Interpreting genomic information for the clinical care of solid neoplasms

Salvador J. Diaz-Cano

Coming to a clinic near you…

RESEARCH Open Access

Evolution of an adenocarcinoma in response to selection by targeted kinase inhibitors

Use of Whole-Genome Sequencing to Diagnose a Cryptic Fusion Oncogene

Clinical assessment incorporating a personal genome

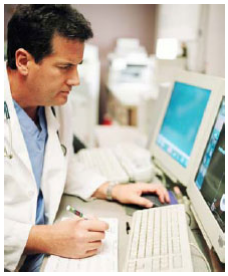
Identification of a Novel *TP53* Cancer Susceptibility Mutation Through Whole-Genome Sequencing of a Patient With Therapy-Related AML

Genetic diagnosis by whole exome capture and massively parallel DNA sequencing

Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease

Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

Why Pathologists? We have access, we know testing



Personalized Risk Prediction, Medication Dosing, Diagnosis/ Prognosis

Physician sends sample to Pathology (blood/tissue)

Access to patient's genome

Just another laboratory test

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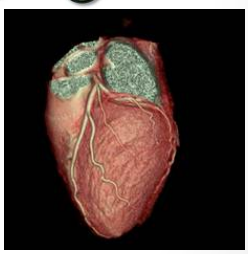
What we will cover today:

- Review current and future molecular testing:
  - Somatic analysis/ Diagnosis/Prognosis
    - Cancer
  - Risk Assessment
    - Pathologists involved in preventive medicine



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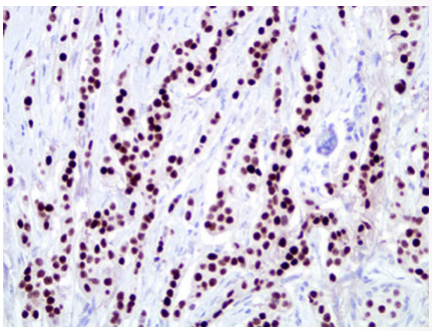
What we could test for? Same Stuff

- Somatic analysis
  - Tumor genomics
    - Diagnosis/Prognosis
    - Response to treatment
  - May change/ evolve/ require repeat testing



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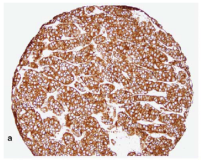
http://www.bcm.edu/breastcenter/pathology/index.cfm?pmid=11149

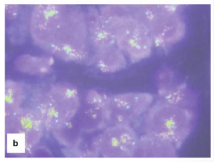
Diagnosis/Prognosis Timeline: Cancer

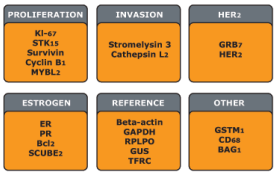
Single gene
- HER2

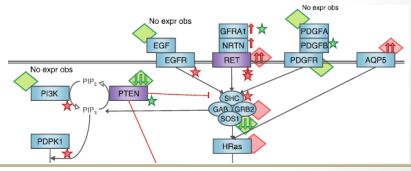
Multi-gene assays
- Breast cancer

Gene chips/Next generation sequencing of tumors
- Expression profiling
- Exome
- Transcriptome
- Whole genome









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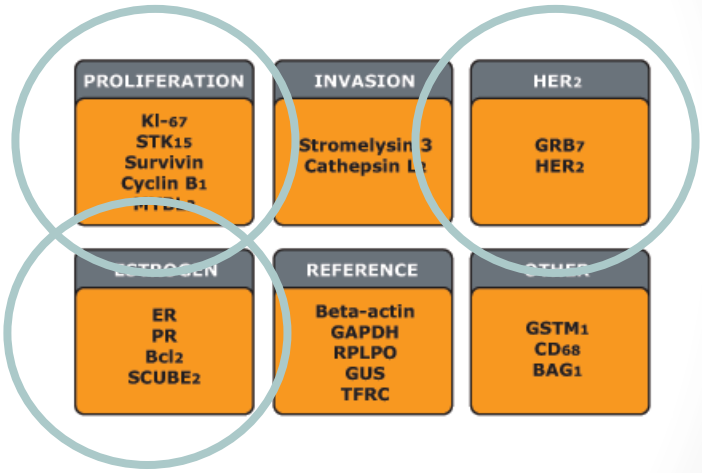
Multi-gene assays in breast cancer



Look familiar?

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Multi-gene assays to determine risk score, need for additional chemo

Recurrence Score=

+0.47 x HER2 Group Score

- 0.34 x ER Group Score

+1.04 x Proliferation group Score

+0.10 x Invasion Group Score

+0.05 x CD68

- 0.08 x GSTM1

- 0.07 x BAG1

For use in ER+, node negative cancer

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Prognostic Value of a Combined Estrogen Receptor, Progesterone Receptor, Ki-67, and Human Epidermal Growth Factor Receptor 2 Immunohistochemical Score and Comparison With the Genomic Health Recurrence Score in Early Breast Cancer

Jack Cuzick, Mitch Dowsett, Silvia Pineda, Christopher Wale, Janine Salter, Emma Quinn, Lila Zabaglo, Elizabeth Mallon, Andrew R. Green, Ian O. Ellis, Anthony Howell, Aman U. Buzdar, and John F. Forbes

- **Oncotype similar predictive value to combined four immunohistochemical stains (ER,PR, HER2, Ki-67)**
- **May offer standardization lacking in IHC**
- **Need to validate**
  - **Prospective trials**

Just another laboratory test

Cuzick J, et al. J Clin Oncol. 2011; 29: 4273

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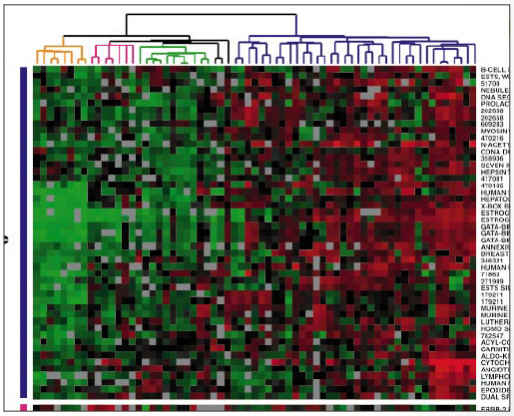
Molecular portraits of human breast tumours

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*

- **Analyzed 8,101 genes on chip microarrays**
- **Reference= pooled cell lines**
- **Breast cancer subgroups**



Perou CM, et al. Nature. 2000; 406, 747

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Cancer Treatment: NGS in AML

Use of Whole-Genome Sequencing to Diagnose a Cryptic Fusion Oncogene

John S. Welch, MD, PhD
Peter Westervelt, MD, PhD
Li Ding, PhD
David E. Larson, PhD
Jeffery M. Klco, MD, PhD
Shashikant Kulkarni, PhD
John Wallis, PhD
Ken Chen, PhD

Context Whole-genome sequencing is becoming increasingly available for research purposes, but it has not yet been routinely used for clinical diagnosis.

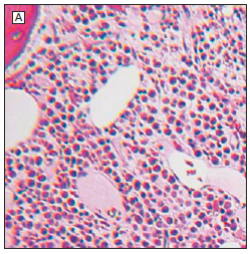
Objective To determine whether whole-genome sequencing can identify cryptic, actionable mutations in a clinically relevant time frame.

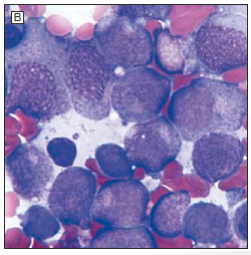
Design, Setting, and Patient We were referred a difficult diagnostic case of acute promyelocytic leukemia with no pathogenic X-*RARA* fusion identified by routine metaphase cytogenetics or interphase fluorescence in situ hybridization (FISH). The case patient was enrolled in an institutional review board–approved protocol, with consent specifically tailored to the implications of whole-genome sequencing. The protocol uses a "movable firewall" that maintains patient anonymity within the entire research team

Welch JS, et al. JAMA, 2011;305, 1577

Case History

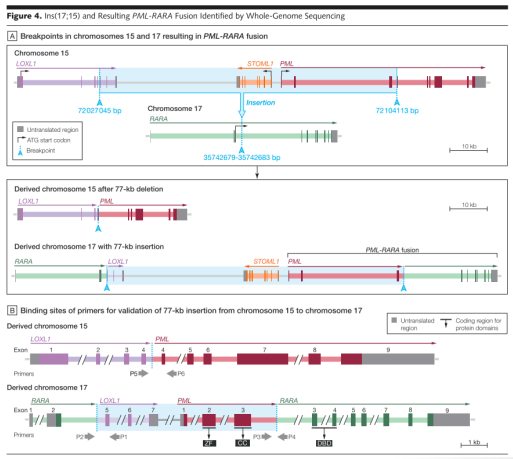
- 39 year old female with APML by morphology
- Cytogenetics and RT-PCR unable to detect PML-RAR fusion
- Clinical question: Treat with ATRA versus allogeneic stem cell transplant





The Findings: Led to appropriate treatment

- Analysis
  - Paired-end NGS
- Findings
  - Cytogenetically cryptic event: novel fusion
- Analysis took 7 weeks
- ATRA Treatment
- Patient still alive 15 months later



Cancer Treatment: NGS of Tumor

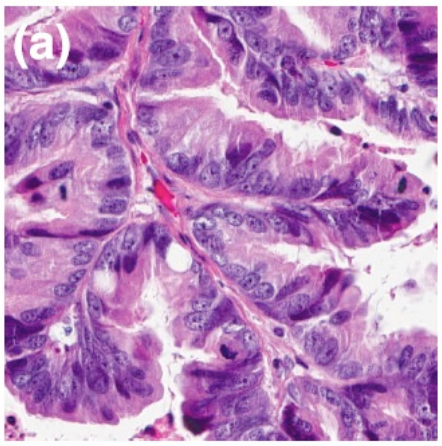
Evolution of an adenocarcinoma in response to selection by targeted kinase inhibitors

Steven JM Jones[1*], Janessa Laskin[2], Yvonne Y Li[1], Obi L Griffith[1], Jianghong An[1], Mikhail Bilenky[1], Yaron S Butterfield[1], Timothee Cezard[1], Eric Chuah[1], Richard Corbett[1], Anthony P Fejes[1], Malachi Griffith[1], John Yee[3], Montgomery Martin[2], Michael Mayo[1], Nataliya Melnyk[4], Ryan D Morin[1], Trevor J Pugh[1], Tesa Severson[1], Sohrab P Shah[4,5], Margaret Sutcliffe[2], Angela Tam[1], Jefferson Terry[4], Nina Thiessen[1], Thomas Thomson[2], Richard Varhol[1], Thomas Zeng[1], Yongjun Zhao[1], Richard A Moore[1], David G Huntsman[3], Inanc Birol[1], Martin Hirst[1], Robert A Holt[1], Marco A Marra[1]

Jones SJM, et al. Genome Biol. 2010;11:R82

Case History

- 78 year old male
- Poorly differentiated papillary adenocarcinoma of tongue
- Metastatic to lymph nodes
- Failed chemotherapy
- Decision to use next-generation sequencing methods



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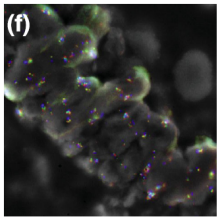
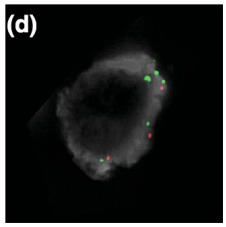
Methods and Results

- Analysis
  - Whole genome
  - Transcriptome
- Findings
  - Upregulation of RET oncogene
  - Downregulation of PTEN





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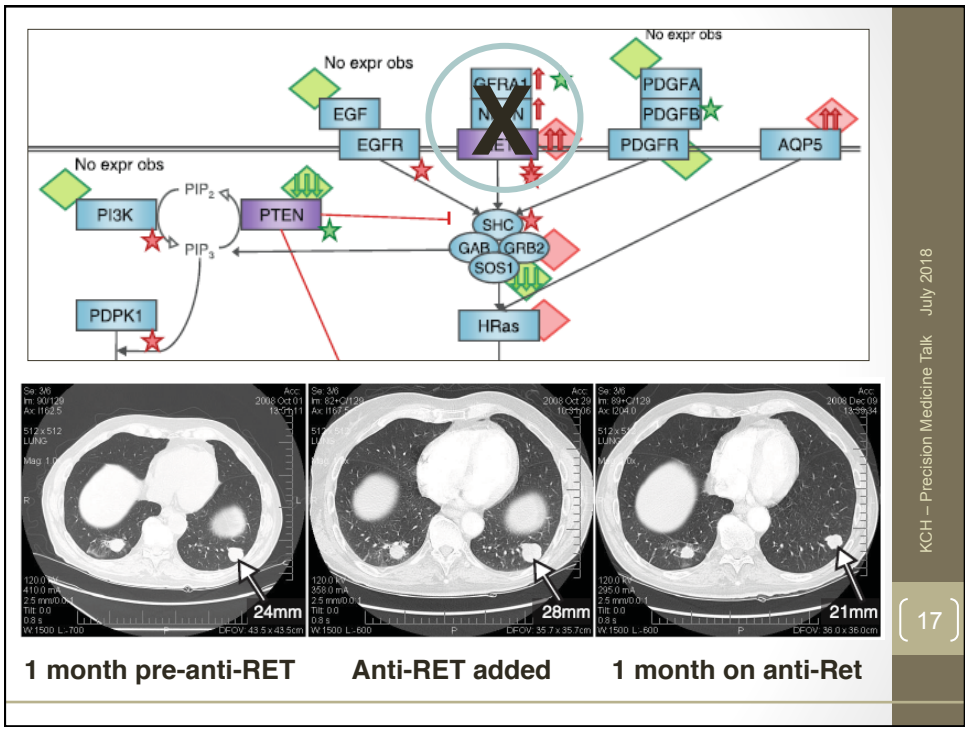
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SOS1
PDPK1
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21mm
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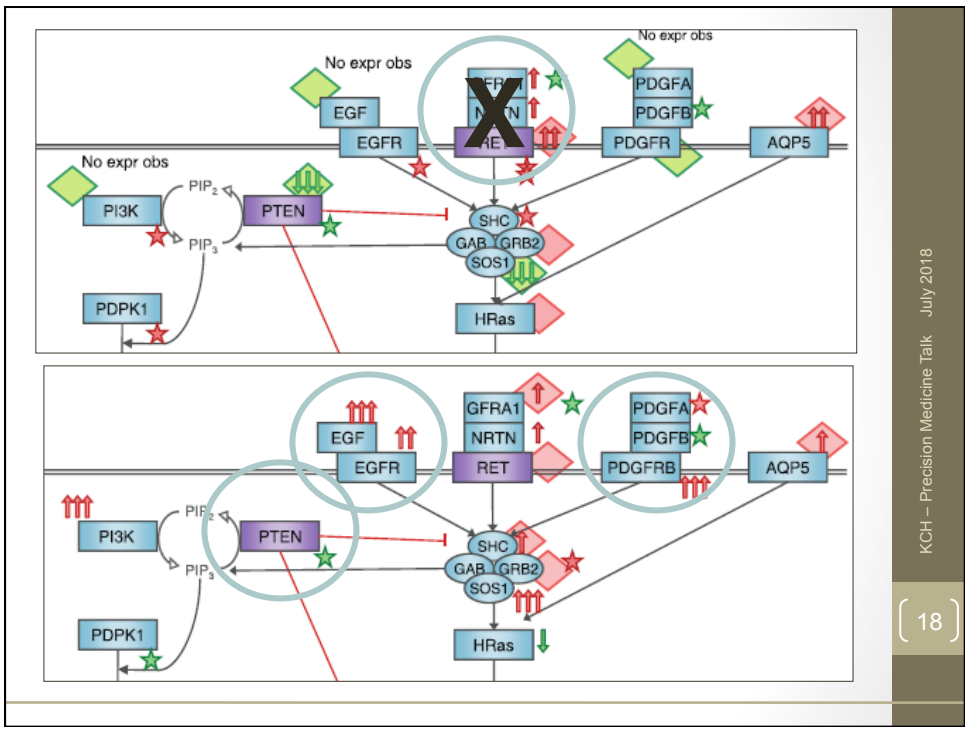
1 month pre-anti-RET
Anti-RET added
1 month on anti-Ret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RET
PDGFRB
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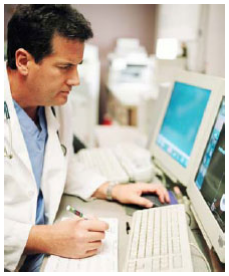
Why Pathologists? We have access, we know testing



Personalized Tumor Treatment Plan

Would like to identify tumor, know prognosis, treatment options

Access to tumor genome

Why pathologists?

"However, to fully use this potentially transformative technology to make informed clinical decisions, standards will have to be developed that allow for CLIA-CAP certification of whole-genome sequencing and for direct reporting of relevant results to treating physicians."

Welch JS, et al. JAMA, 2011;305:1577

What we will cover today:

- Review current and future molecular testing:
  - Somatic analysis/ Diagnosis/Prognosis
    - Cancer
  - Risk Assessment
    - Pathologists involved in preventive medicine

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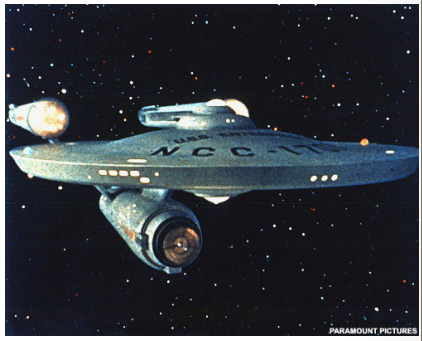
What we could test for – Something New

- Risk prediction
  - Pathologists involved in preventive medicine
    - Predict risk of disease
    - Predict drug response (pharmacogenomics)
- Germline
  - Heritable genomic targets
  - Does not change during lifetime



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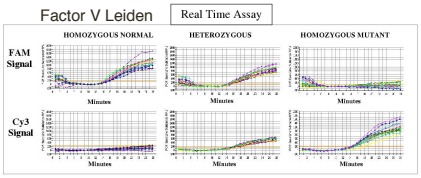
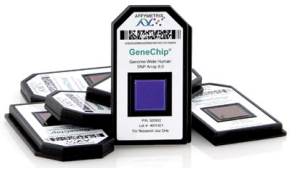
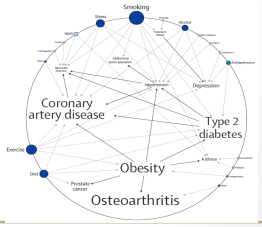
Risk Prediction: Timeline

- Single gene
- Multigene assays
  - Direct-to-consumer
- Next generation sequencing







Alsmadi OA, et al. BMC Genomics 2003 4:21

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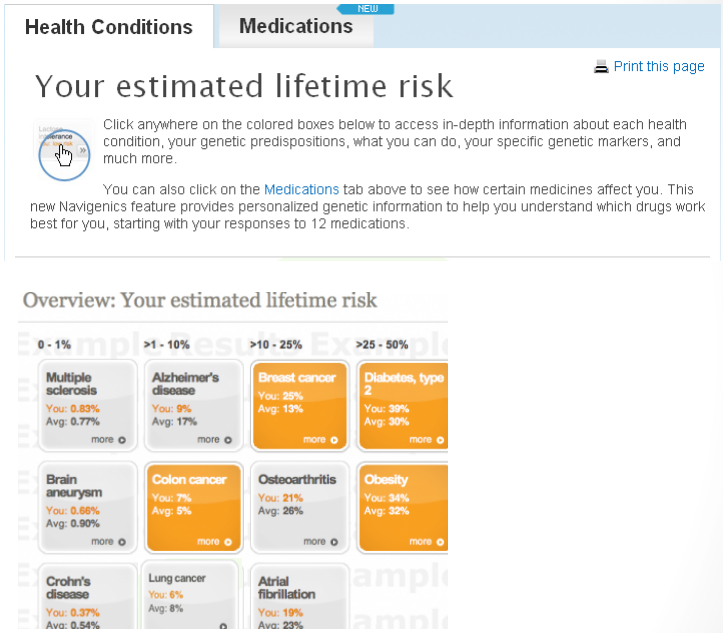

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Hereditary Risk Prediction: How is risk calculated?

- Analysis of SNPs (up to a million)
  - Genome wide association studies (GWAS)
- Case-control studies
  - Odds ratios
- Using odds ratios to determine individual patient risk

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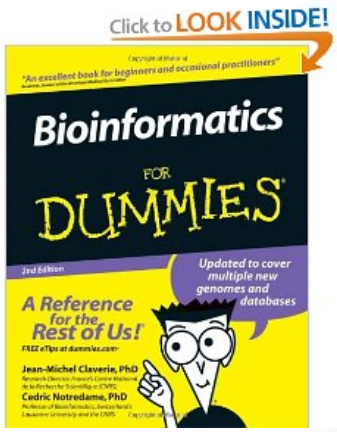
Just another test: Case-control study

- Adequate selection criteria for cases/ controls
- # of patients = reasonable ORs (<=1.3)
- Assays appropriate
  - Enough variation
  - Proper controls
- Statistics appropriate
- Detect known variants
- Reproducible results
  - Different populations
  - Different samples
- Pathophysiologic basis



Pearson TA, Manolio TA. JAMA 2008; 298:1335

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Just another test: Selection

- Lung cancer risk
- "Old School Study"
  - Cases and controls were matched based on age, smoking status, race and month of blood collection
- "Genomic Study":
  - Cases and controls were frequency matched by sex, age center, referral (or of residence) area and period of recruitment

Table 1. Distribution of Cases and Controls According to Matching Factors.

Factor	Cases	Controls
	%	
Age (yr)*		
<45	6.1	6.1
45–54	23.2	23.4
55–64	46.4	44.9
65–74	19.2	20.1
>75	6.1	4.5
Sex		
Male	68.7	68.4
Cigarette smoking history in 1974		
Never smoked	9.1	9.2
Formerly smoked	25.2	25.5
Currently smokes (no. of cigarettes per day)		
0–14	9.1	9.7
15–24	30.3	35.2
25–34	16.2	9.7
>35	10.1	10.7
Month of study participation		
September	38.4	35.7
October	35.4	38.3
November	26.2	26.0

*Age on October 1, 1974.

Menkes MS, et al. NEJM 1986;315:1250;
Hung RJ, et al. Nature Genetics. 2008; 452:633

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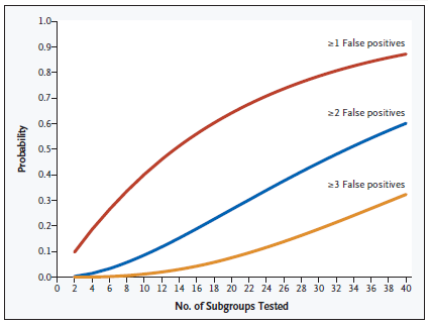
A word about statistics…

- **20 tests, "significant" if p=0.05**
  - **$(.95)^N$ = chance all tests "not significant"**
  - **$1-(.95)^N$ = chance one test "significant**
  - **$1-(.95)^{20}$= 64%**
  - **Bonferroni correction p = 0.0025**
- **Need to adjust for number of tests run**
  - **For 1 million SNP GWAS p < 0.00000005**



Just another laboratory test

Lagakos SW. NEJM 2006;354:16

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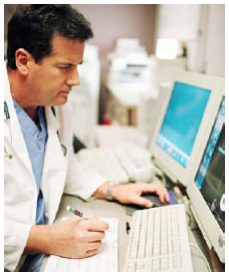
Why Pathologists? We have access, we know testing



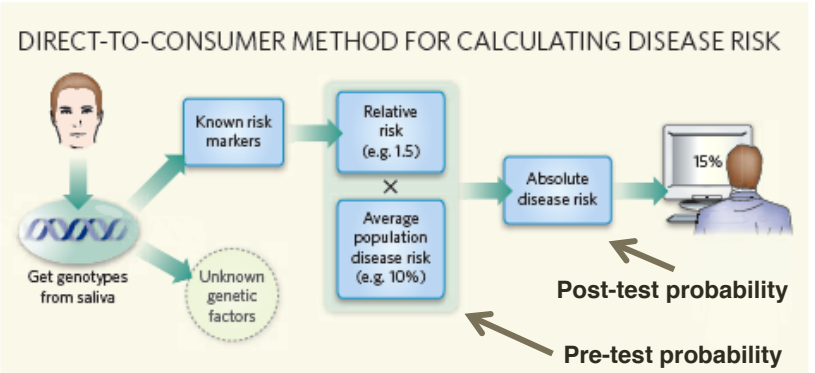
Personal Risk Prediction

Would like to determine patient risk for disease

Access to patient's chip results

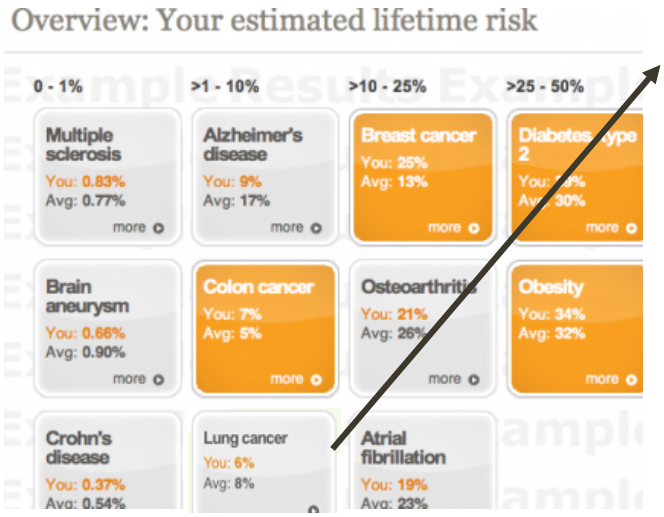
Not so simple!!

DTC: A simplistic calculation



How about family history? Environment?

Ng PC, et al. Nature. 2009; 461: 724



- "Avg" (average risk for your ethnic group = pre-test probability): 8%
- OR from SNP is 0.75 ***25% decreased risk****
- "You" (post-test probability): 8% x 0.75 = 6%
- Absolute decreased risk: = 2%
- Same OR if 80% vs. 60%
- Absolute decreased risk: 20%

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What we could test for – Integrated approach

- Germline
  - Heritable genomic targets
  - Does not change during lifetime
- Pathology Clues
  - Multicentricity
  - Histological features
  - Perilesional tissue reaction

- Familial tumor syndromes are good models due to:
  - Synchronic and metachronic tumors
  - Range of precursor lesions and established neoplasms are frequent
- Germline *RET* mutation (multiple endocrine neoplasia 2) has high penetrance and shows AMH-PCC and CCH-MTC

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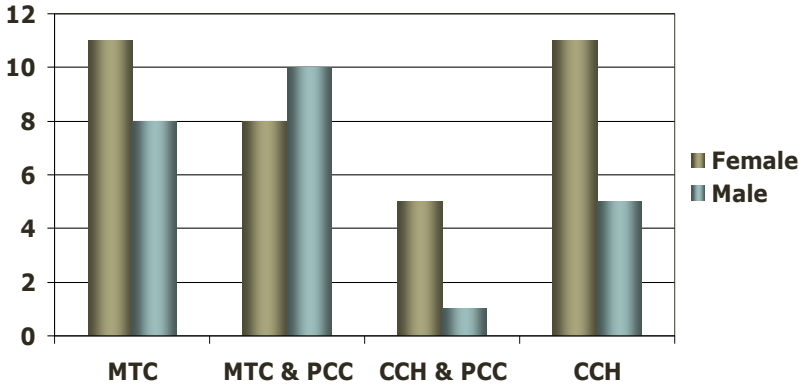
Molecular Genetics in CCH & AMH Patients



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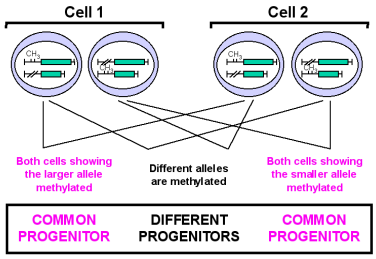
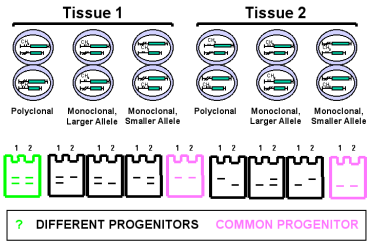
Clonality Assays - Cell and Tissue Comparisons





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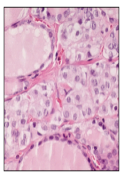
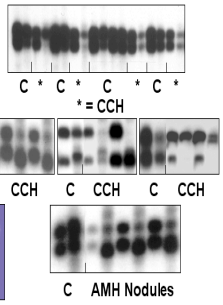
Clonality in Preinvasive Lesions

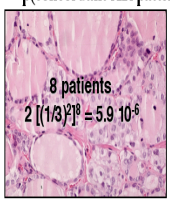
AR Allele Pattern in MEN-2A

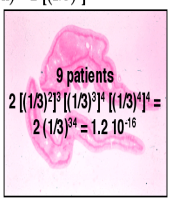




Early Monoclonal Expansions in MEN-2A Results

p(AR pattern in tissue) = 1/3
No of AR Allele (informative patients) = 2
n = No of lesions compared
x = No of patients
p(concordant AR pattern) = $2\,[(1/3)^{n}]^{x}$





Journal of Pathology
J Pathol 2000; **192**: 221–228.
DOI: 10.1002/1096-9896(2000)9999:9999<::AID-PATH679>3.0.CO;2-B

Original Paper

Clonal patterns in phaeochromocytomas and MEN-2A adrenal medullary hyperplasias: histological and kinetic correlates†

Salvador J. Diaz-Cano[1,2]*, Manuel de Miguel[3], Alfredo Blanes[4], Robert Tashjian[2], Hugo Galera[3] and Hubert J. Wolfe[2]

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[2] Department of Pathology, Tufts University – New England Medical Center, Boston, MA, USA
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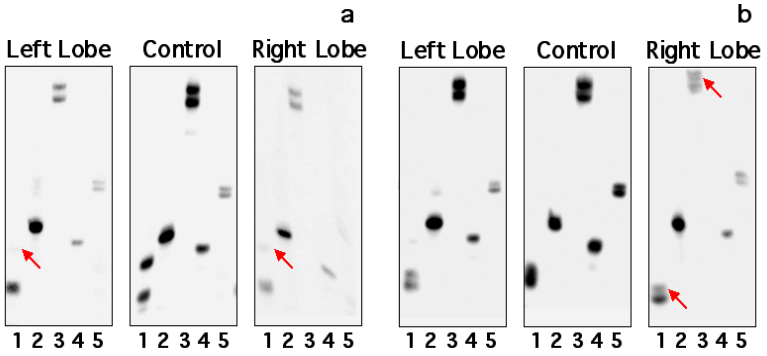
Received: 3 September 1999
Revised: 7 December 1999
Accepted: 24 March 2000
Published online: 26 June 2000

Abstract

The relationship among histological features, cell kinetics, and clonality has not been studied in adrenal medullary hyperplasias (AMHs) and phaeochromocytomas (PCCs). Thirty-four PCCs (23 sporadic and 11 MEN-2A (multiple endocrine neoplasia type 2A)-related tumours, the latter associated with AMH) from females were included in this study. Representative samples were histologically evaluated and microdissected to extract DNA and evaluate the methylation pattern of the androgen receptor alleles. At least two tissue samples (from the peripheral and internal zones in each tumour) were analysed with appropriate tissue controls run in every case. The same areas were selected for MIB-1 staining and *in situ* end labelling (ISEL). Malignant PCCs were defined by histologically confirmed distant metastases. All monoclonal AMH nodules from the same patient showed the same X-chromosome inactivated. Six sporadic PCCs revealed liver metastases (malignant PCC) and eight additional sporadic PCCs showed periadrenal infiltration (locally invasive PCC). All informative PCCs were monoclonal, except for five locally invasive PCCs and one benign PCC that revealed polyclonal patterns. Those cases also showed a fibroblastic stromal reaction with prominent blood vessels, focal smooth muscle differentiation, and significantly higher MIB-1 (126.8 ± 29.9) and ISEL (50.9 ± 12.8) indices. Concordant X-chromosome inactivation in nodules from a given patient suggests that MEN-2A AMH is a multifocal monoclonal condition. A subgroup of PCCs characterized by balanced methylation of androgen receptor alleles, high cellular turnover, and stromal proliferation also shows locally invasive features. Copyright © 2000 John Wiley & Sons, Ltd.

Keywords: phaeochromocytomas; adrenal medullary hyperplasias; MEN-2A; X-chromosome inactivation; proliferation; apoptosis; stromal reaction

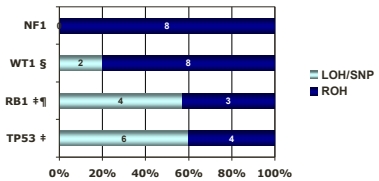
TSG Microsatellite Pattern in MEN-2A CCH



1 & 2 = *TP53*, 3 = *RB1*, 4 = *WT1*, 5 = *NF1*

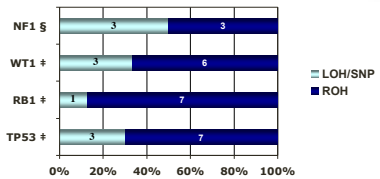
Microsatellite Patterns in MEN2

C-cell Hyperplasias



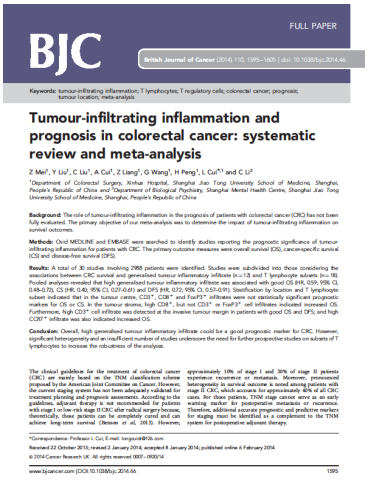
§ = Discordant LOH patterns in both lobes.
‡ = Concordant LOH patterns in both lobes.
¶ = Discordant SNP patterns in both lobes with concordant TP53 LOH patterns in 2 cases.

Adrenal Medullary Hyperplasias



§ = Discordant LOH patterns in nodules from 2 patients (67%).
‡ = Concordant LOH patterns in nodules from 3 patients (42%), but in different TSG in each patient

Inflammation and Cancer



BJC

FULL PAPER

British Journal of Cancer (2014) 110, 1595–1605 | doi: 10.1038/bjc.2014.46

Keywords: tumour-infiltrating inflammation; T lymphocytes; T regulatory cells; colorectal cancer; prognosis; tumour location; meta-analysis

Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis

Z Mei[1], Y Liu[2], C Liu[1], A Cui[3], Z Liang[3], G Wang[3], H Peng[3], L Cui[3,4] and C Li[2]

[1]Department of Colorectal Surgery, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China and [2]Department of Biological Psychiatry, Shanghai Mental Health Centre, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China

Background: The role of tumour-infiltrating inflammation in the prognosis of patients with colorectal cancer (CRC) has not been fully evaluated. The primary objective of our meta-analysis was to determine the impact of tumour-infiltrating inflammation on survival outcomes.

Methods: Ovid MEDLINE and EMBASE were searched to identify studies reporting the prognostic significance of tumour-infiltrating inflammation for patients with CRC. The primary outcome measures were overall survival (OS), cancer-specific survival (CS) and disease-free survival (DFS).

Results: A total of 30 studies involving 2988 patients were identified. Studies were subdivided into those considering the associations between CRC survival and generalised tumour inflammatory infiltrate (n=12) and T lymphocyte subsets (n=18). Pooled analyses revealed that high generalised tumour inflammatory infiltrate was associated with good OS (HR, 0.59; 95% CI, 0.48–0.72), CS (HR, 0.40; 95% CI, 0.27–0.61) and DFS (HR, 0.72; 95% CI, 0.57–0.91). Stratification by location and T lymphocyte subset indicated that in the tumour centre, $CD3^+$, $CD8^+$ and $FoxP3^+$ infiltrates were not statistically significant prognostic markers for OS or CS. In the tumour stroma, high $CD8^+$, but not $CD3^+$ or $FoxP3^+$ cell infiltrates indicated increased OS. Furthermore, high $CD3^+$ cell infiltrate was detected at the invasive tumour margin in patients with good OS and DFS; and high $CCR7^+$ infiltrate was also indicated increased OS.

Conclusion: Overall, high generalised tumour inflammatory infiltrate could be a good prognostic marker for CRC. However, significant heterogeneity and an insufficient number of studies underscore the need for further prospective studies on subsets of T lymphocytes to increase the robustness of the analyses.

The clinical guidelines for the treatment of colorectal cancer (CRC) are mainly based on the TNM classification scheme proposed by the American Joint Committee on Cancer. However, the current staging system has not been adequately validated for treatment planning and prognosis assessments. According to the guidelines, adjuvant therapy is not recommended for patients with stage I or low-risk stage II CRC after radical surgery because, theoretically, these patients can be completely cured and can achieve long-term survival (Benson et al, 2013). However, approximately 10% of stage I and 20% of stage II patients experience recurrence or metastasis. Moreover, pronounced heterogeneity in survival outcome is noted among patients with stage II CRC, which accounts for approximately 40% of all CRC cases. For those patients, TNM stage cannot serve as an early warning marker for postoperative metastasis or recurrence. Therefore, additional accurate prognostic and predictive markers for staging must be identified as a complement to the TNM system for postoperative adjuvant therapy.

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Received 22 October 2013; revised 2 January 2014; accepted 8 January 2014; published online 6 February 2014

REPORTS

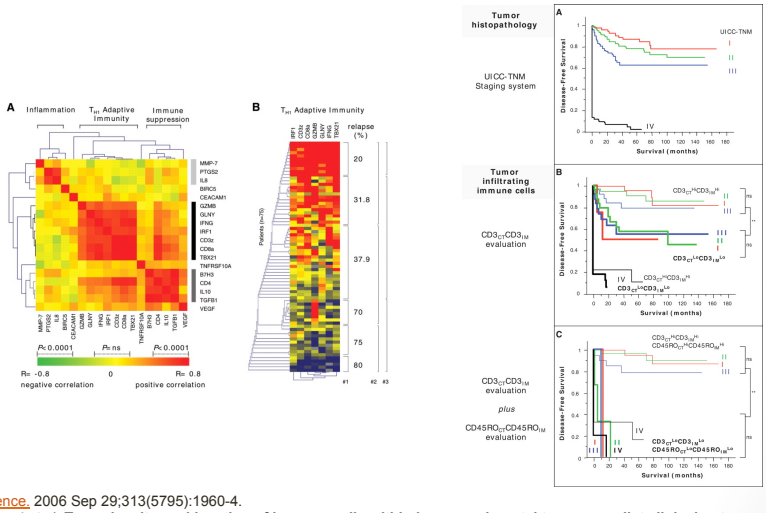
Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon,[1]* Anne Costes,[1] Fatima Sanchez-Cabo,[2] Amos Kirilovsky,[3] Bernhard Mlecnik,[3] Christine Lagorce-Pagès,[3] Marie Tosolini,[3] Matthieu Camus,[1] Anne Berger,[4] Philippe Wind,[4] Franck Zinzindohoué,[4] Patrick Bruneval,[4] Paul-Henri Cugnenc,[4] Zlatko Trajanoski,[2] Wolf-Herman Fridman,[4,5] Franck Pagès[3,5]*

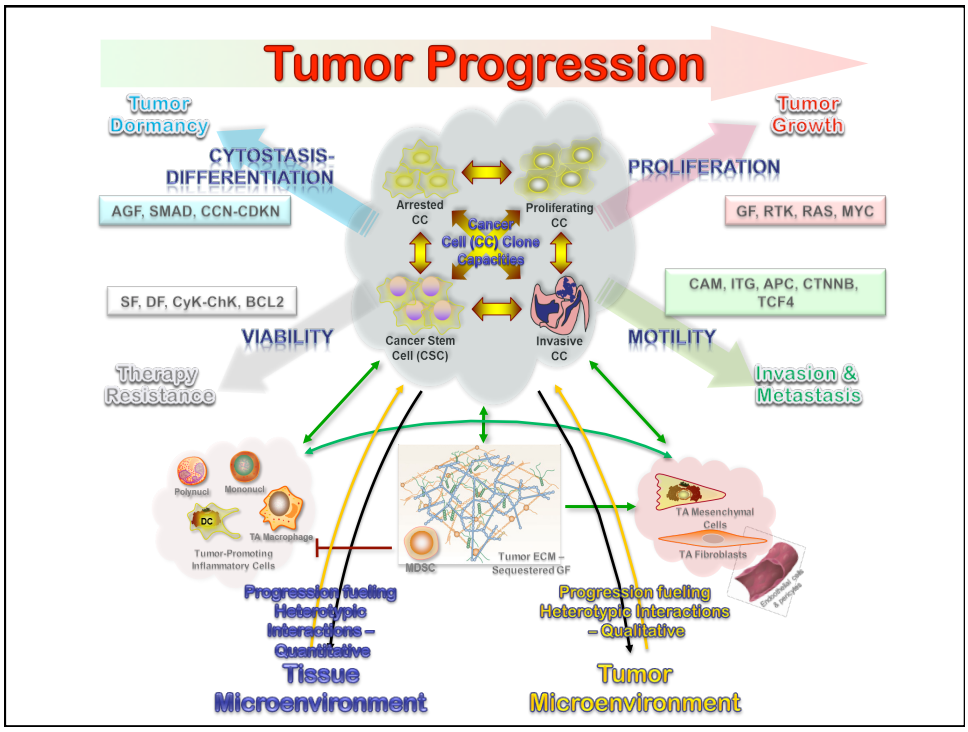
The role of the adaptive immune response in controlling the growth and recurrence of human tumors has been controversial. We characterized the tumor-infiltrating immune cells in large cohorts of human colorectal cancers by gene expression profiling and in situ immunohistochemical staining. Collectively, the immunological data (the type, density, and location of immune cells within the tumor samples) were found to be a better predictor of patient survival than the histopathological methods currently used to stage colorectal cancer. The immune signature can be established for individual patients, and these data support the hypothesis that the adaptive immune response influences the behavior of human tumors. In situ analysis of tumor-infiltrating immune cells may therefore be a valuable prognostic tool in the treatment of colorectal cancer and possibly other malignancies.

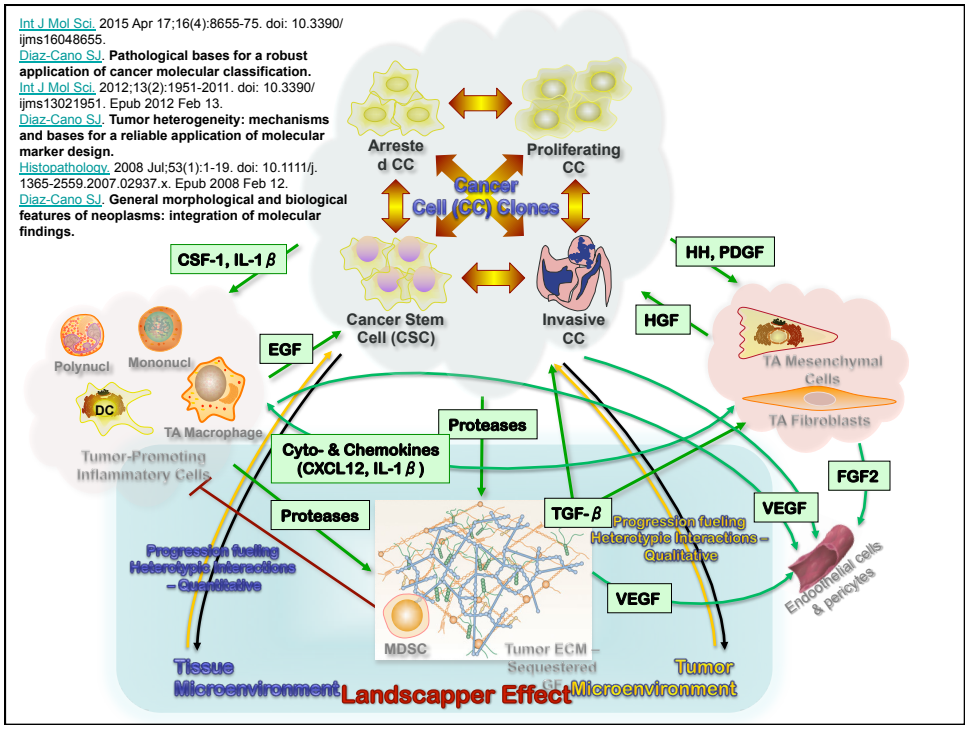
Tumors in mice and humans often contain infiltrates of immune cells. Experiments with immune-deficient mice have provided data supporting the role of adaptive immunity in cancer immunosurveillance (1–4). Tumor cells can express antigens and become targets for a T cell–mediated adaptive immune response (5, 6). The differentiation of naïve $CD4^+$ T cells into T helper type 1 (T_H1) cells producing interferon gamma (IFN-γ) promotes $CD8^+$ T cell–mediated adaptive immunity (7). In mice, immune cells appear to prevent the development of tumors and inhibit tumor progression (1, 4, 6). Anti-tumor immunity also leads to immunoediting, a process favoring the eventual outgrowth of tumor cells with reduced immunogenicity (3).

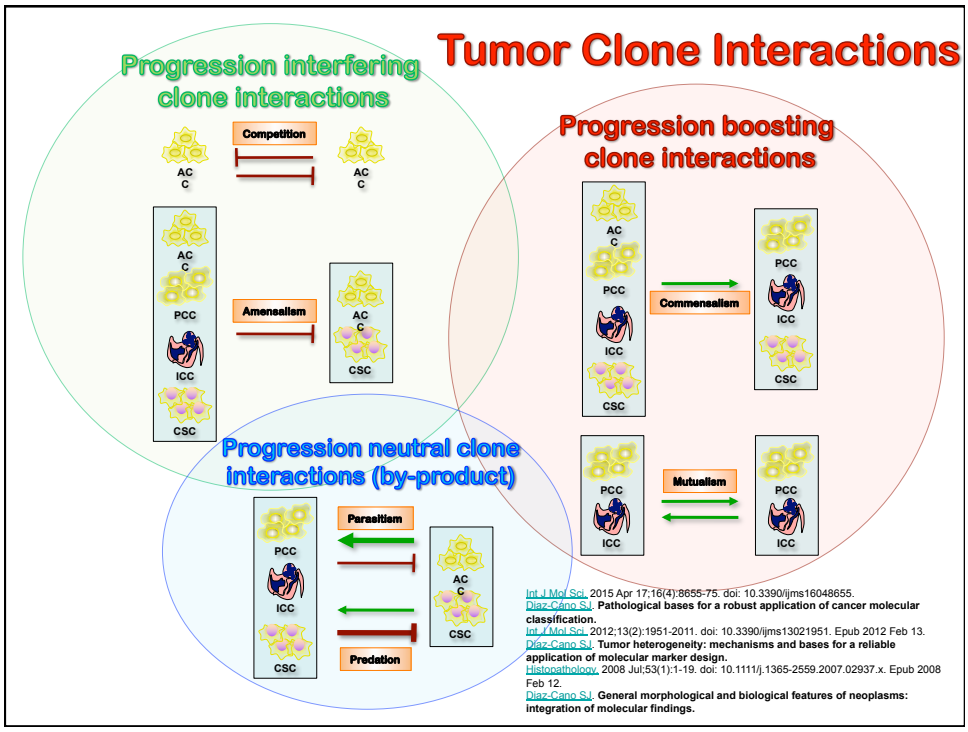
Inflammation and Cancer



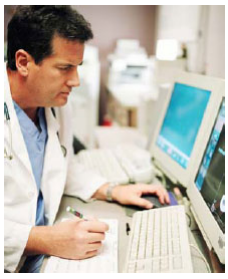
Science. 2006 Sep 29;313(5795):1960-4.
Galon J et al. **Type, density, and location of immune cells within human colorectal tumors predict clinical outcome.**


Tumor Progression
Tumor Dormancy
CYTOSTASIS-DIFFERENTIATION
AGF, SMAD, CCN-CDKN
Tumor Growth
PROLIFERATION
GF, RTK, RAS, MYC
Arrested CC
Proliferating CC
Cancer Cell (CC) Clone Capacities
Cancer Stem Cell (CSC)
Invasive CC
SF, DF, CyK-ChK, BCL2
VIABILITY
CAM, ITG, APC, CTNNB, TCF4
MOTILITY
Therapy Resistance
Invasion & Metastasis
Polynucl
Mononucl
DC
TA Macrophage
Tumor-Promoting Inflammatory Cells
MDSC
Tumor ECM – Sequestered GF
TA Mesenchymal Cells
TA Fibroblasts
Endothelial cells & pericytes
Progression fueling Heterotypic Interactions – Quantitative
Progression fueling Heterotypic Interactions – Qualitative
Tissue Microenvironment
Tumor Microenvironment


Int J Mol Sci. 2015 Apr 17;16(4):8655-75. doi: 10.3390/ijms16048655.
Diaz-Cano SJ. Pathological bases for a robust application of cancer molecular classification.
Int J Mol Sci. 2012;13(2):1951-2011. doi: 10.3390/ijms13021951. Epub 2012 Feb 13.
Diaz-Cano SJ. Tumor heterogeneity: mechanisms and bases for a reliable application of molecular marker design.
Histopathology. 2008 Jul;53(1):1-19. doi: 10.1111/j.1365-2559.2007.02937.x. Epub 2008 Feb 12.
Diaz-Cano SJ. General morphological and biological features of neoplasms: integration of molecular findings.
Arrested CC
Proliferating CC
Cancer Cell (CC) Clones
Cancer Stem Cell (CSC)
Invasive CC
CSF-1, IL-1β
HH, PDGF
HGF
EGF
Polynucl
Mononucl
DC
TA Macrophage
Tumor-Promoting Inflammatory Cells
TA Mesenchymal Cells
TA Fibroblasts
Proteases
Cyto- & Chemokines (CXCL12, IL-1β)
FGF2
VEGF
TGF-β
Progression fueling Heterotypic Interactions – Qualitative
Progression fueling Heterotypic Interactions – Quantitative
Endothelial cells & pericytes
MDSC
Tumor ECM – Sequestered GF
Tissue Microenvironment
Landscapper Effect
Tumor Microenvironment



Why Pathologists? We have access, we know testing



Personal Risk Prediction

Would like to determine patient risk for disease

Access to patient's chip results

Not so simple!!

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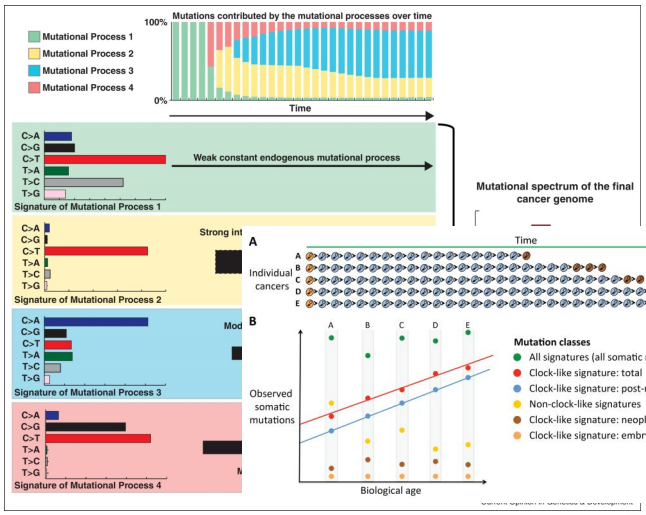
Mutational Processes – Cancer as Genomic Disease



Cell PRESS

Cell 2012 149, 979-993DOI: (10.1016/j.cell.2012.04.024)

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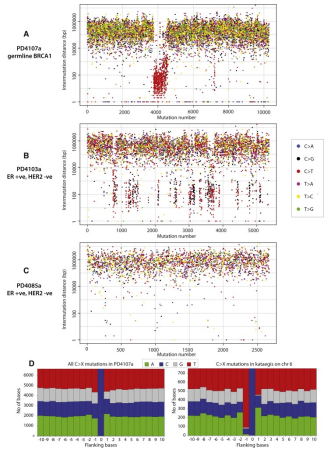
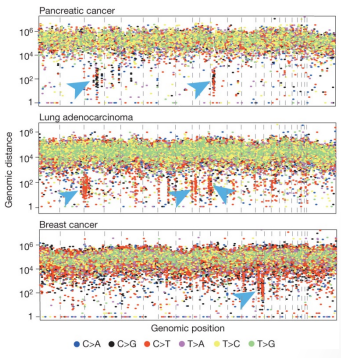
Regional Hypermutation of Base Substitutions



Kataegis in three cancers



LB Alexandrov *et al. Nature* 000, 1-7 (2013) doi:10.1038/nature12477

Cell PRESS

Cell 2012 149, 979-993DOI: (10.1016/j.cell.2012.04.024)

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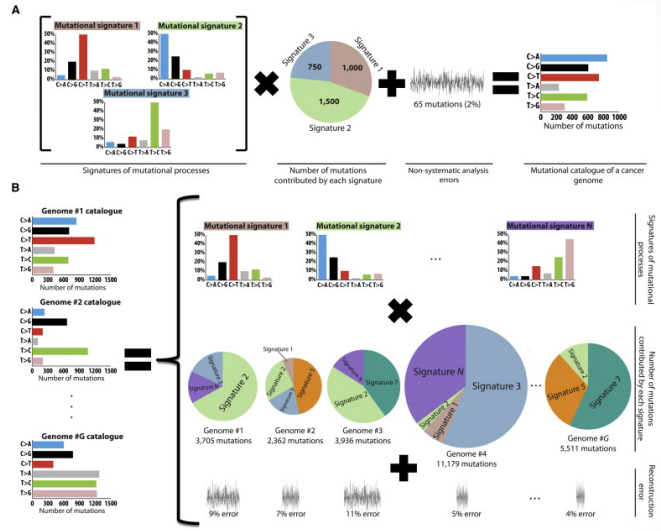
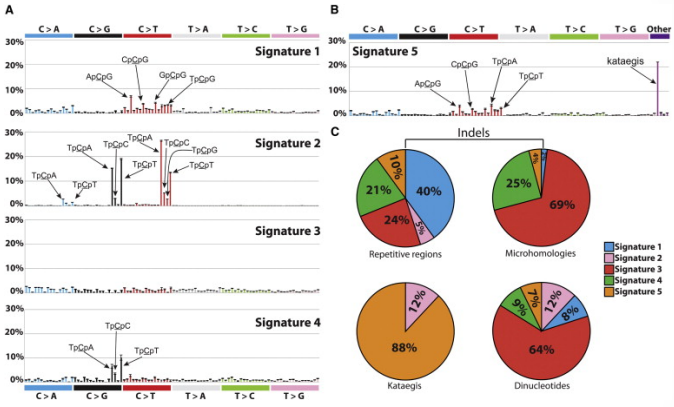
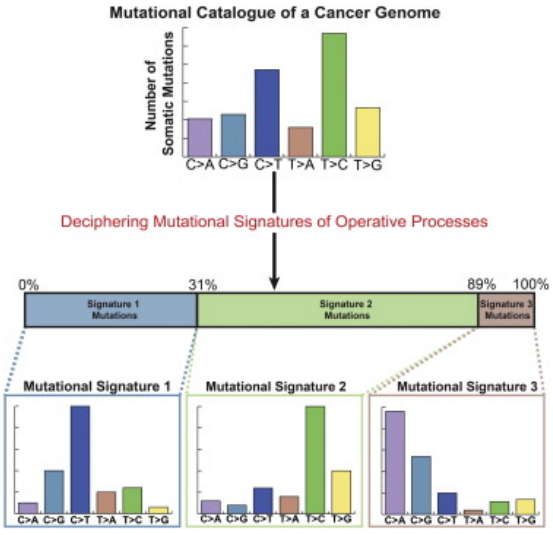


Cell Reports 2013 3, 246-259DOI: (10.1016/j.celrep.2012.12.008)

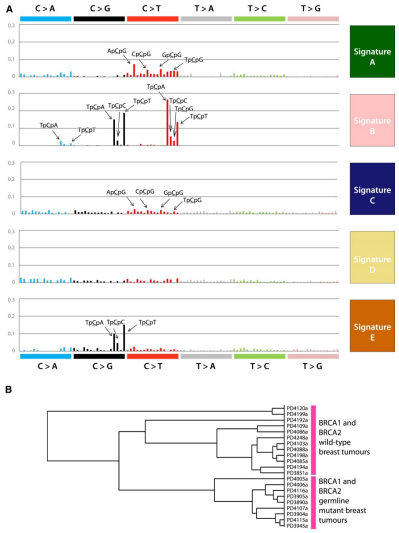


Cell Reports 2013 3, 246-259DOI: (10.1016/j.celrep.2012.12.008)

Mutational Signatures in Cancer

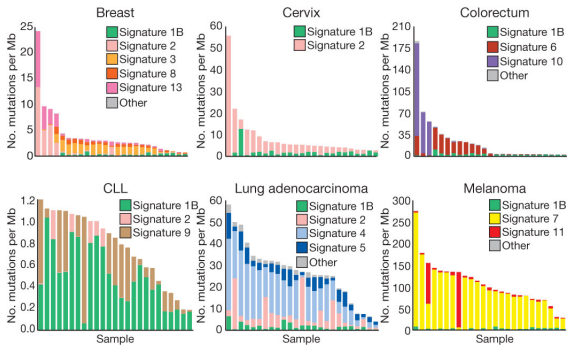


Cell PRESS *Cell Reports* 2013 3, 246-259DOI: (10.1016/j.celrep.2012.12.008)



Cell PRESS *Cell* 2012 149, 979-993DOI: (10.1016/j.cell.2012.04.024)

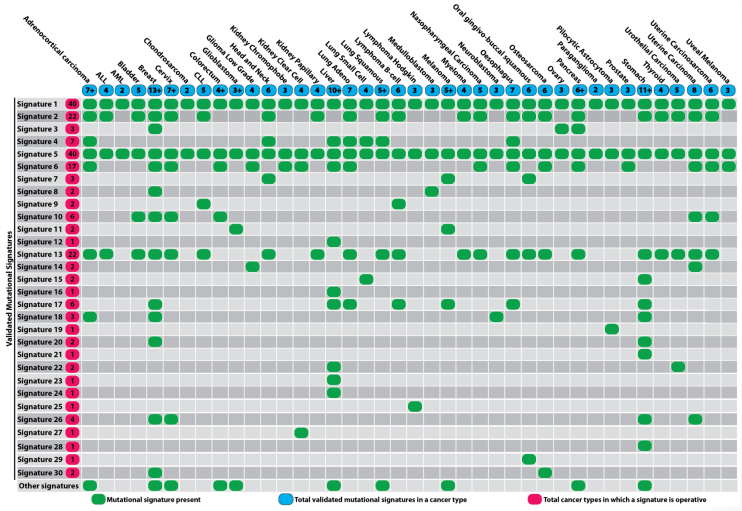
The contributions of mutational signatures to individual cancers of selected cancer types.



Nature. 2013 Aug 22;500(7463):415-21. doi: 10.1038/nature12477. Epub 2013 Aug 14.
LB Alexandrov *et al.* Signatures of mutational processes in human cancer

nature

Mutational Signatures by Cancer Subtype



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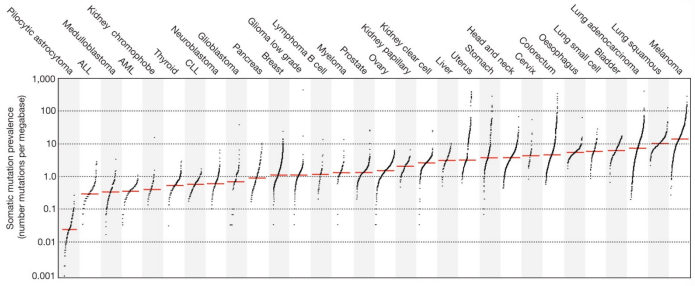
The prevalence of somatic mutations across human cancer types.



Nature. 2013 Aug 22;500(7463):415-21. doi: 10.1038/nature12477. Epub 2013 Aug 14.
LB Alexandrov *et al.* Signatures of mutational processes in human cancer

nature

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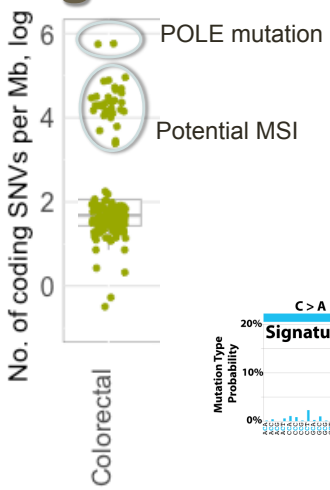
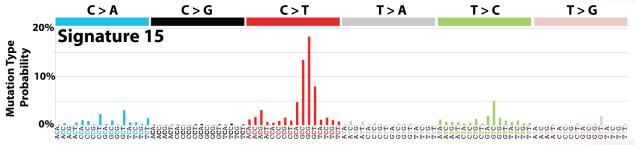
Mutational burden and signatures



Signature 1	0.58
Signature 15	0.42



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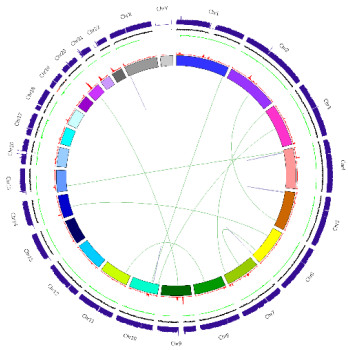
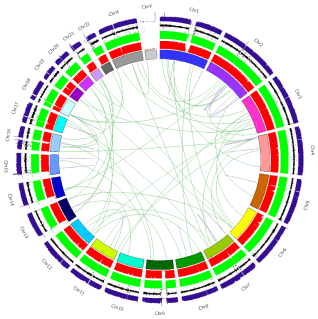
Circus plots - comparison with MMR proficient colorectal tumor

MMR proficient



MMR deficient



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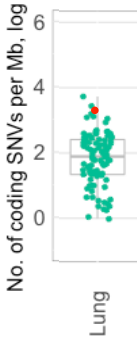
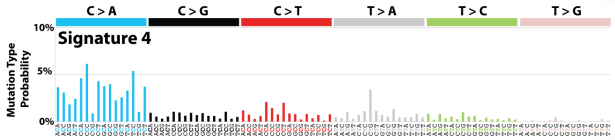
Mutational burden and signatures



Signature 4 – associated with smoking identified



Pathogenic germline cancer susceptibility variants

The following variants have been identified on analysis for pertinent germline findings (known pathogenic or likely pathogenic variants in cancer susceptibility genes relevant to the tumour type).

No pertinent germline findings detected

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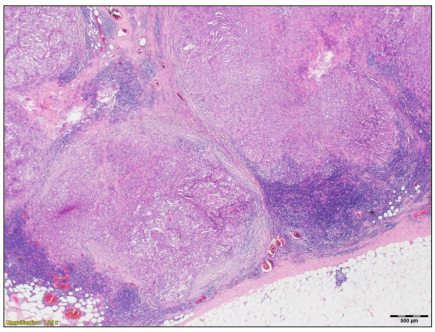

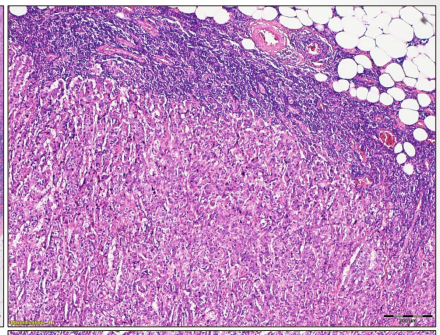

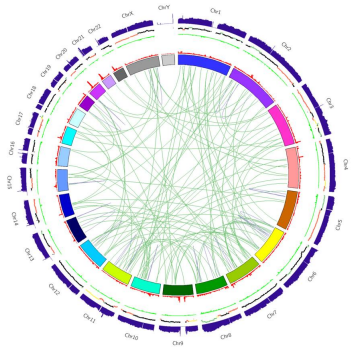

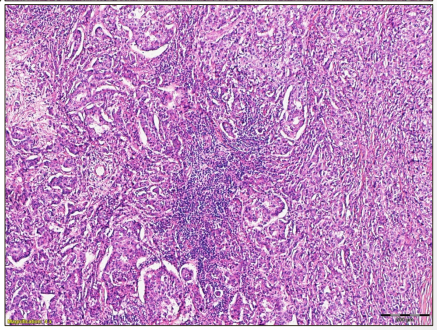

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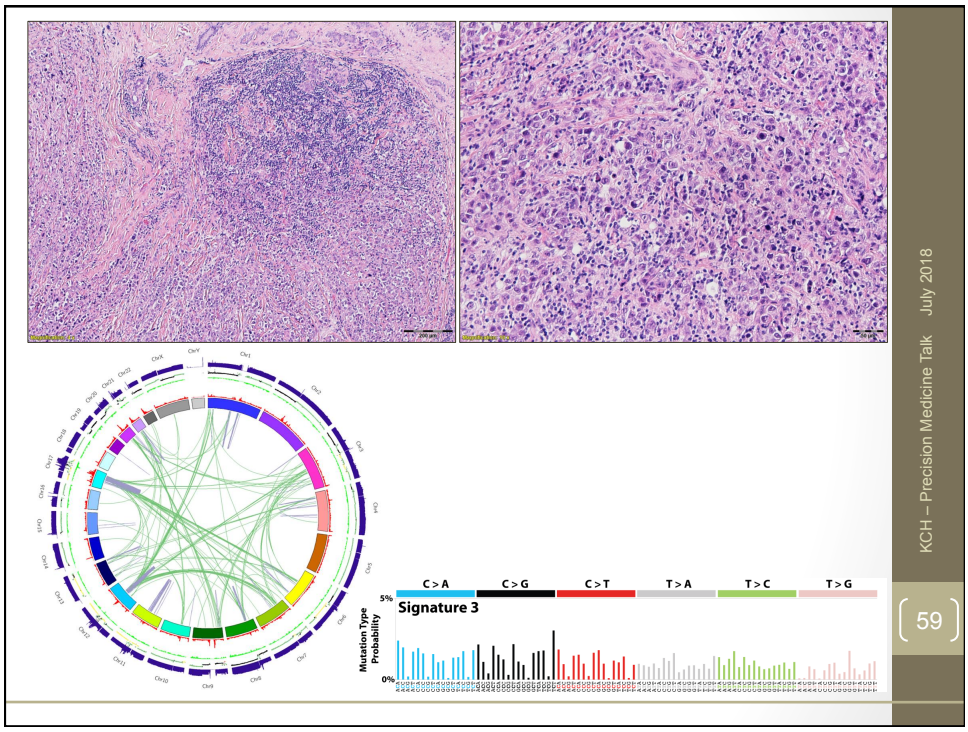
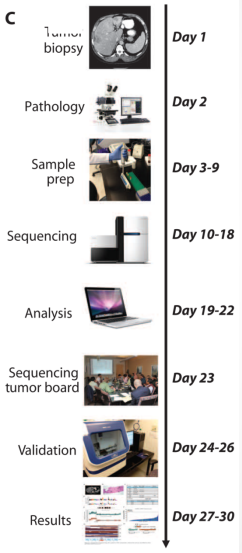


Summary

- Genomic-era technologies involve
  - Typical roles of pathologists
    - Cancer diagnosis/prognosis/guide treatment
  - New roles for pathologists
    - Predict disease risk
    - Predict drug response
  - Conceptual basis
    - Role of inflammation and grading
    - Tumor progression and microenvironment
    - Cancer as genomic disease
- Just another test
  - Issues with case-control studies
  - Issues of pre- and post-test probability
    - Accurately assessing pre-test probability
  - Need to validate



Roychowdhury S, et al. Sci Transl Med. 2011; 3: 111ra121

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