



2001

nature

www.nature.com/nature

Vol 464 | Issue no. 7289 | 1 April 2010

The human genome at ten

Nearly a decade on from the completion of the draft sequence of the human genome, researchers should work with the same intensity and focus to apply the results to health.

The knowledge about the human genome and the explosion of new tools and technologies are bringing unprecedented knowledge about genes involved in human health and disease

ORIGINAL ARTICLE

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

James R. Lupski, M.D., Ph.D., Jeffrey G. Reid, Ph.D., Claudia Gonzaga-Jauregui, B.S., David Rio Deiros, B.S., David C.Y. Chen, M.Sc., Lynne Nazareth, Ph.D., Matthew Bainbridge, M.Sc., Huyen Dinh, B.S., Chyn Jing, M.Sc., David A. Wheeler, Ph.D., Amy L. McGuire, J.D., Ph.D., Feng Zhang, Ph.D., Pawel Stankiewicz, M.D., Ph.D., John J. Halperin, M.D., Chengyong Yang, Ph.D., Curtis Gehman, Ph.D., Danwei Guo, M.Sc., Rola K. Irikat, B.S., Warren Tom, B.S., Nick J. Fantin, B.S., Donna M. Muzny, M.Sc., and Richard A. Gibbs, Ph.D.

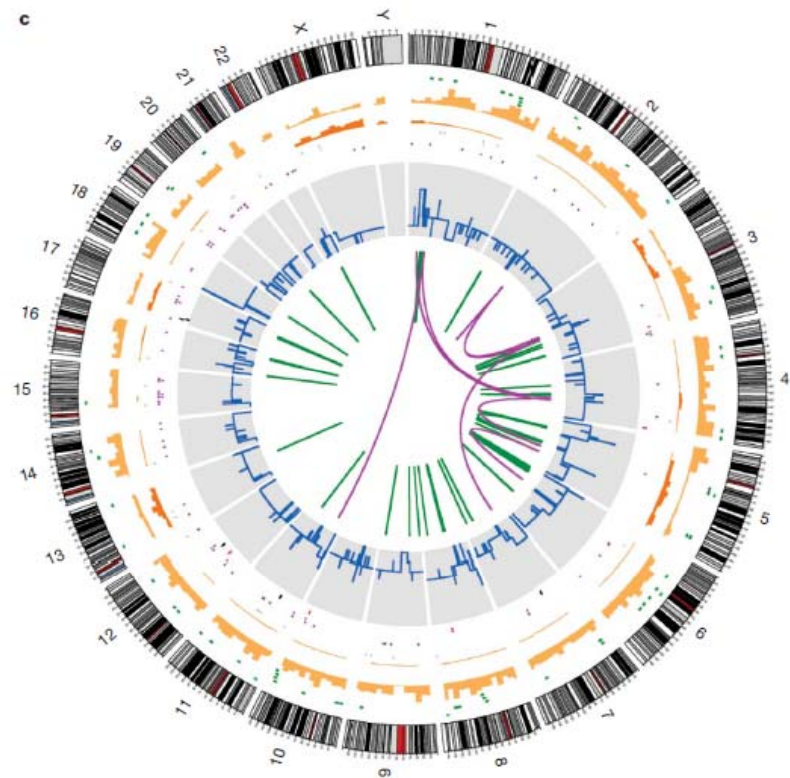
N Engl J Med 2010;362:1181-91.

ARTICLES

A small-cell lung cancer genome with complex signatures of tobacco exposure

Erin D. Pleasance¹, Philip J. Stephens¹, Sarah O'Meara^{1,2}, David J. McBride¹, Alison Meynert³, David Jones¹, Meng-Lay Lin¹, David Beare¹, King Wai Lau¹, Chris Greenman¹, Ignacio Varela¹, Serena Nik-Zainal¹, Helen R. Davies¹, Gonzalo R. Ordoñez¹, Laura J. Mudie¹, Calli Latimer¹, Sarah Edkins¹, Lucy Stebbings¹, Lina Chen¹, Mingming Jia¹, Catherine Leroy¹, John Marshall¹, Andrew Menzies¹, Adam Butler¹, Jon W. Teague¹, Jonathon Mangion², Yongming A. Sun⁴, Stephen F. McLaughlin⁵, Heather E. Peckham⁵, Eric F. Tsung⁵, Gina L. Costa⁵, Clarence C. Lee⁵, John D. Minna⁶, Adi Gazdar⁶, Ewan Birney³, Michael D. Rhodes⁴, Kevin J. McKernan⁵, Michael R. Stratton^{1,7}, P. Andrew Futreal¹ & Peter J. Campbell^{1,8}

Cancer is driven by mutation. Worldwide, tobacco smoking is the principal lifestyle carcinogenicity through >60 chemicals that bind and mutate DNA. Using mass sequencing a small-cell lung cancer cell line, NCI-H209, to explore the mutational burden, a total of 22,910 somatic substitutions were identified, including 134 in coding exons. The effects of transcription-coupled repair and a second, more general, expression-linked repair mechanism were identified. A tandem duplication that duplicates exons 3–8 of *CHD7* in frame, and fusion genes, indicating that *CHD7* may be recurrently rearranged in this disease. Next-generation sequencing to provide unprecedented insights into mutational processes associated with cancer.

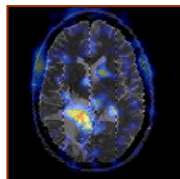




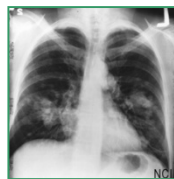
TCGA: Connecting multiple sources, experiments, and data types

Three forms of cancer

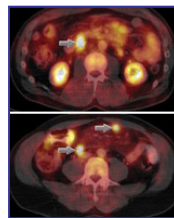
glioblastoma multiforme (brain)



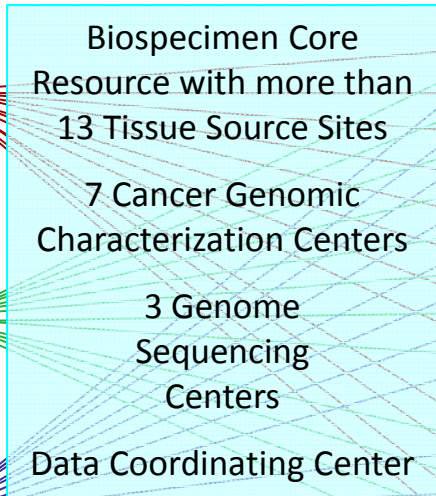
squamous carcinoma (lung)



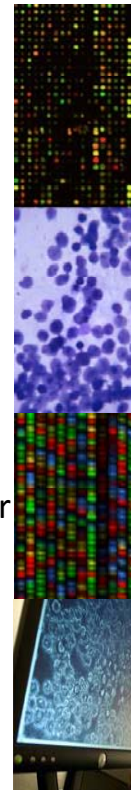
serous cystadenocarcinoma (ovarian)



Multiple data types

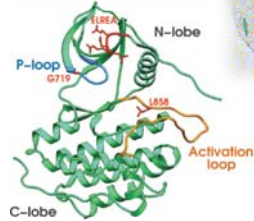
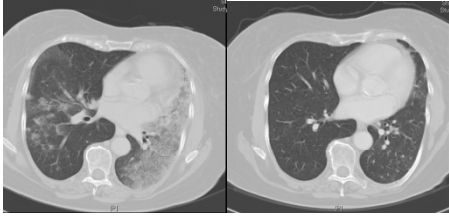


- Clinical diagnosis
- Treatment history
- Histologic diagnosis
- Pathologic status
- Tissue anatomic site
- Surgical history
- Gene expression
- Chromosomal copy number
- Loss of heterozygosity
- Methylation patterns
- miRNA expression
- DNA sequence



20 Solid tumor types-500 cases/500 controls each

Before 2.5 Years



No small molecule or biologics available

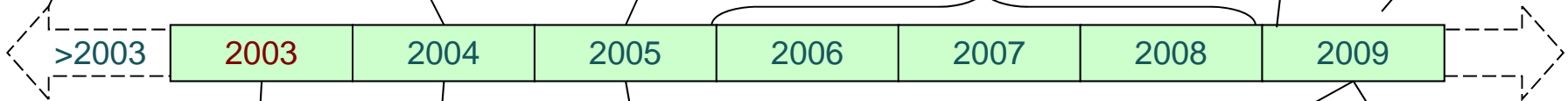
Tarceva approved on Phase III data. Increase in median PFS 7 weeks

Iressa Phase III trials failed; FDA changes label & limits distribution

PFS for EGFR+ patients treated with Tyrosine Kinase Inhibitors greater than 18 months

In EGFR mutation negative patients, Chemotherapy better than Tyrosine Kinase Inhibitors

Iressa approved in EU with EGFR test



Iressa approved based on Phase II data RR 11-18%

EGFR mutations can predict responsiveness

K-Ras mutations and some EGFR mutations confer resistance

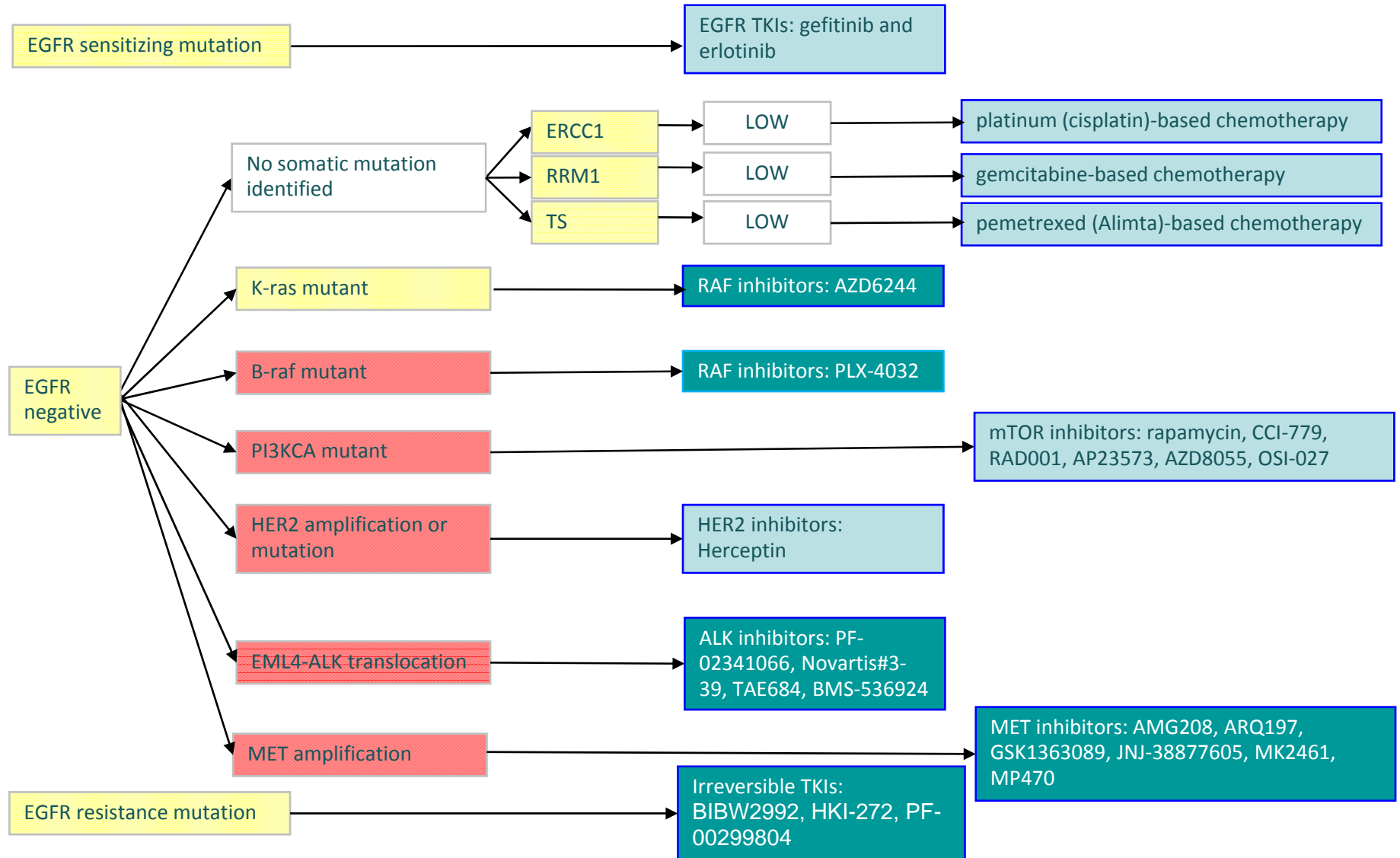


Some EGFR negative patients have ERBB2 mutations (therapy with Herceptin)

Some EGFR negative patients have ALK4 activation (therapy with PF-2341066)

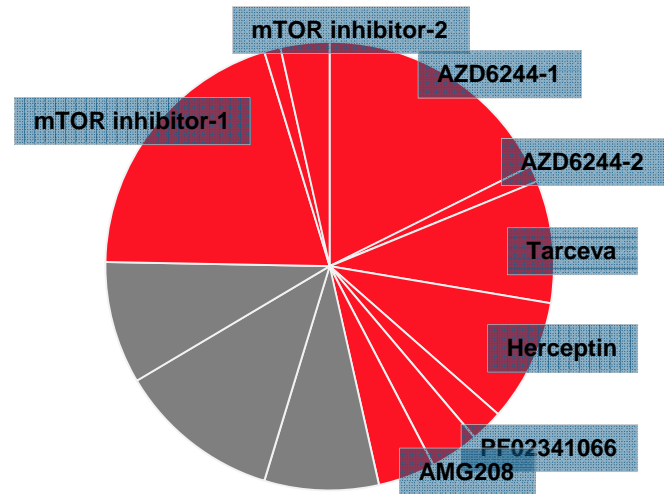
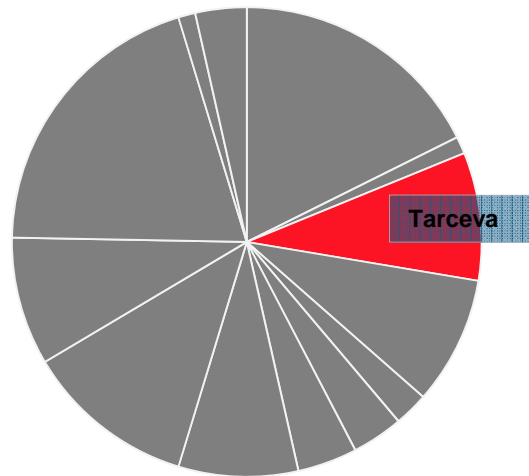
Emerging approaches for Non-small Cell Lung Cancer

Test for mutations in EGFR, K-RAS, B-RAF, PIK3CA, HER2, EML4-ALK, and MET



TODAY

2-3 YEARS

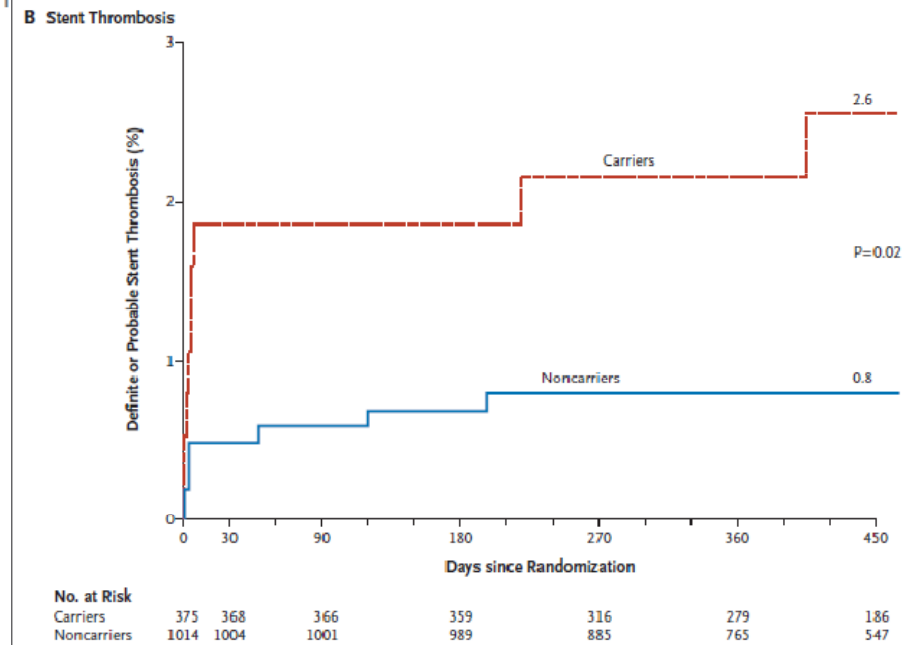


ORIGINAL ARTICLE

Cytochrome P-450 Polymorphisms and Response to Clopidogrel

Jessica L. Mega, M.D., M.P.H., Sandra L. Close, Ph.D., Stephen D. Wiviott, M.D.,
Lei Shen, Ph.D., Richard D. Hockett, M.D., John T. Brandt, M.D.,
Joseph R. Walker, Pharm.D., Elliott M. Antman, M.D.,
William Macias, M.D., Ph.D., Eugene Braunwald, M.D.,
and Marc S. Sabatine, M.D., M.P.H.

CYP2C19



Personalized Medicine at Point of Care

- **Integrate patient's genomic profile with clinical data. Ensure clinical, molecular data incorporated into medical record in usable format**
- **Educate physicians**
- **Support physician decisions**
 - Guide physician to appropriate molecular diagnostics
 - Support interpretation of test results



Physician Education

- Training in Medical School through the clinical years
- Training in Residency programs
- Continuing Medical Education