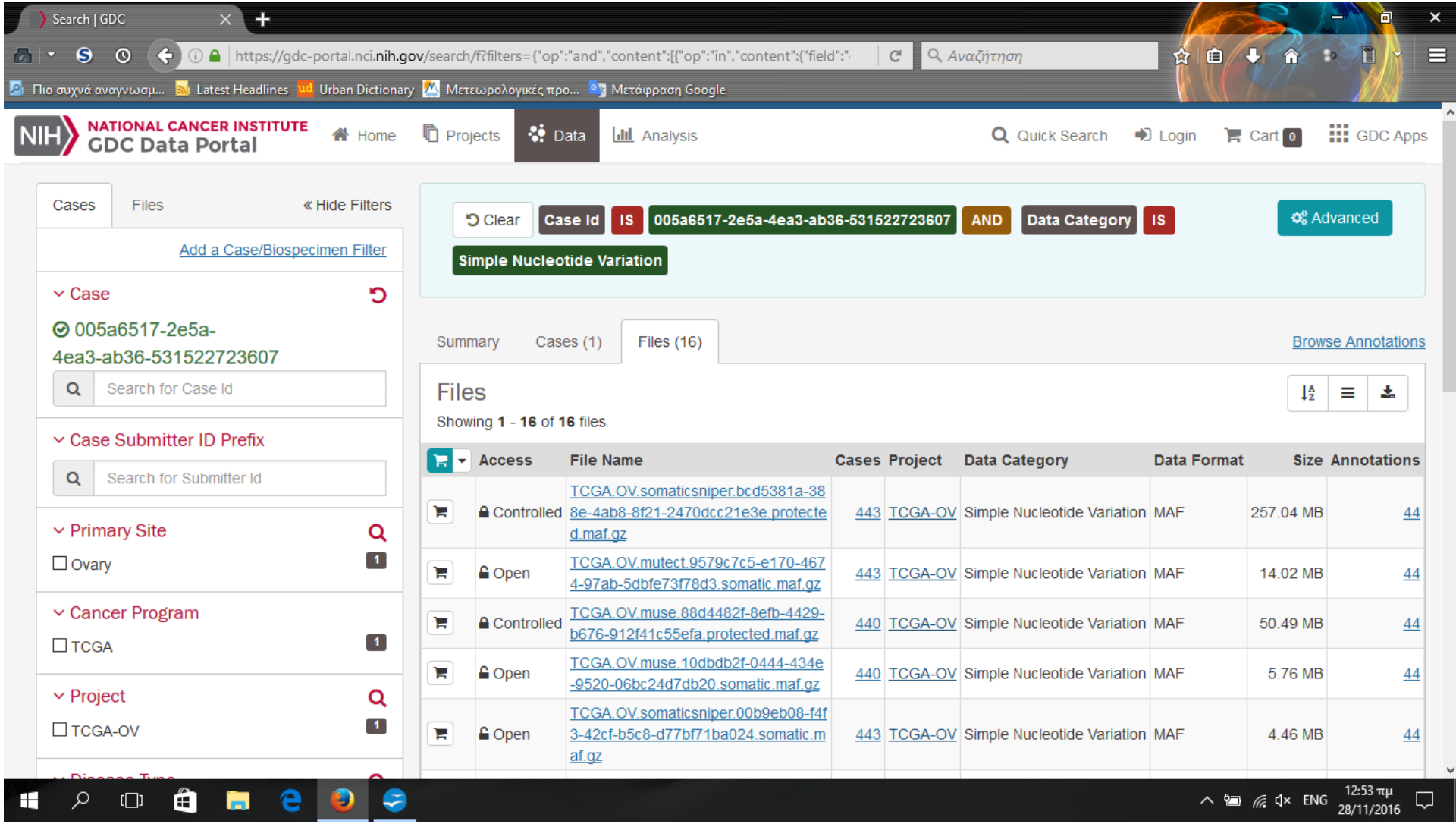

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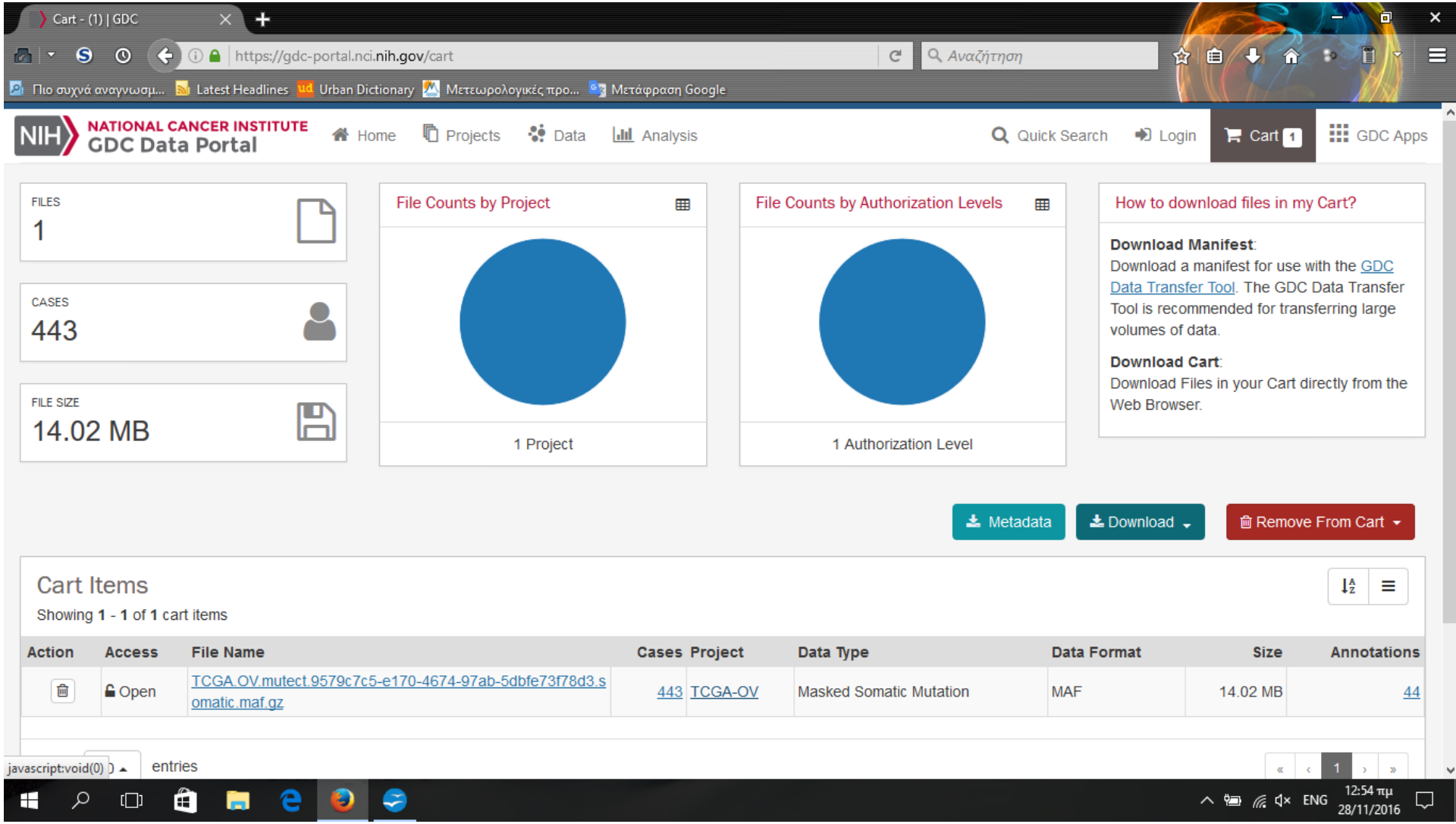

Web links for TCGA:

- http://www.cbioportal.org/ (cBioPortal for cancer genomics)
- https://genome-cancer.ucsc.edu/proj/site/hgHeatmap/ (UCSC cancer genomics Browser)
- https://dcc.icgc.org/ (international cancer genome consortium data portal)

More data:

- http://cancer.sanger.ac.uk/cosmic/browse/genome (catalogue of somatic mutations in cancer genome browser)
- http://www.intogen.org/search (integrative oncogenomics)