ESMO 2012
Special Symposium
The impact of the cancer genome project and high-throughput analyses on personalised oncology: Today and tomorrow

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The International Cancer Genome Consortium
(2008-today; 16 countries)

Goals:

- ✓ **catalogues of somatic mutations in 500 tumours in 50 different cancer types and/or subtypes (25,000 tumors)**

- ✓ **Make the data available to the entire research community**

International Cancer Genome Consortium

The Cancer Genome Atlas

- 20 cancer types

  (poor prognosis and overall public health impact)
- Approx. 2,500 cancer samples sequenced

1. The mutation load in cancer is abundant

- ✓ **Some cancer genomes carry up-to 100,000 point mutations**
- ✓ **Not all are relevant to cancer**

  Driver mutations have been positively selected and confer growth advantage on the cells ('cancer genes') (5–7 predicted)

  Passenger mutations were present when cancer cells acquired the drivers and do not confer growth advantage
- ✓ **300-400 genes show recurrent somatic mutations in cancer with strong evidence that contribute to cancer development (cancer genes)**
- ✓ **Statistical and functional evidence in favour of many more driver mutations (less selective growth advantage?)**
- ✓ **Studies in mice have suggested that more than 2,000 genes, when appropriately altered, may have the potential to contribute to cancer development**

Hundreds of tumors of the same tumor subtype are to be sequenced to identify all recurrent mutations (>5%)

2. The mutation load in cancer is heterogenous

- ✓ **Number of mutations:** from 1,000 to 100,000 point mutations

- ✓ **Distribution of mutations among tumor types:** low frequency of common mutations (10% of colon cancers with BRAF mutation)

- ✓ **Type of mutations:** Point mutations of coding or non-coding DNA; Inter- and intra-chromosomal rearrengements; copy number variations

Ex.: whole genome sequencing of a lung cancer genome
-23,000 point mutations
- only 134 (0.6%) in exomes

Q.: What do the other 22,776 mutations represent? (some are recurrent)

Many cancer genome projects sequence exomes (financial constraints)

Whole-genome sequences of hundreds of tumors are needed

3. Chemotherapy changes the cancer genome

- ✓ induces mutations
  (gliomas that recur after temozolomide carry huge numbers of mutations)
- ✓ Recurrences are clonal
- ✓ Resistance-associated mutations might be present
  at onset in rare tumor clones

4. Rare cancer-predisposing genes can be identified

(>5% allelic frequency; e.g. PALB2 and pancreatic cancer)

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5. Cancer-relevant mutations of mitochondrial genomes (unclear role in cancer development)

6. Unknown oncogenic DNA viruses

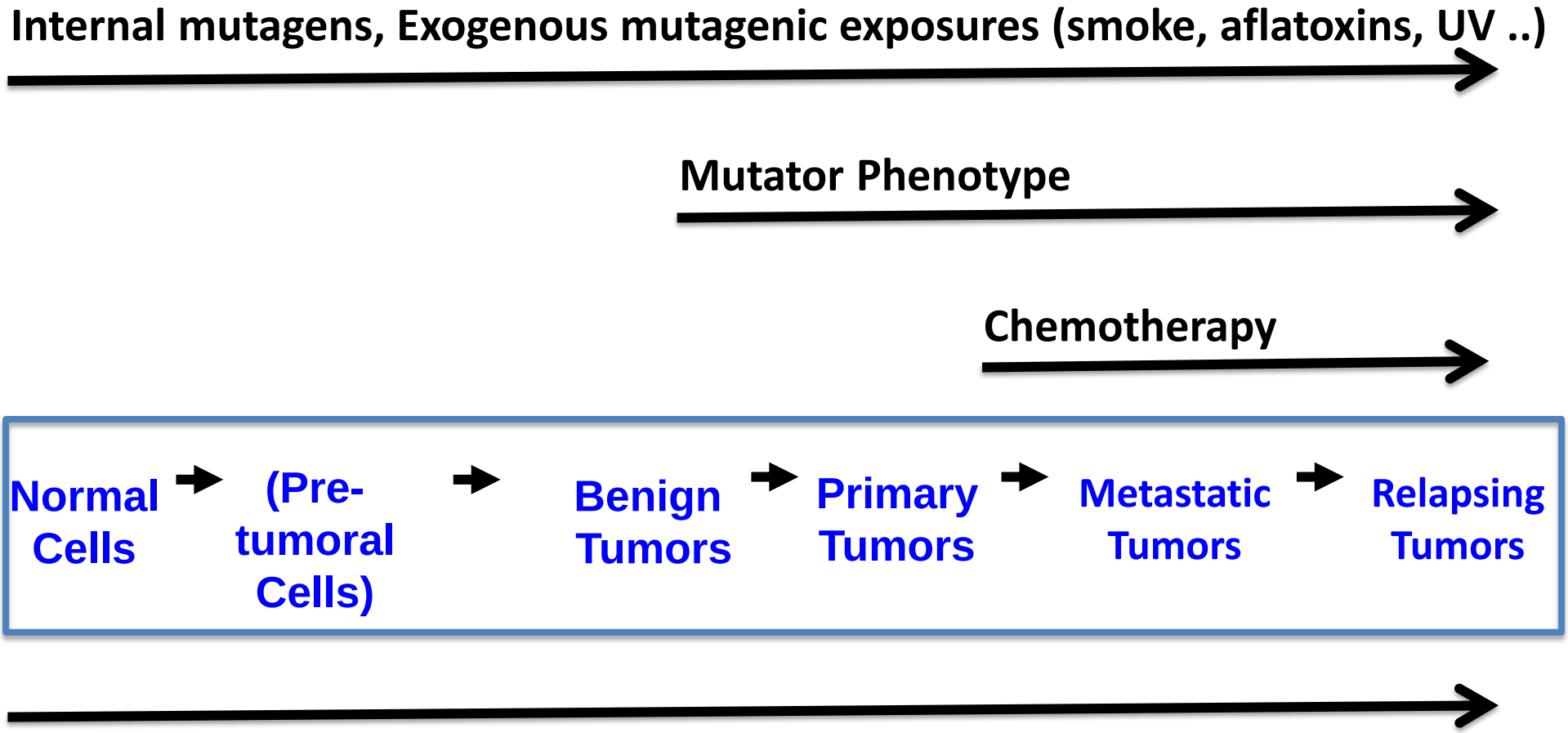
Benefits of cancer-genome projects for patients (biomarkers of clinical utility)

- ✓ **Identification of new prognostic markers**
  Ex: as IDH1 and IDH2 mutations in several types of gliomas

- ✓ **Identification of new therapeutic targets (druggable mutations)**
  Ex: PIK3CA14, BRAF15,EGFR mutations, NF1, KDR10, PIK3R1, histone methyltransferases and demethylases.

More sophisticated clinical trials are needed (that deconvolute tumor-phenotype complexity)

Genomes of tumors at different stages of development



Adaptation to the changing environment is mediated by epigenomic changes

Upstream signals:

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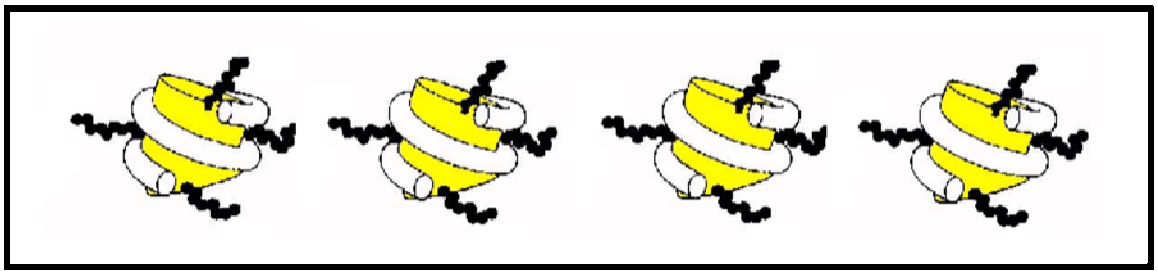
Enzyme-catalyzed (HDAC, HAT, HMT, DNMT)
chromatin modifications
(permanent or transient)



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Regulation of transcription, replication,
Genome stability

Epigenomic changes:

- ✓ are inherited (through mitosis or the germline)
- ✓ are causally linked to oncogenesis
- ✓ might be molecular markers of the carcinogenic effects of specific environmental factors and lifestyles

The International Human Epigenomic Consortium (2011-on)

Goal:

to decipher at least 1000 epigenomes within the next 7-10 years (DNA methylation, histone modifications, chromatin accessibility; coding and non-coding RNAs)

Conclusions:

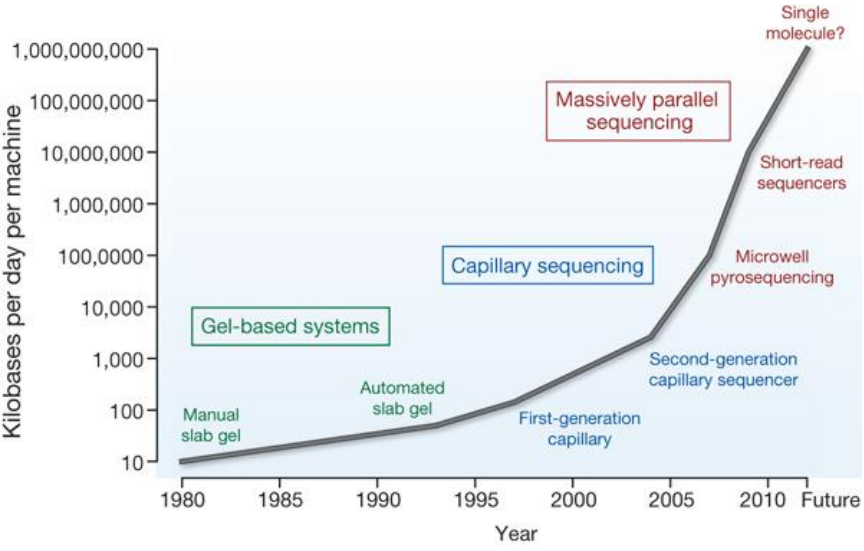
- ✓ **More cancer genomes need to be sequenced (WGA, epigenomes)**

- ✓ **Clinical trials needed to test validity of the identified biomarkers (prognosis, treatment stratification)**

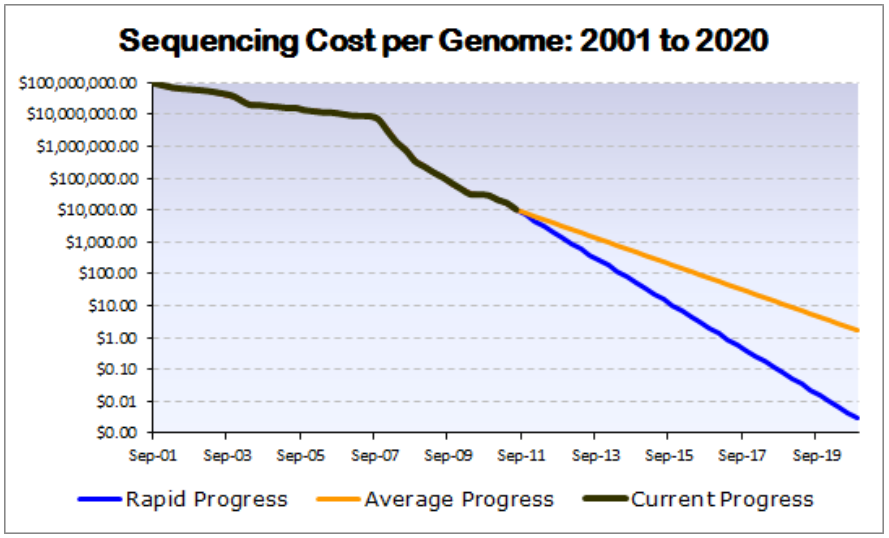
Expected*: Routine genome-sequence as part of the clinical evaluation of cancer patients and as part of their continuing clinical management *(PERSONALIZED ONCOLOGY)

Not so distant future……

From 10 to 1 billion Kb/day



From 100 bill to 10,000 $



Improvements in the rate and costs of DNA sequencing over the past 10-20 years and into the future