

The molecular road map of HCC

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No Disclosure

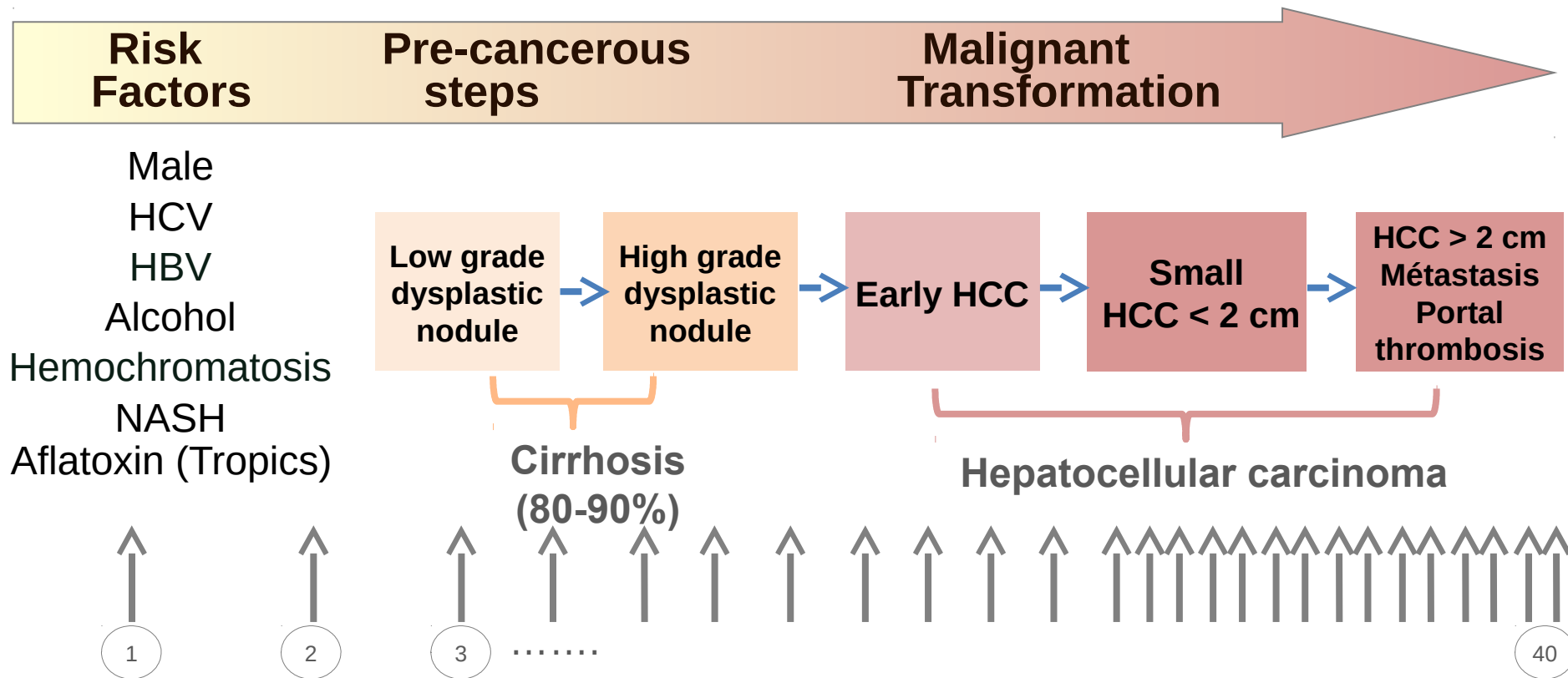
Jessica Zucman-Rossi

Inserm U1162 lab:

« Functional Genomics of solid tumors »

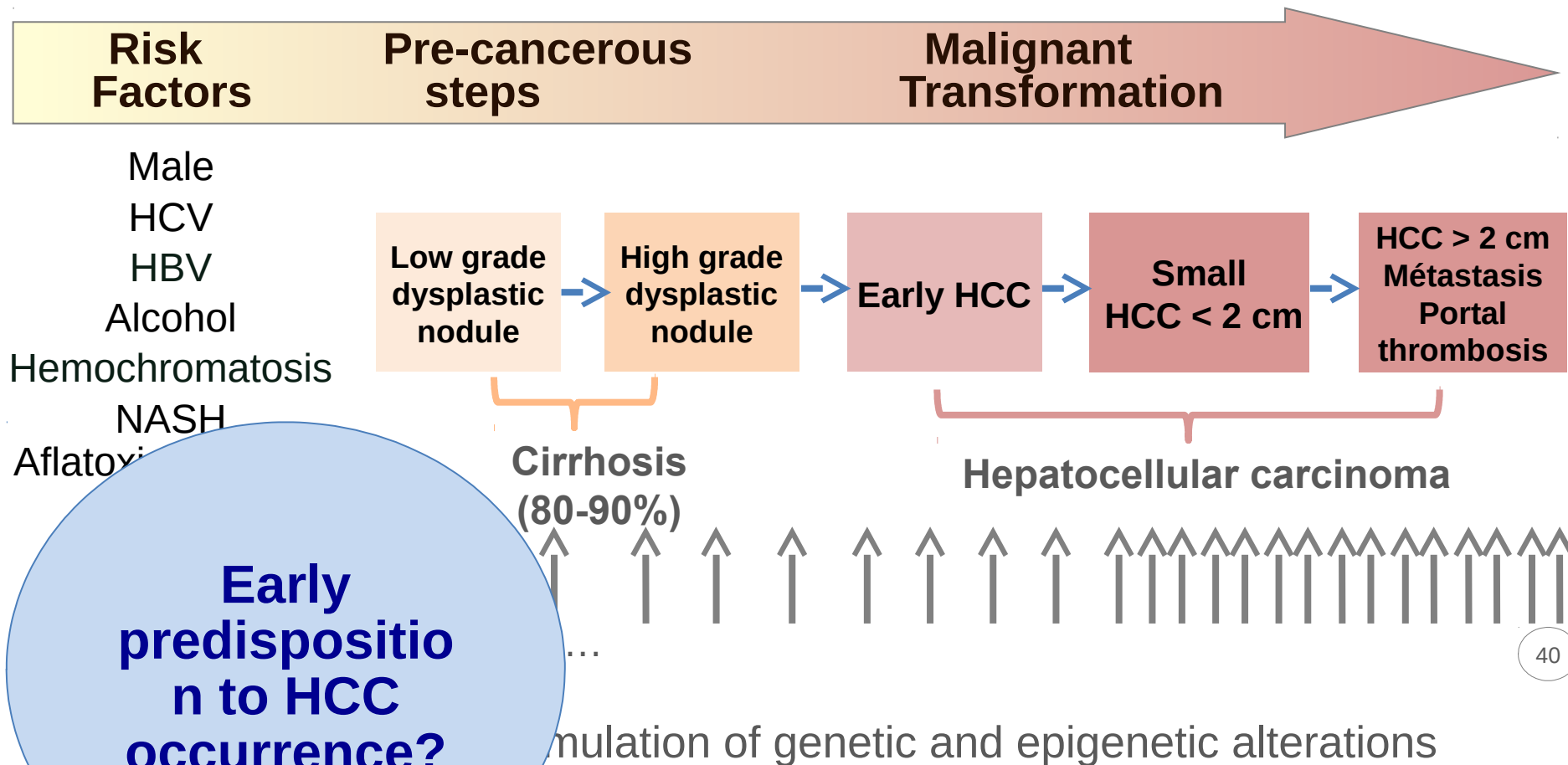
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Hepatocarcinogenesis is a multistep disease

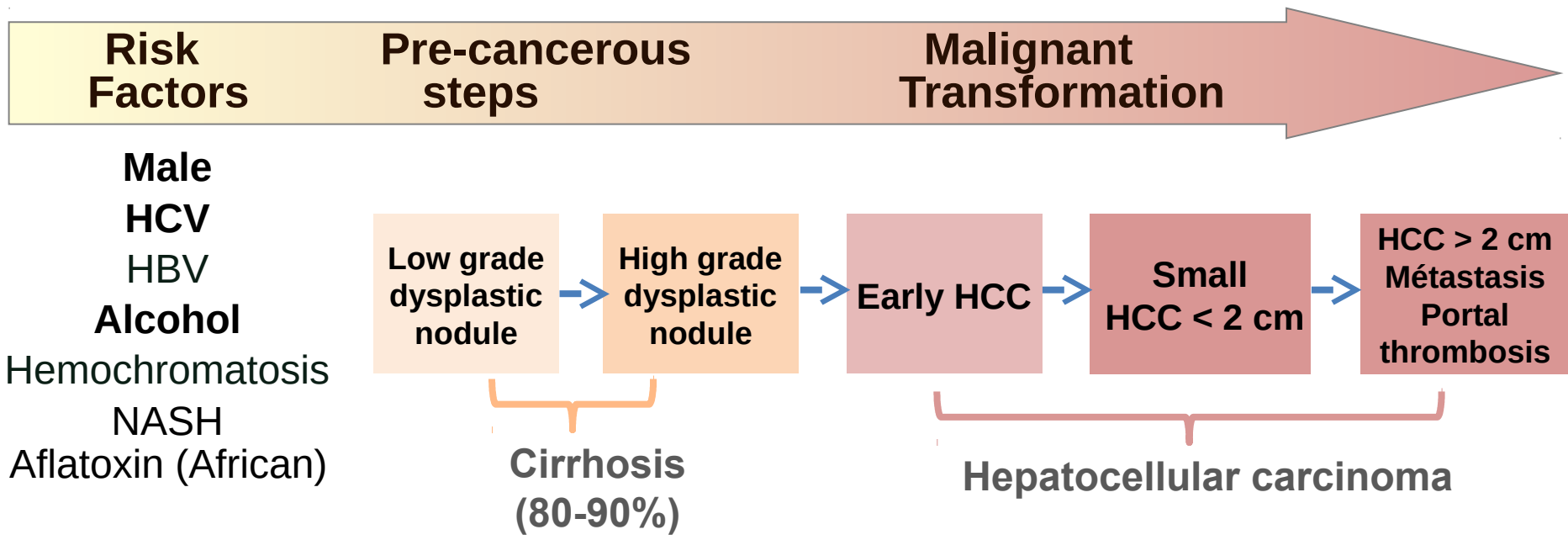


Replicative senescence Oxydative stress
Telomerase reactivation

Hepatocarcinogenesis is a multistep disease



Hepatocarcinogenesis is a multistep disease



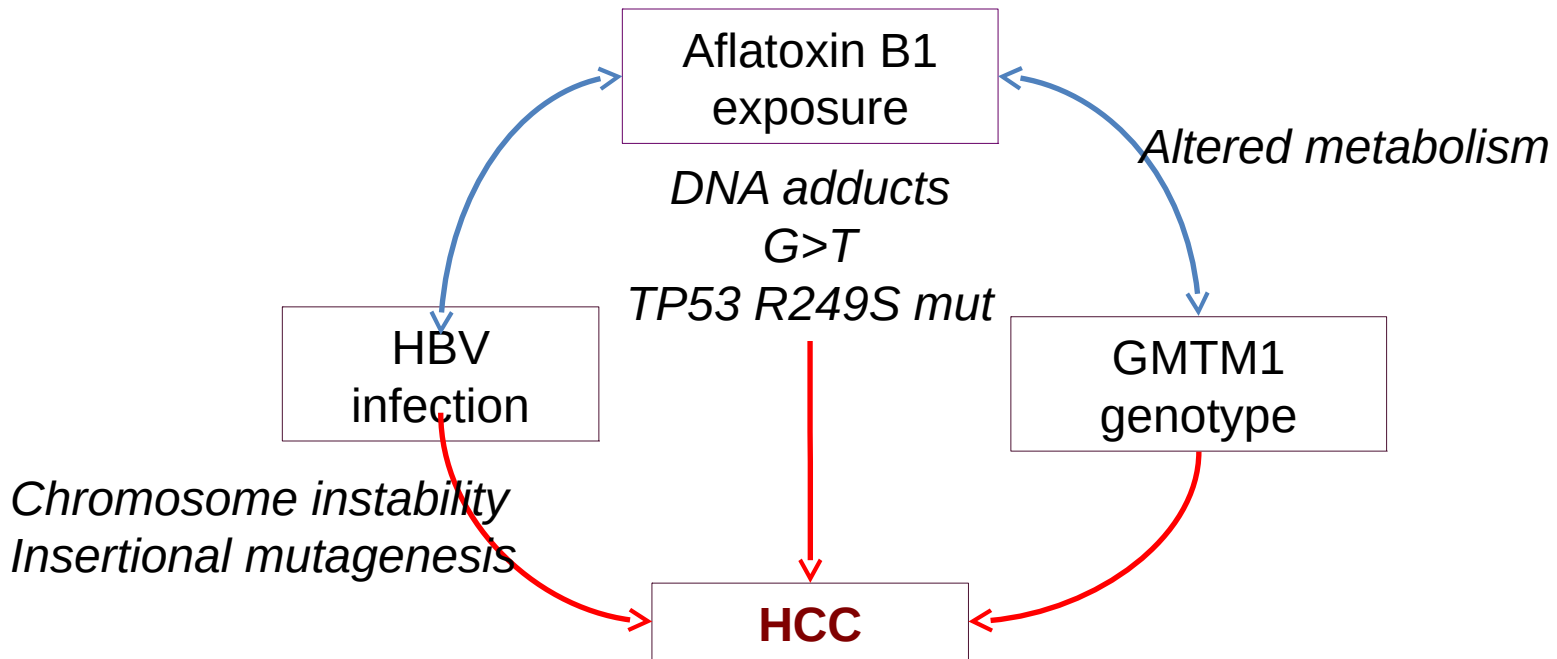
Genetic predisposition:

- EGF 61*G
- MICA,
- PNPLA3, TM6SF2
- MPO
- CAT
- HFE.....

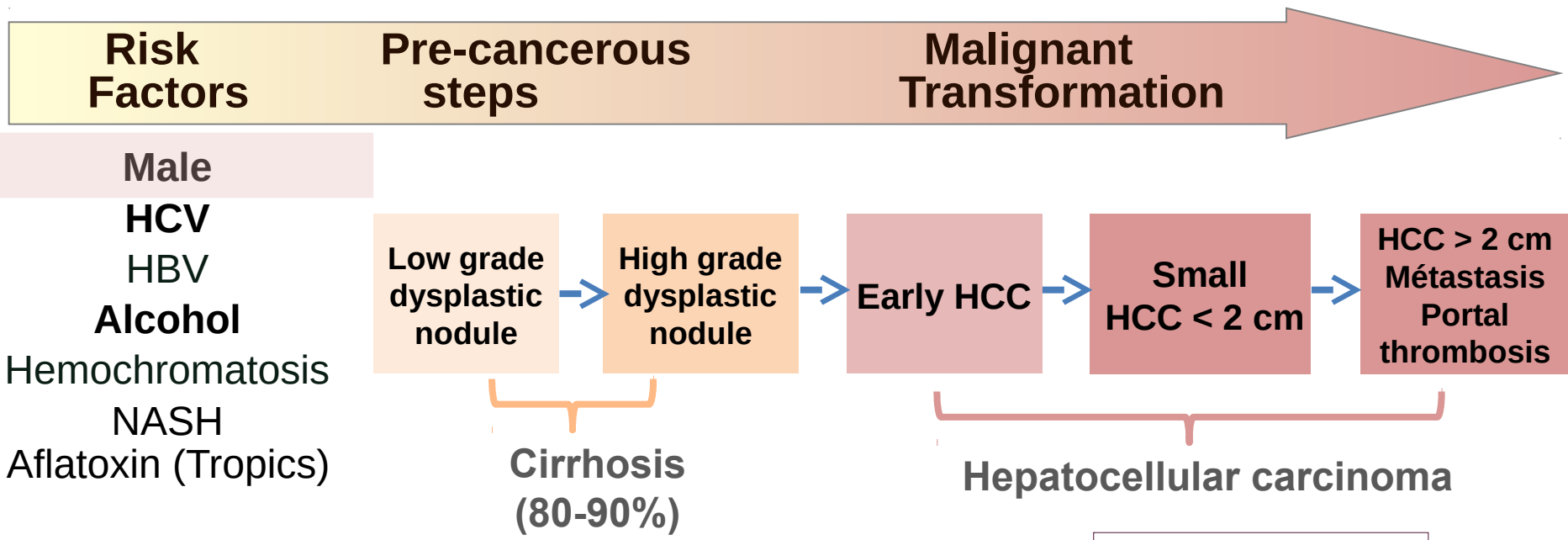
Genetic variants ↔ Risk factors

Reviewed in Goossens et al, 2015; Nahon, zucman-rossi, J Hepatol

Exposure and genetic variant cooperation: the AFB1 example

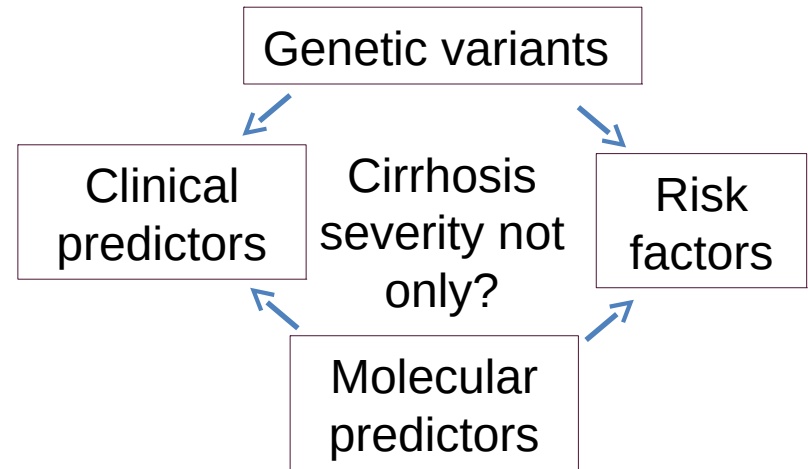


Hepatocarcinogenesis is a multistep disease

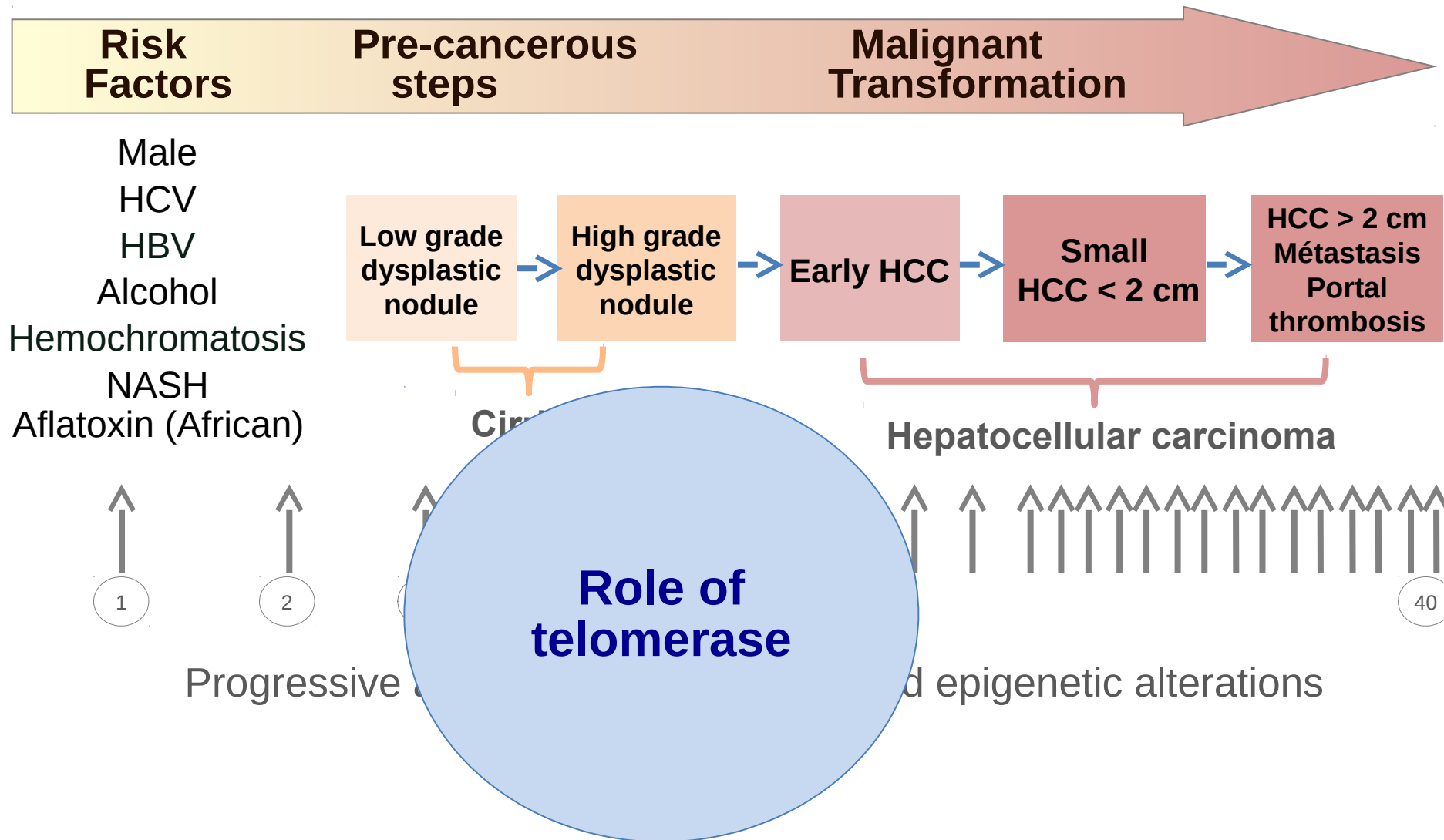


« Molecular predisposition »:

- 186-Gene signature (Hoshida et al, NEJM 2009)
- Activated HSC (HBV, Ji Hepatology 2015)
- HIR and 65-Gene signature (HBV, Kim, Plos Med 2014)



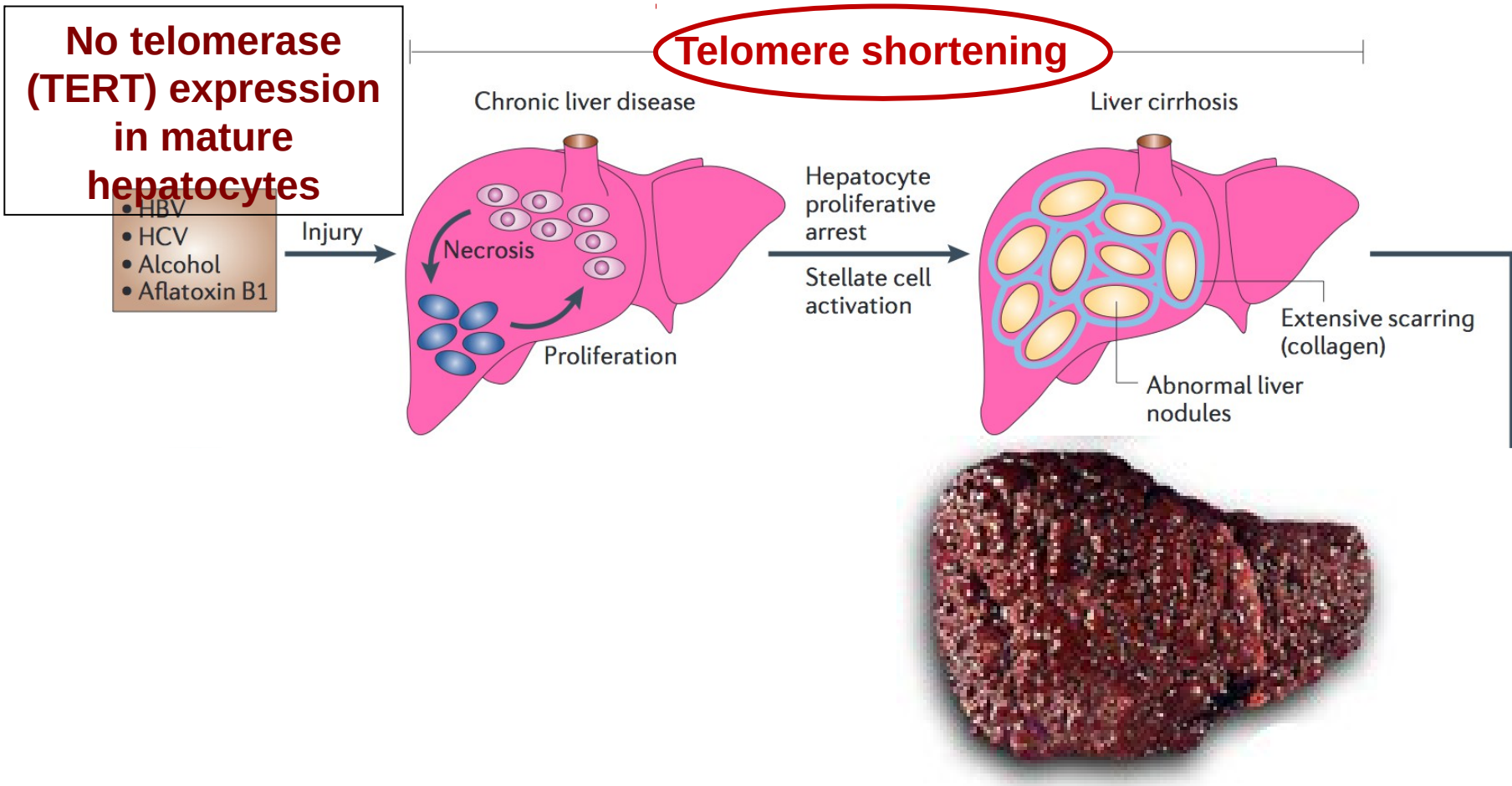
Hepatocarcinogenesis is a multistep disease



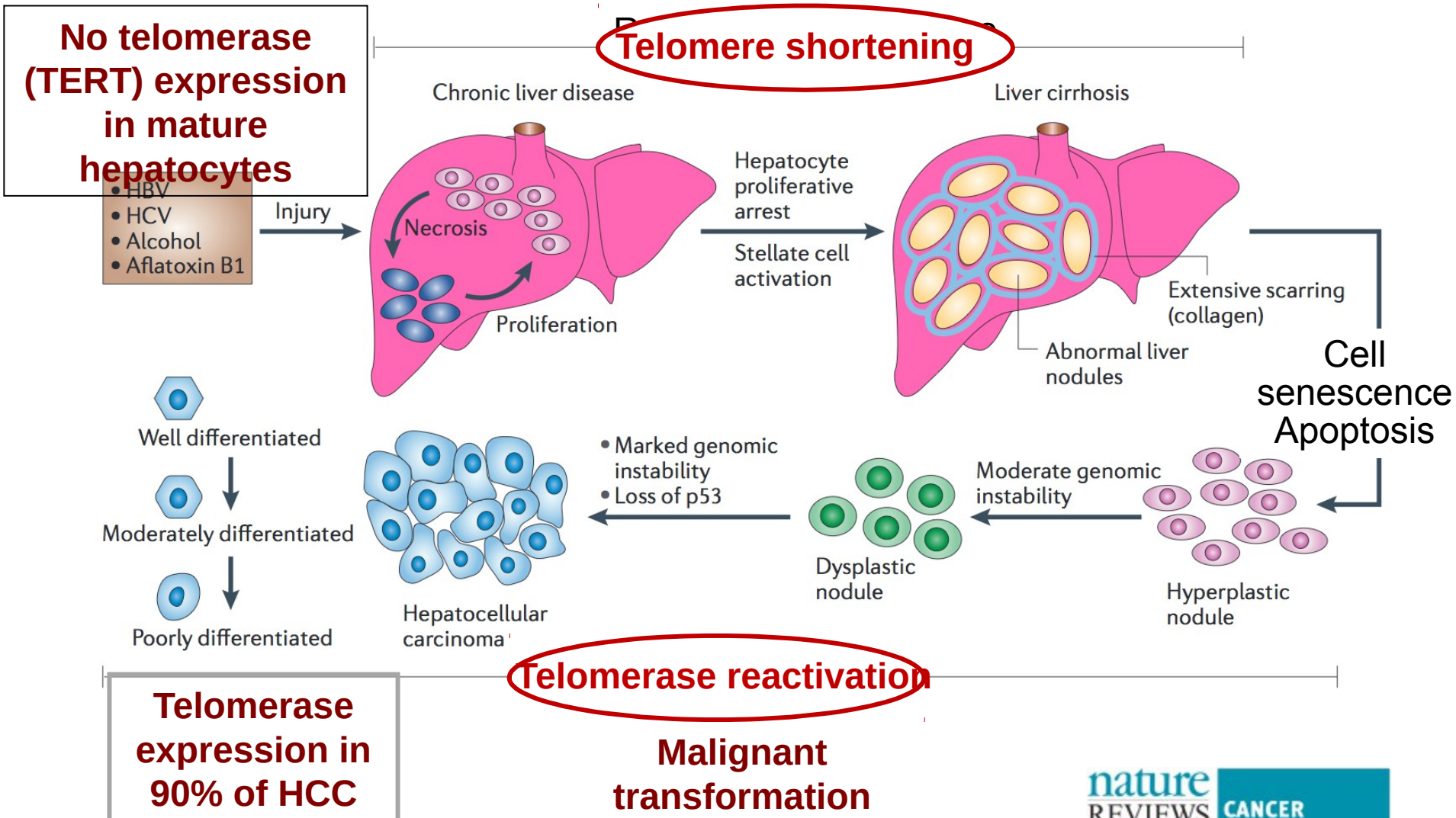
Dual role of telomeres and telomerase in liver carcinogenesis

**No telomerase
(TERT) expression
in mature
hepatocytes**

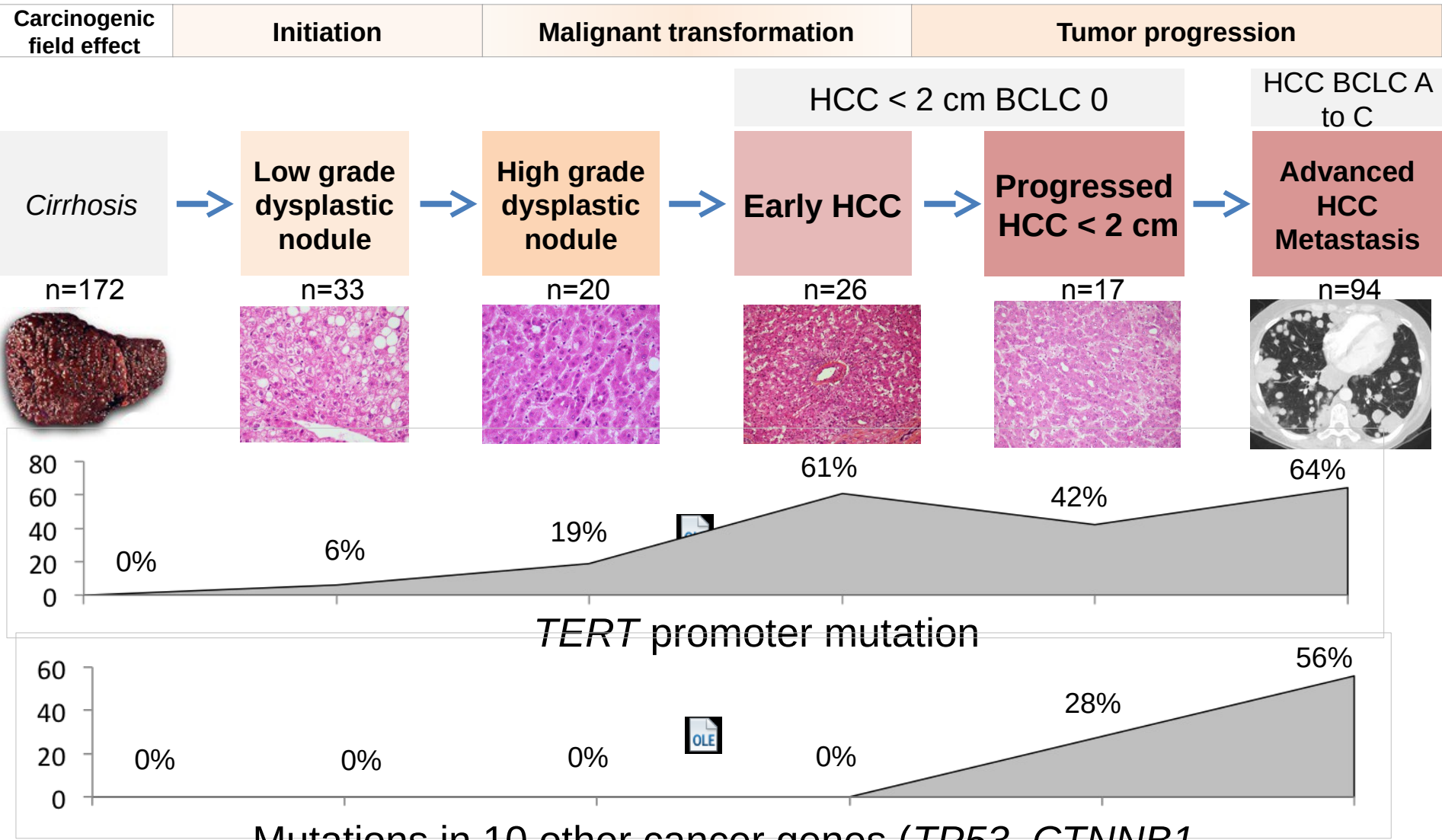
Dual role of telomeres and telomerase in liver carcinogenesis



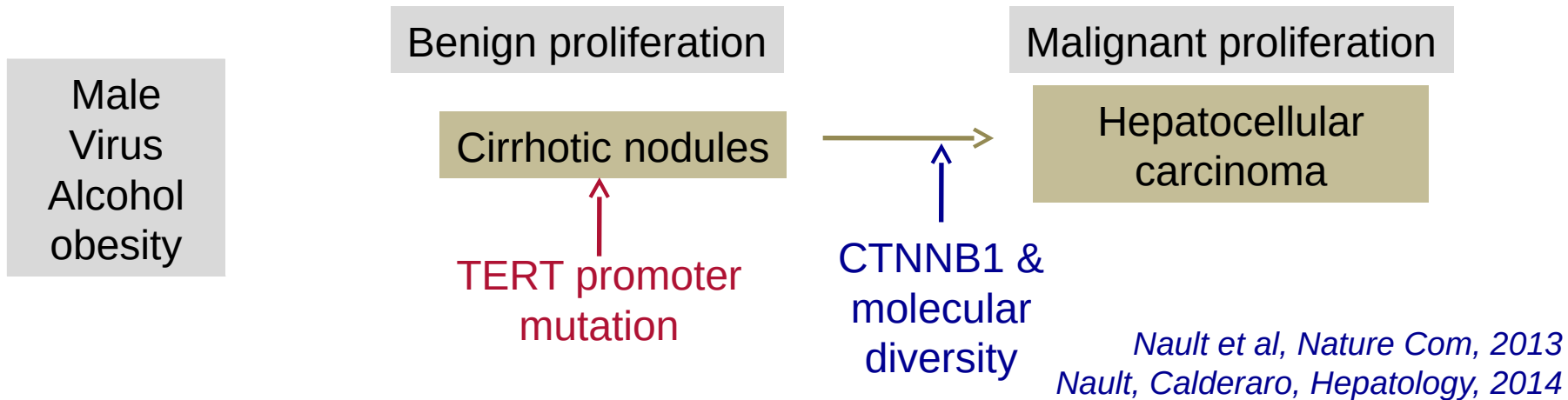
Dual role of telomeres and telomerase in liver carcinogenesis



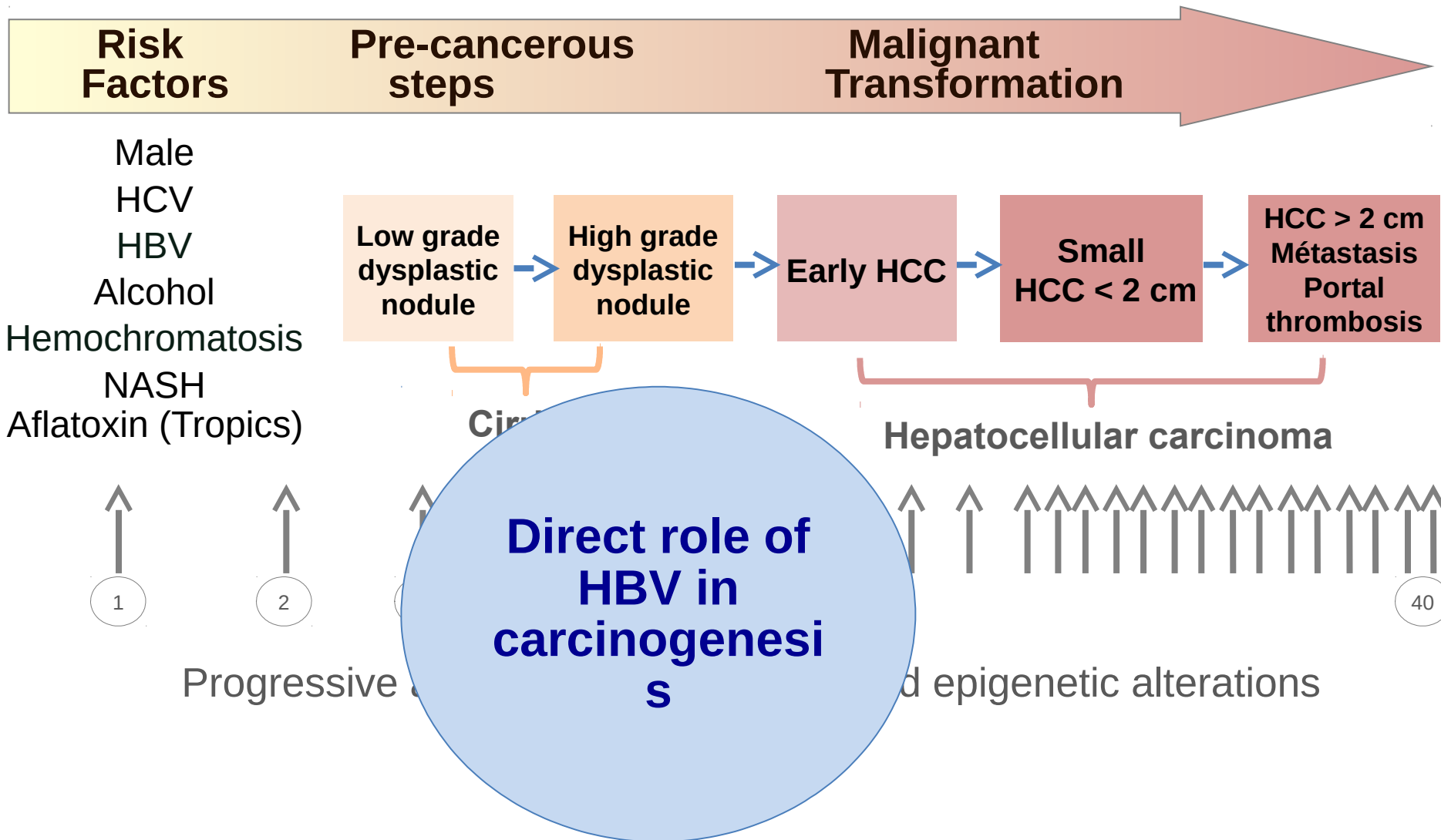
Role of TERT promoter mutation in malignant progression



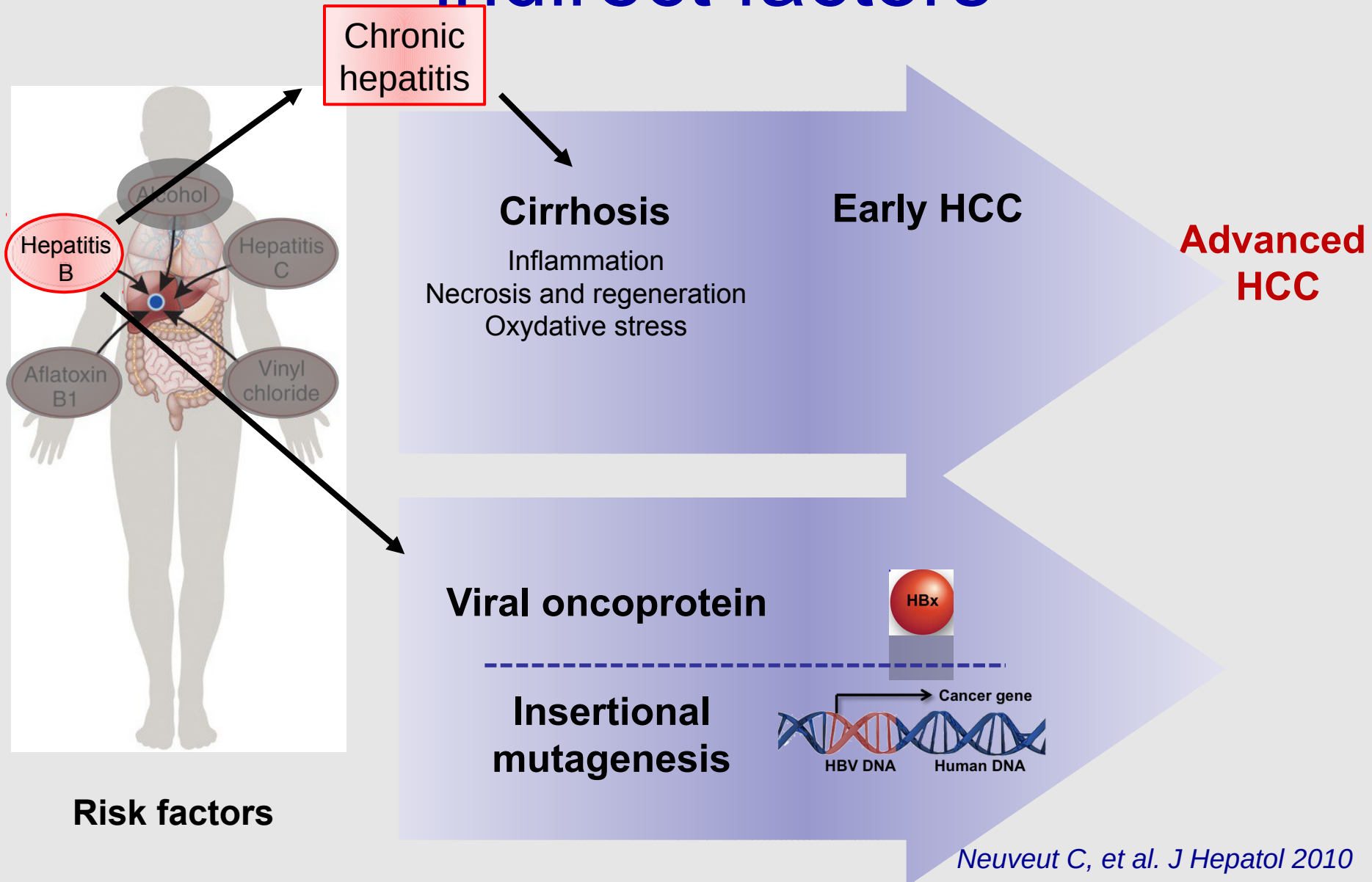
Telomerase promoter mutation is the earliest recurrent genomic alteration in HCC



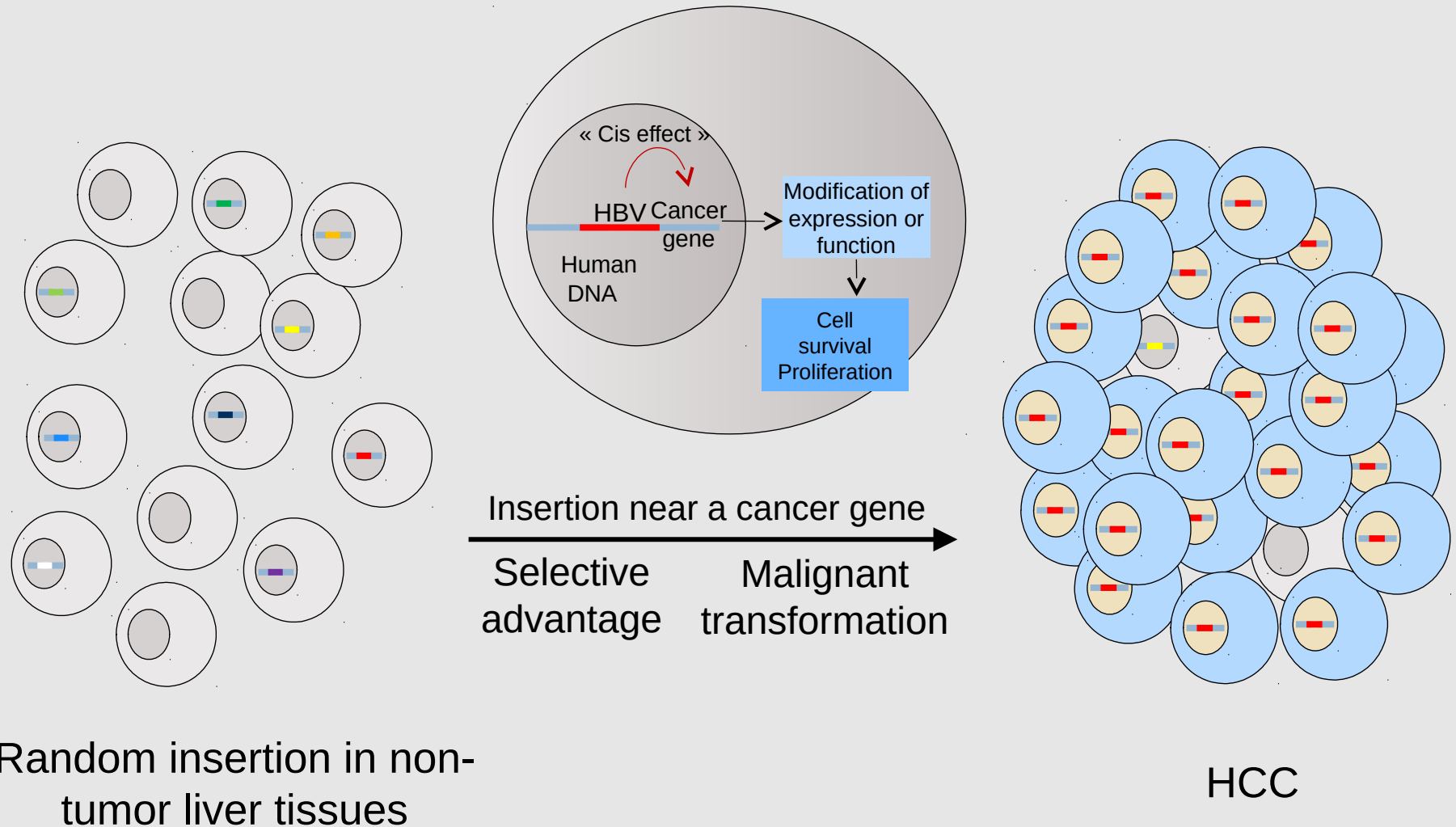
Hepatocarcinogenesis is a multistep disease



Chronic HBV infection: direct and indirect factors



HBV integration plays an important role to induce genome mutagenesis



Random insertion in non-tumor liver tissues

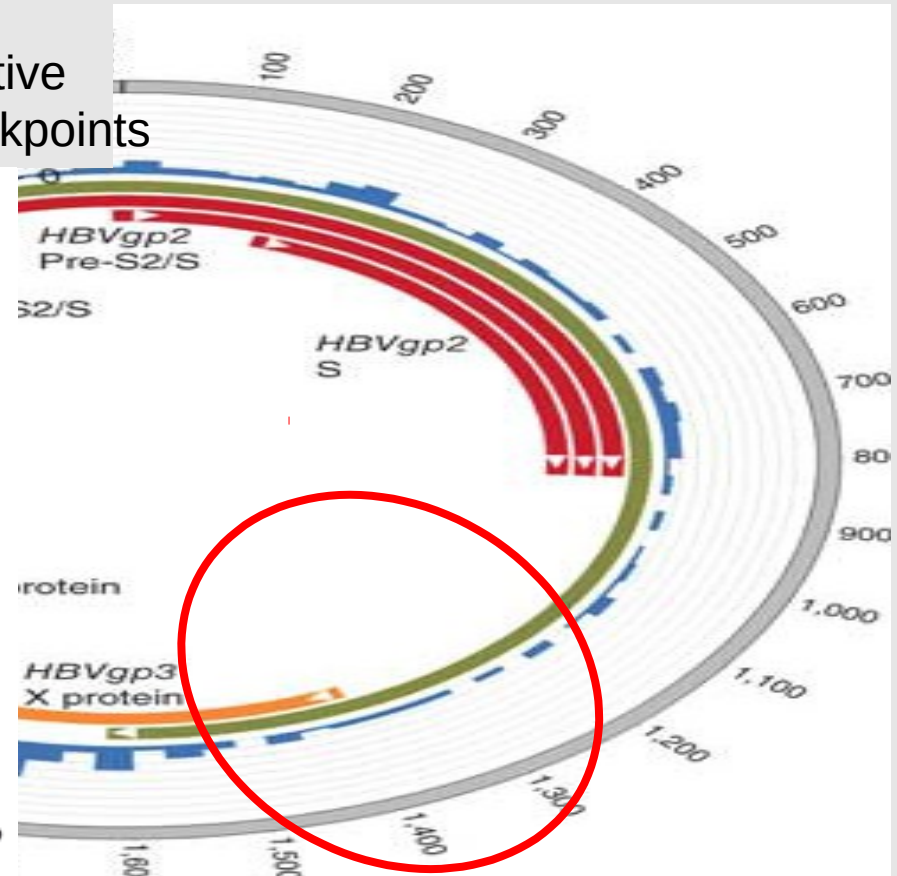
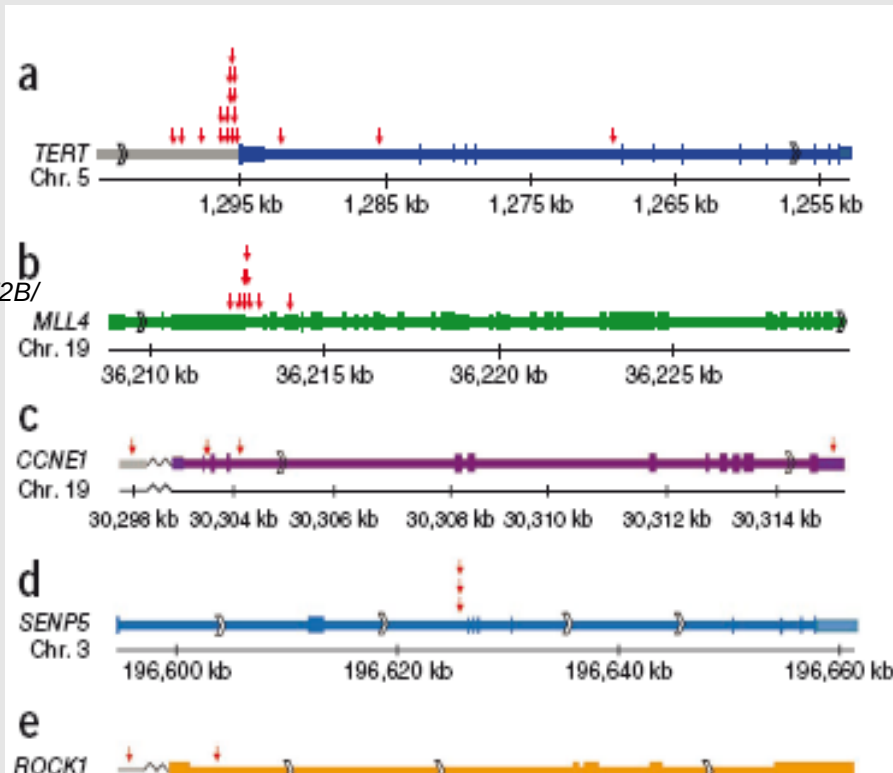
HCC

HBV integration plays an important role to induce genome mutagenesis



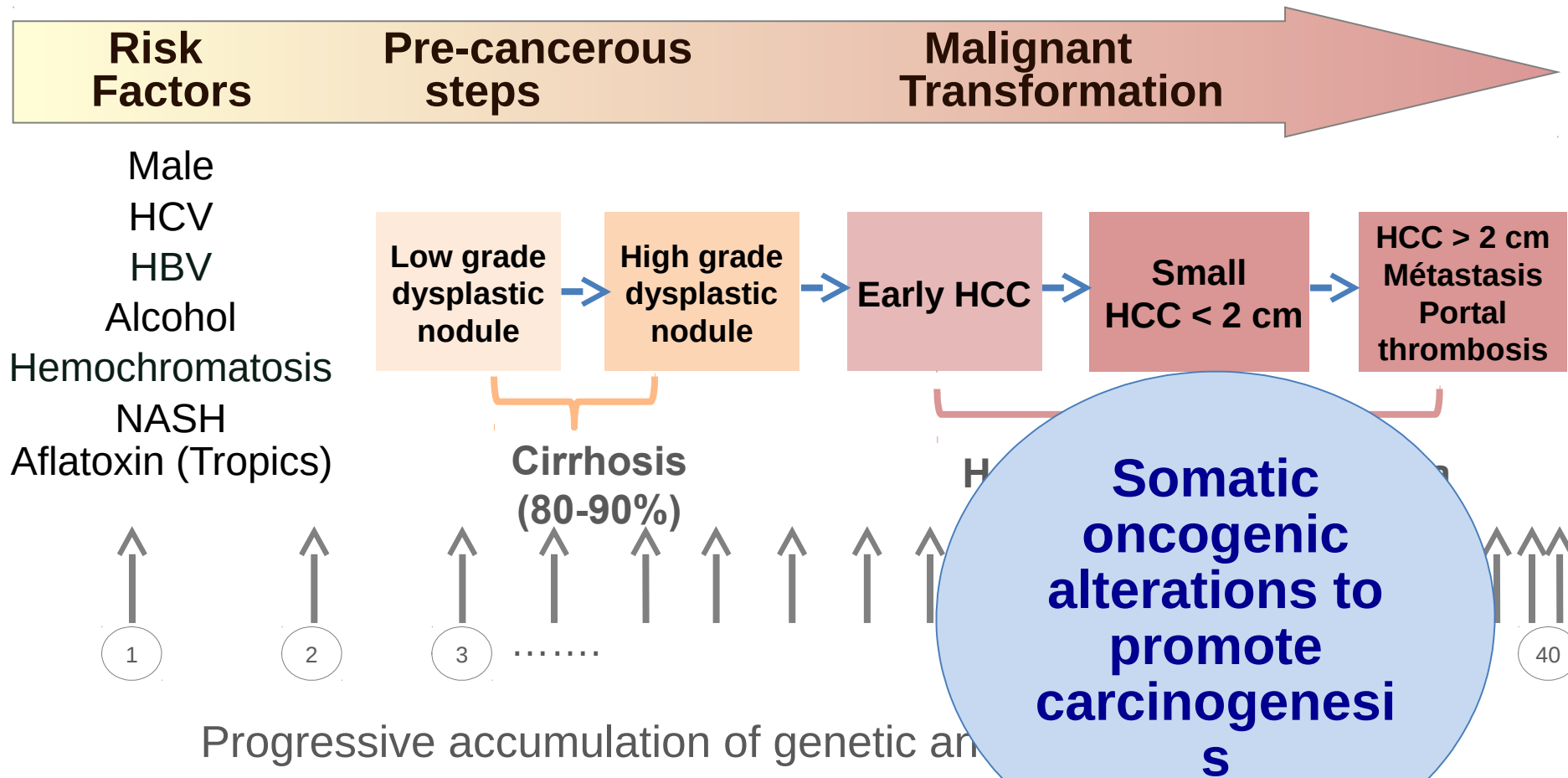
HBV clonal integration is more frequent in the tumors than in adjacent liver tissues

Study on Chinese individuals: 81 HBV-positive HCCs
399 HBV integration breakpoints



40% of the breakpoints located near the **viral enhancer** and the gene X and core ORFs

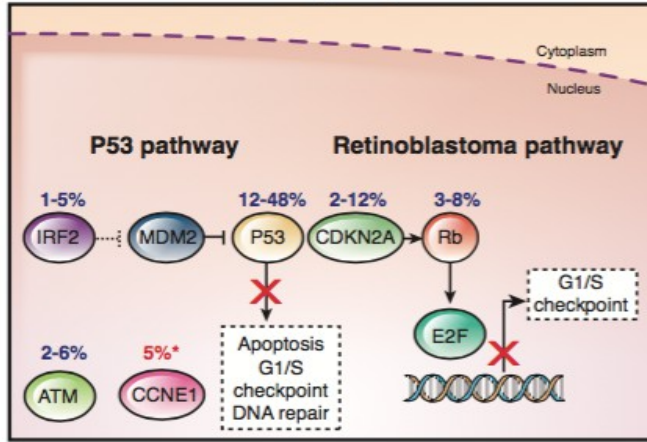
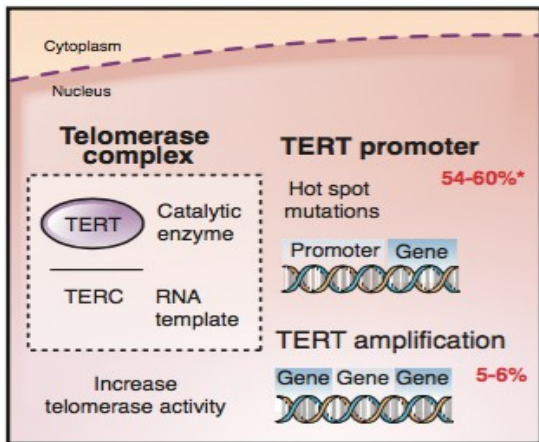
Hepatocarcinogenesis is a multistep disease



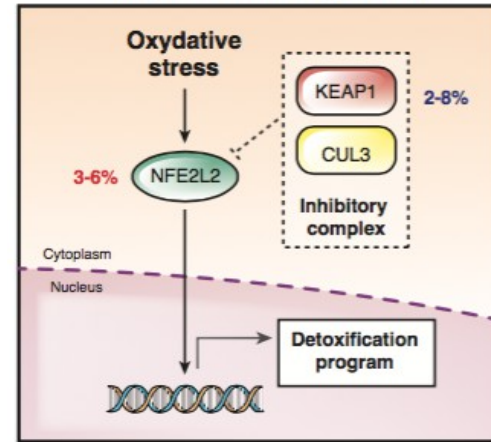
The genetic landscape of hepatocellular carcinoma

Cell cycle gene

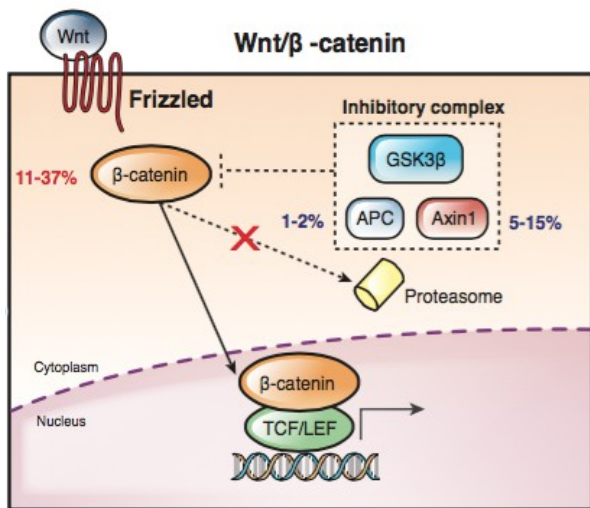
Telomere maintenance



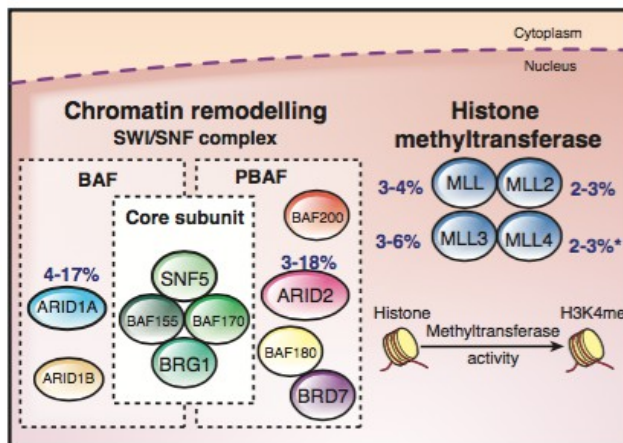
Oxydative stress pathway



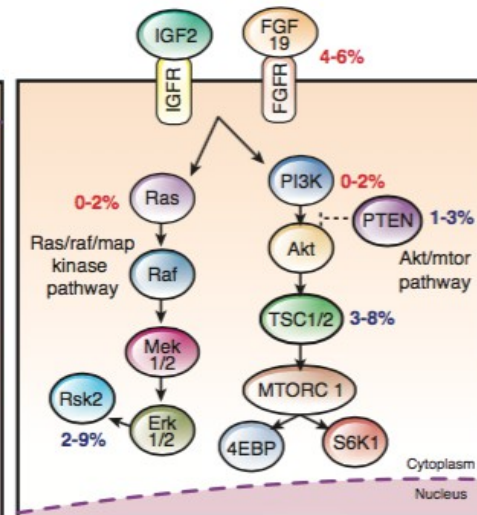
Wnt/β-catenin



Epigenetic modifier



Akt/mTOR and map kinase pathway

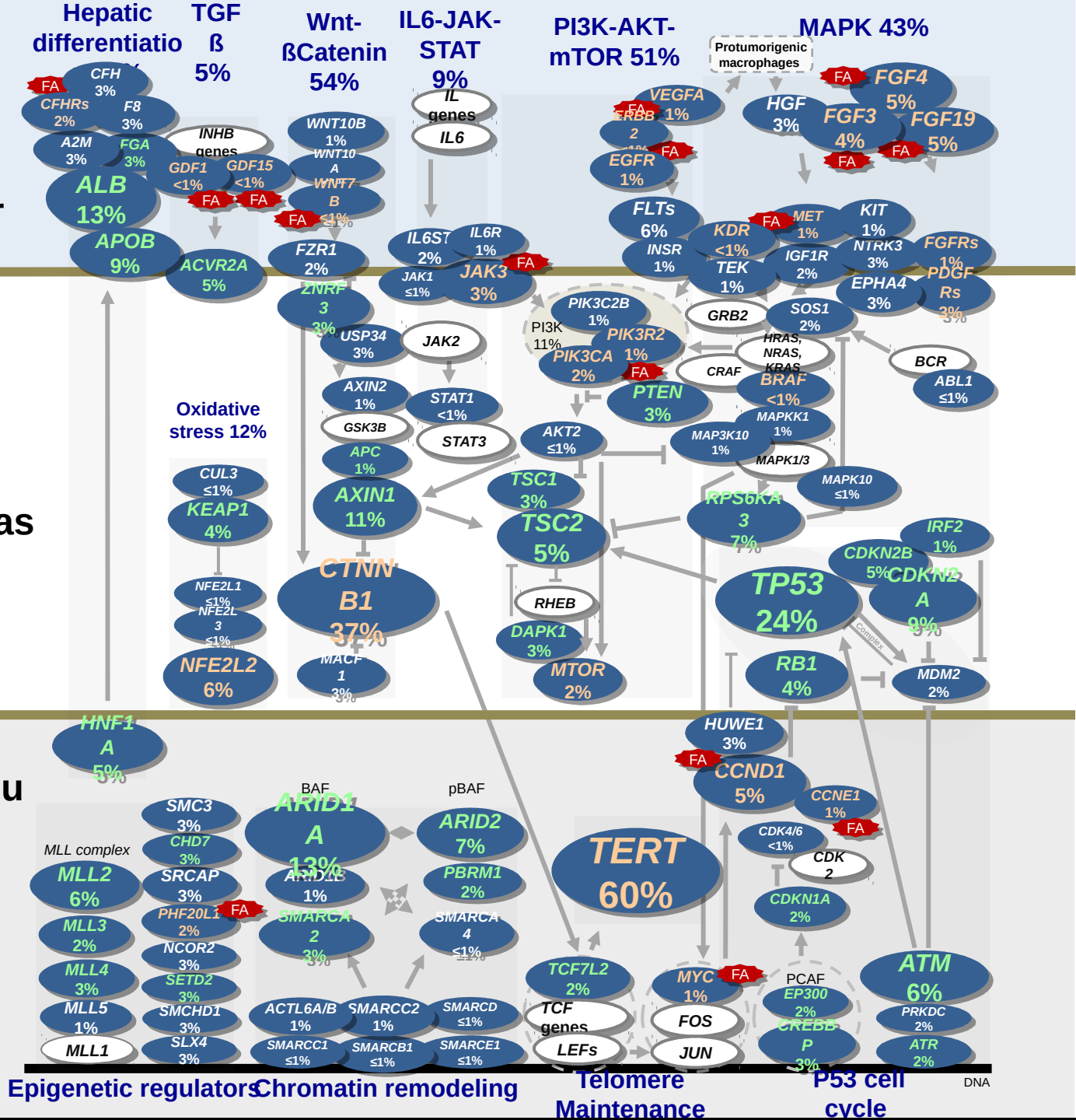


Relations between the driver genes in HCC

Extra cellular space

Cytoplasm

Nucleus



Schulze, Imbeaud, Letouzé et al, Nature Genetics, March 30th, 2015

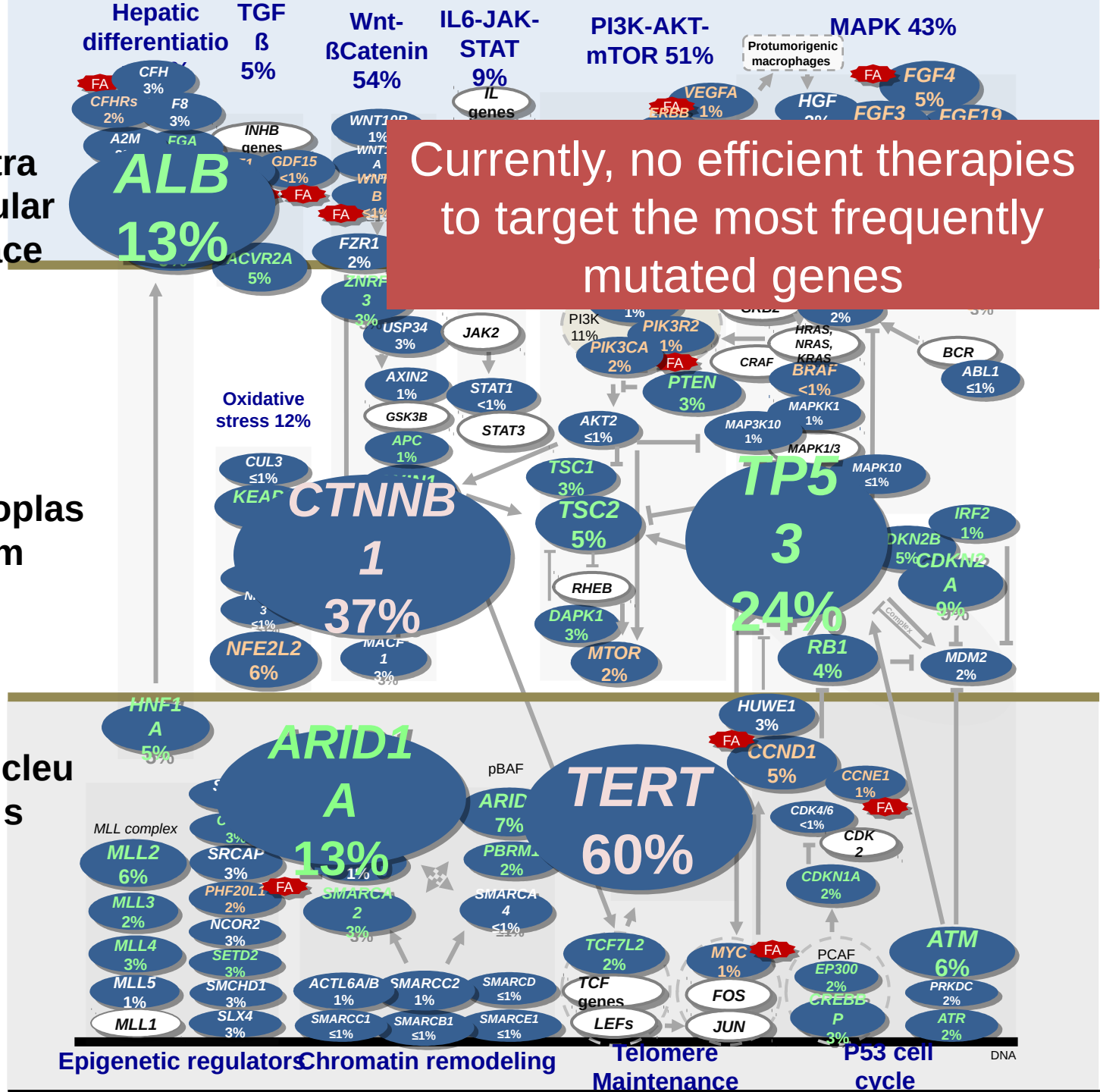
Landscap e of the targetable driver genes in HCC

Extra
cellular
space

Cytoplas
m

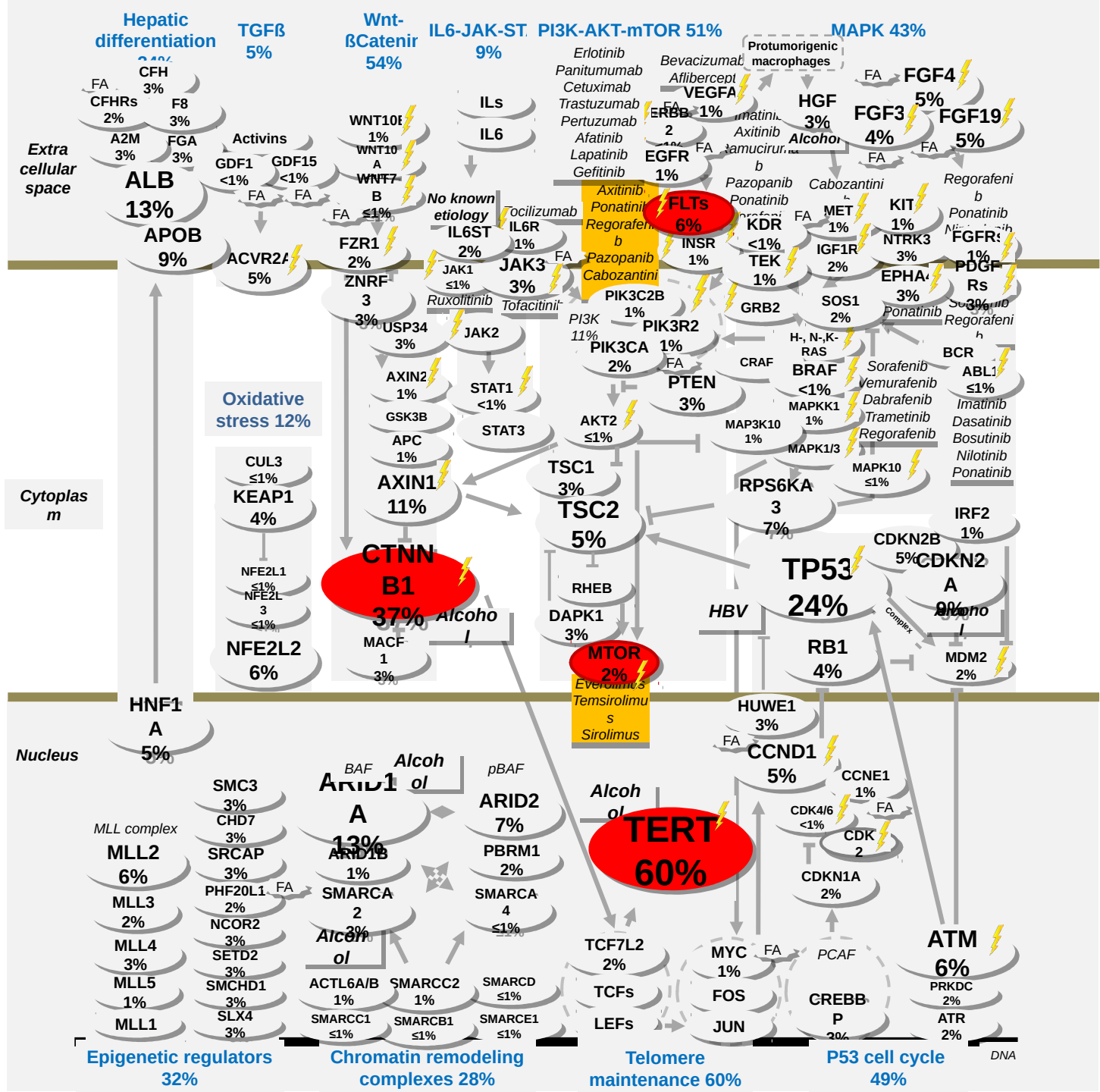
Nucleu
s

Currently, no efficient therapies
to target the most frequently
mutated genes



Schulze, Imbeaud,
Letouzé et al,
Nature Genetics,
March 30th, 2015

Treatment Patient example #1



Drugs in clinical use

Drugs in clinical trial

Treatment

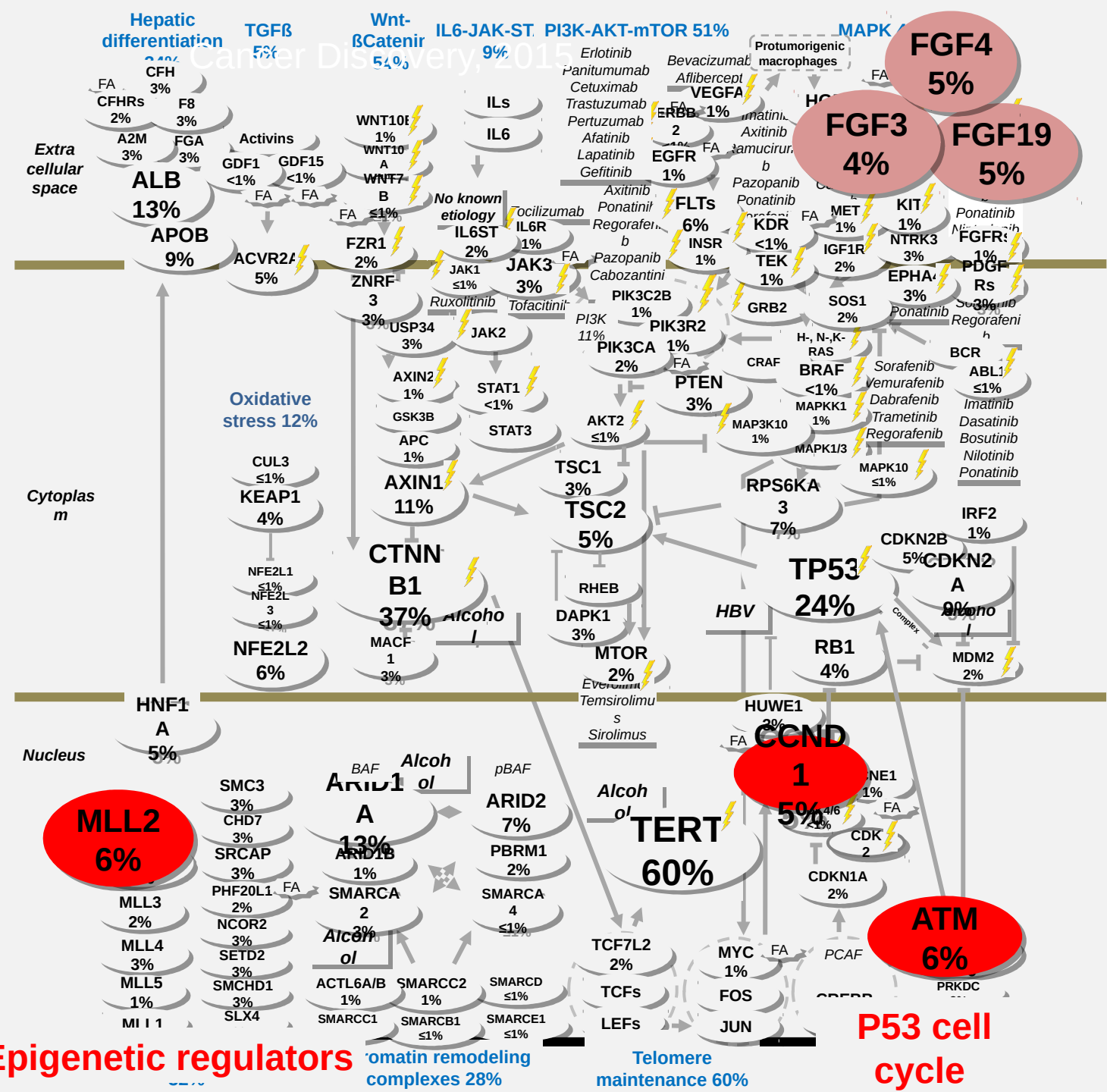
to Patient example



FGFR4 inhibitors (phase 1/2)

Drugs in clinical use

Drugs in clinical trial



Epigenetic regulators

Chromatin remodeling complexes 28%

Telomere maintenance 60%

P53 cell cycle

Conclusions

- Genomics identified a high heterogeneity in HCC with several oncogenes and tumor suppressor genes recurrently mutated
- **TERT promoter mutation is the earliest recurrent event involved in malignant transformation in cirrhosis and adenoma**
 - **Biomarker and target**
- **Signatures of HBV and genotoxic exposure**
 - => **Molecular epidemiology including somatic and germline variants**
 - **Several gene alterations could be targeted by specific therapies**
 - **First step to develop genome based clinical trials**

Inserm UMR1162

Liver tumors

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▶ 15-17 September 2017

▶ Seoul, South Korea

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