Consensus molecular subtypes of Colorectal Cancer

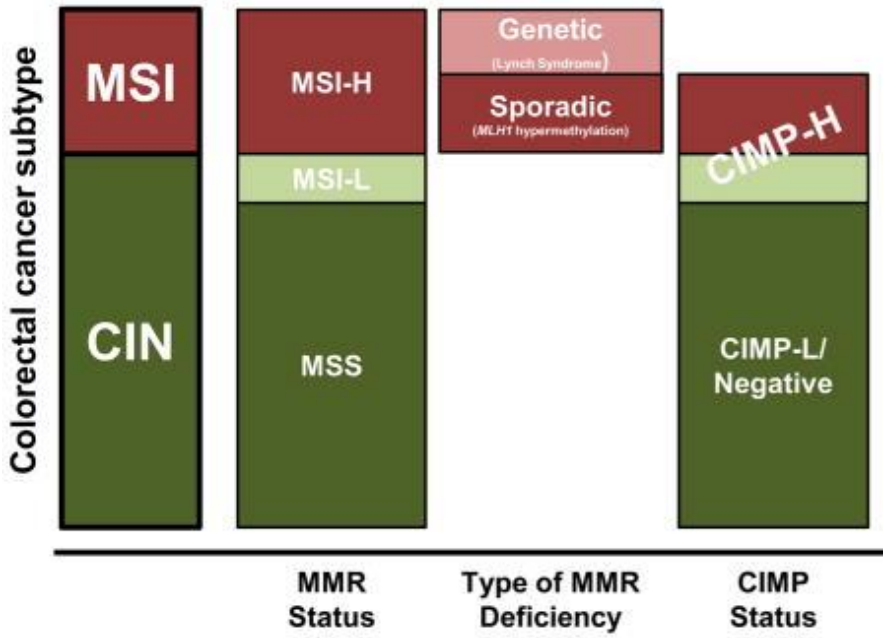
Rodrigo Dienstmann, MD

REALITY:

The evolution of biomarkers for matched targeted therapies in CRC has been restrictive (until recently).

Consensus molecular subtypes of Colorectal Cancer

PAST:



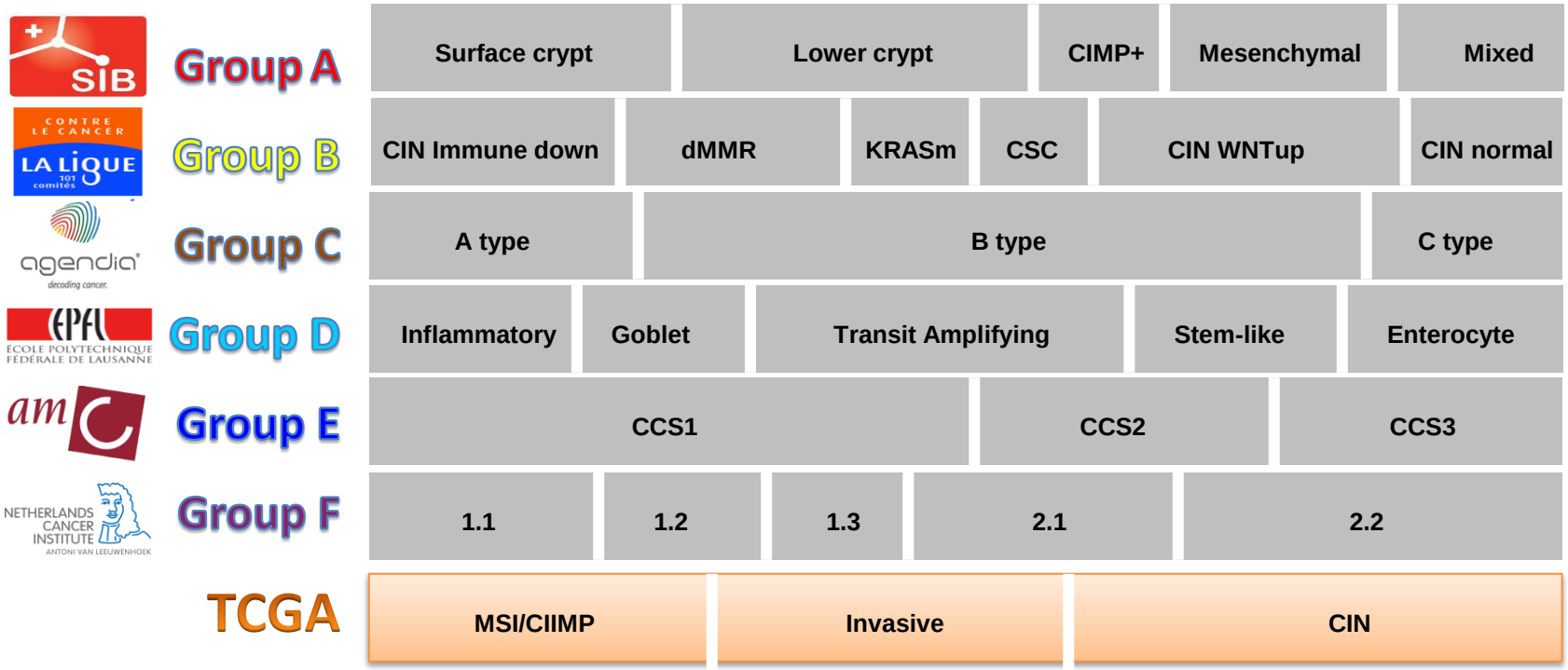
Vilar & Tabernero. Cancer Discov 2013

HYPOTHESIS:

Intrinsic gene expression (immune) subtyping:

- increase the biological understanding of the disease;
- optimize patient stratification based on differences in outcome and response patterns to targeted agents.

Colorectal cancer intrinsic subtypes – published classifiers



Budinska, 2013; Marisa, 2013; Roepman, 2013; Sadanandam, 2013; De Sousa e Melo, 2013; Schlicker, 2012; TCGA, 2012

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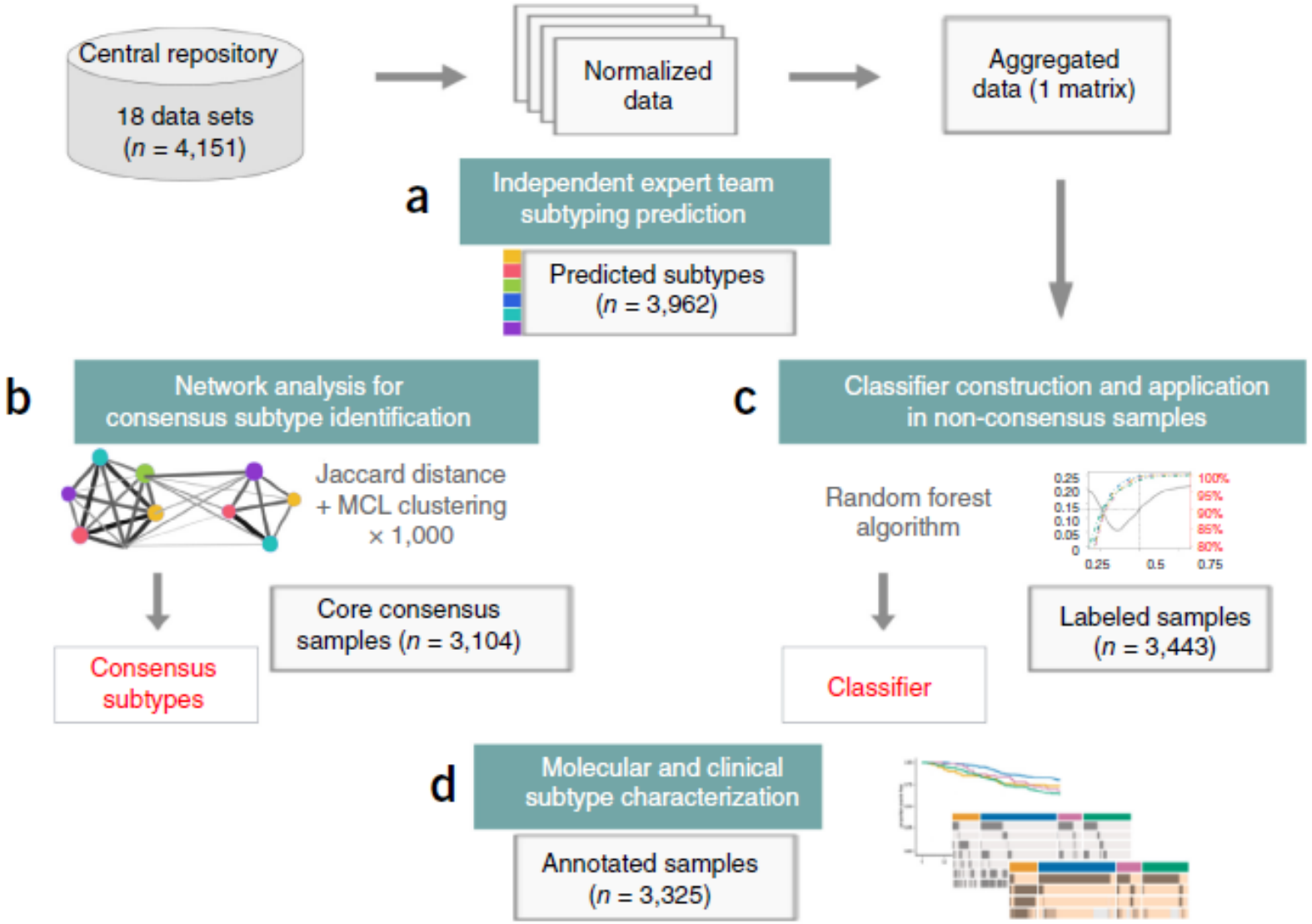

Guinney, Dienstmann et al, Nat Med 2015

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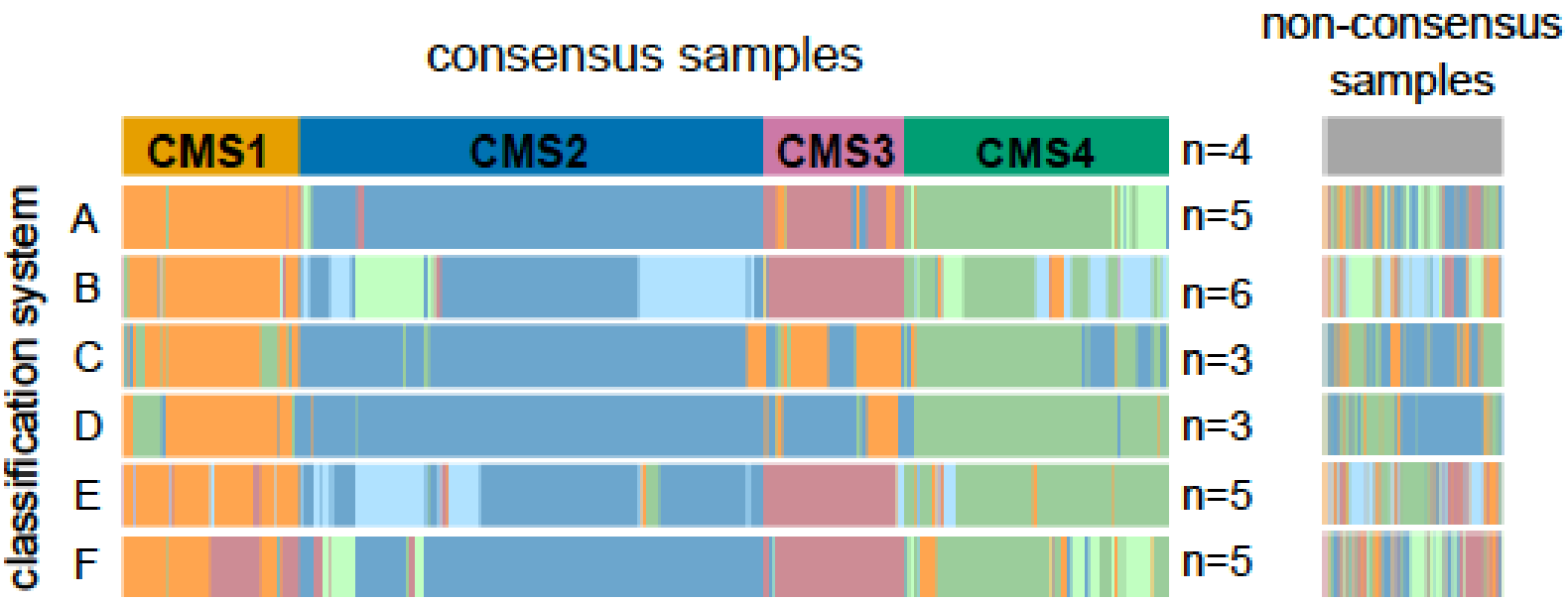

Guinney, Dienstmann et al, Nat Med 2015

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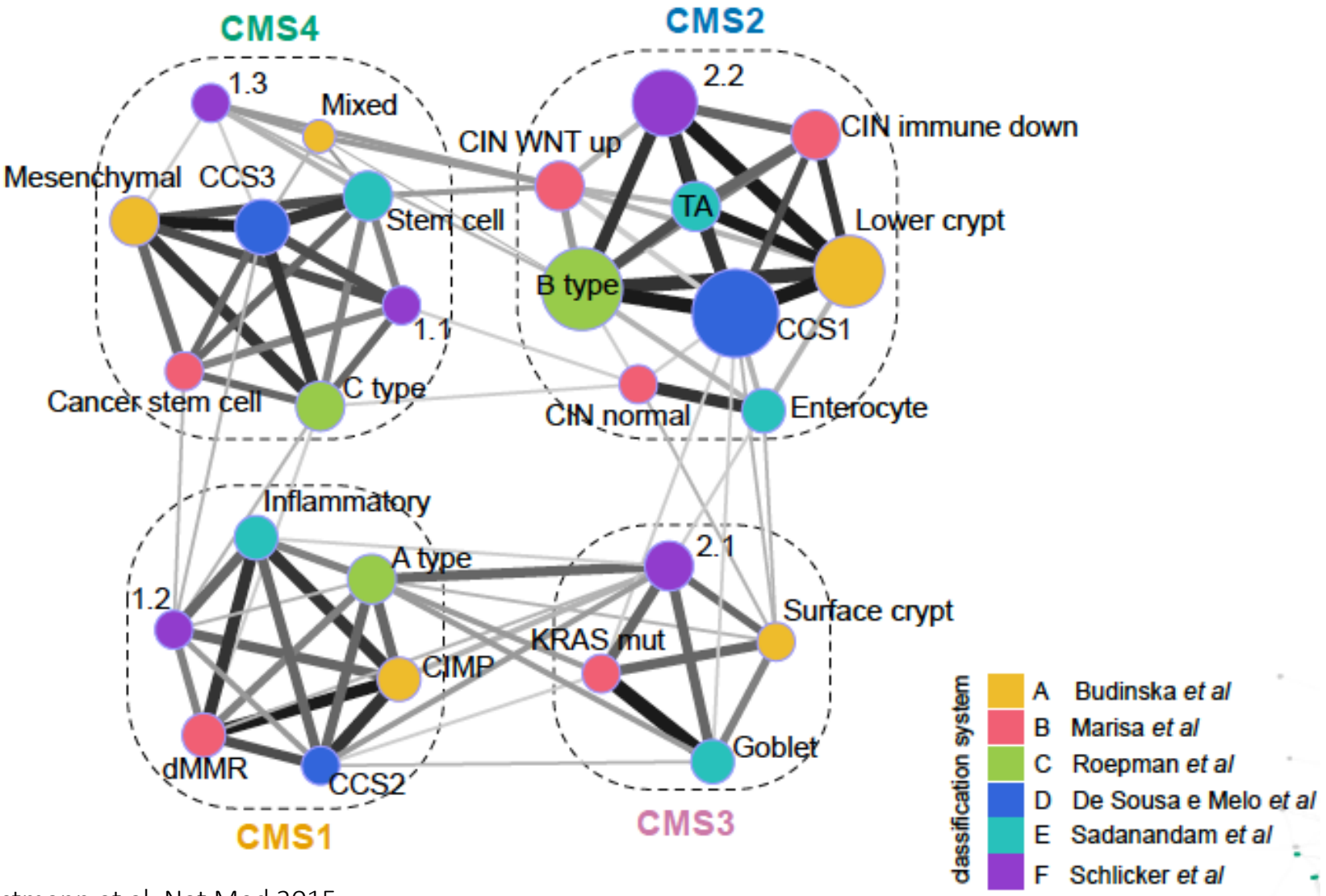


Guinney, Dienstmann et al, Nat Med 2015

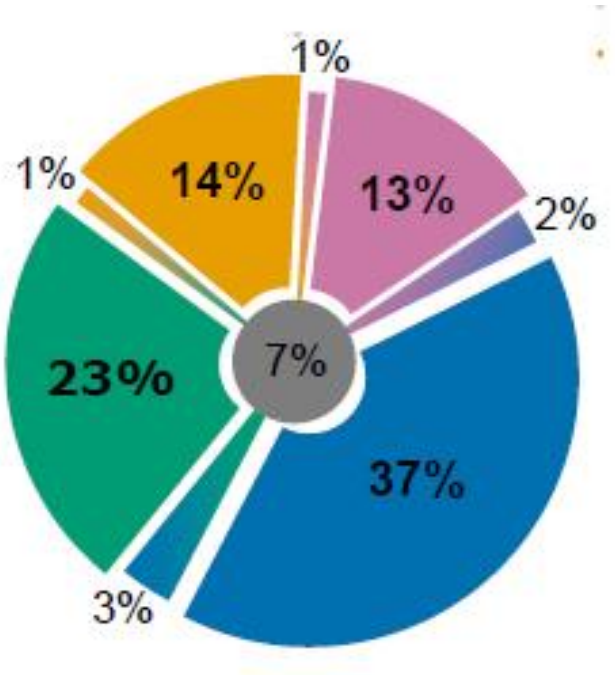
Consensus molecular subtypes of Colorectal Cancer

CMS1
MSI Immune

CMS2
Canonical

CMS3
Metabolic

CMS4
Mesenchymal



Guinney, Dienstmann et al, Nat Med 2015

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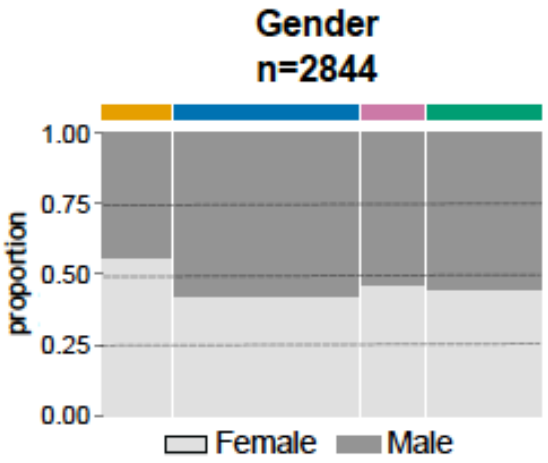

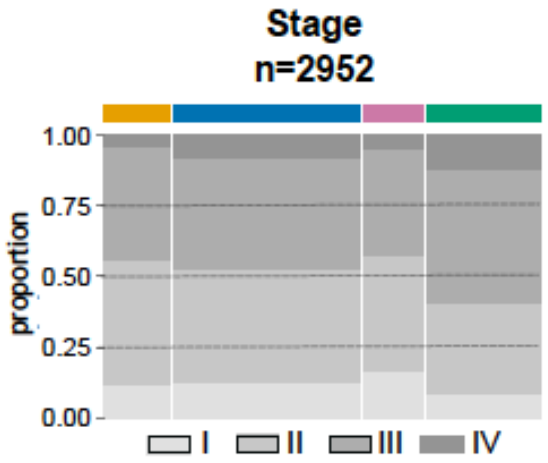

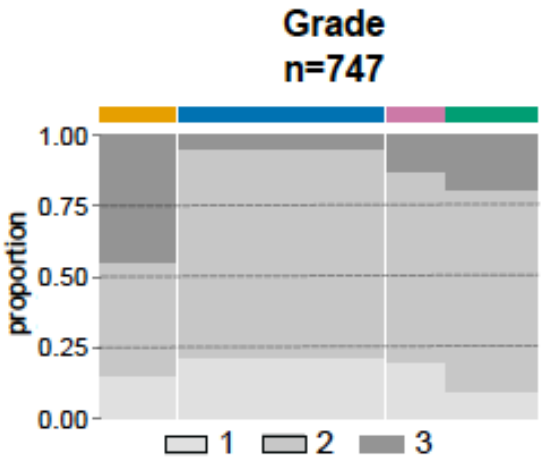

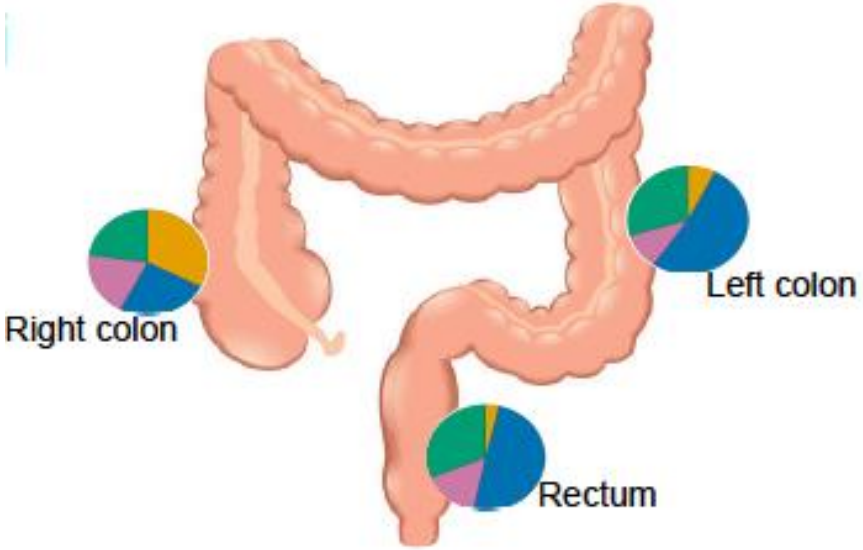

Guinney, Dienstmann et al, Nat Med 2015

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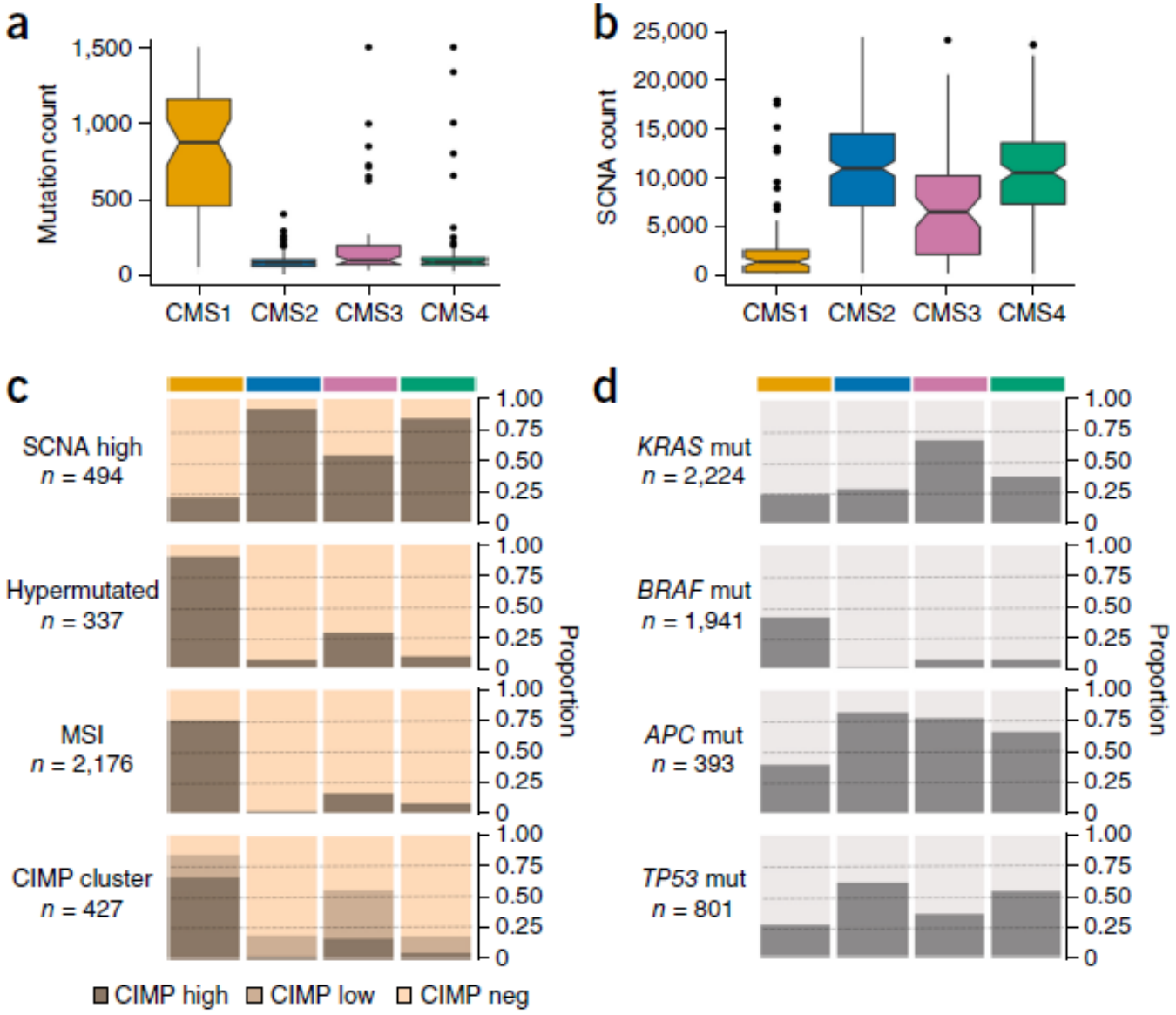

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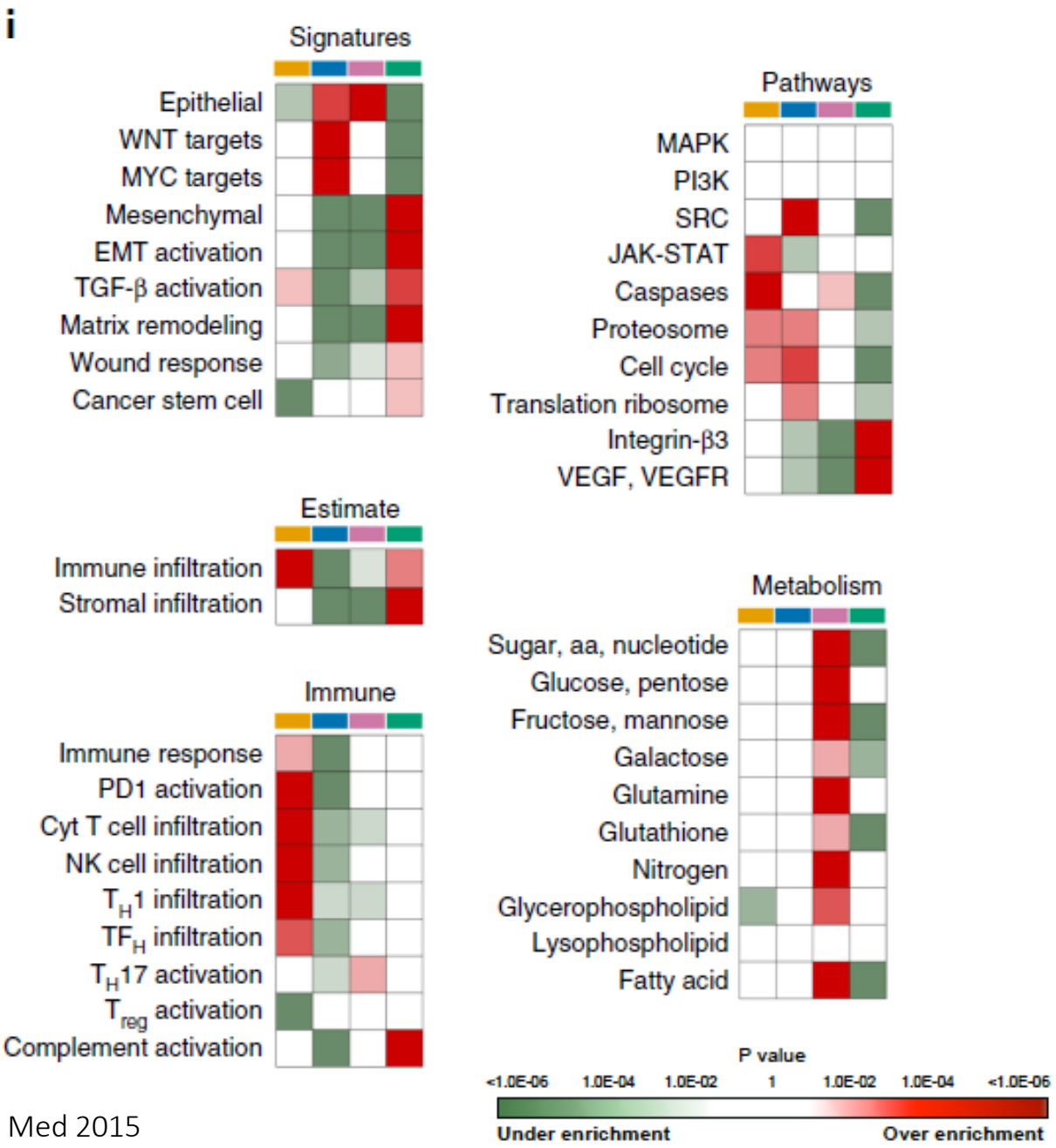
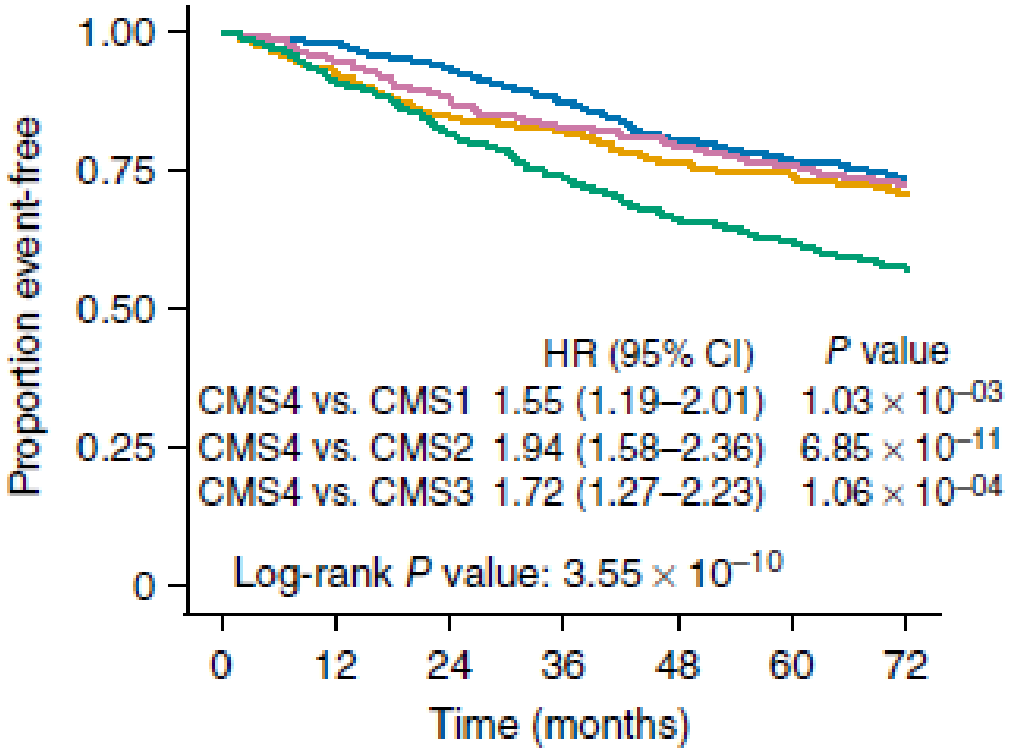


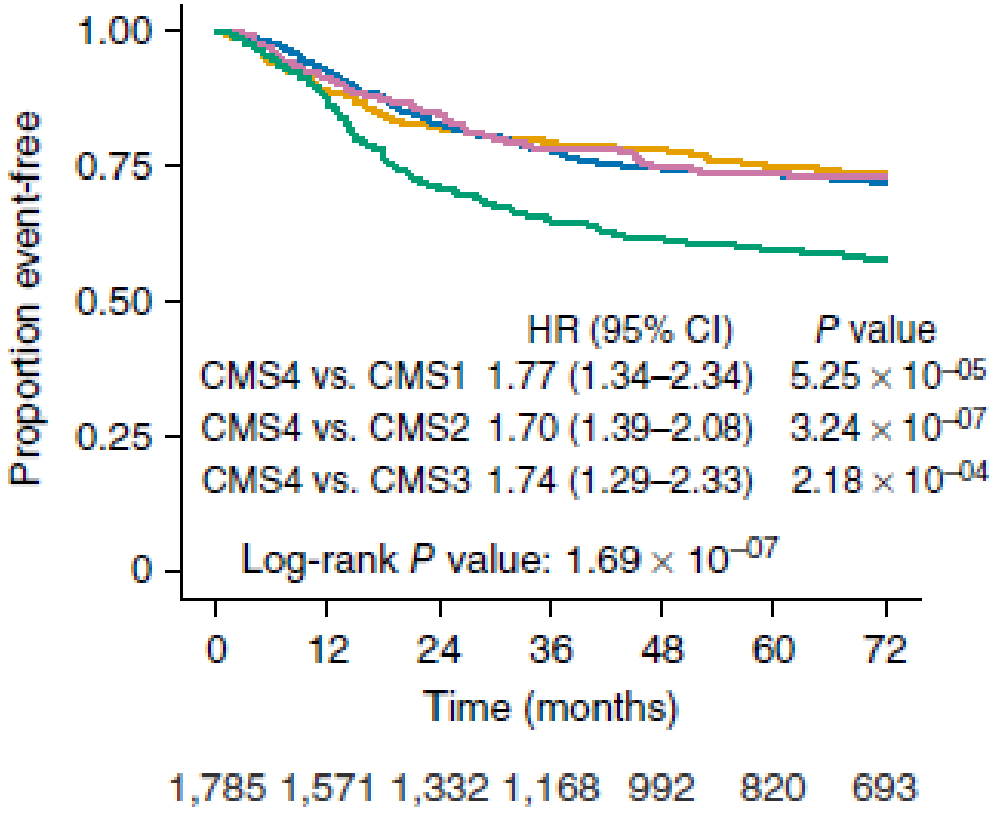
Guinney, Dienstmann et al, Nat Med 2015

Overall survival



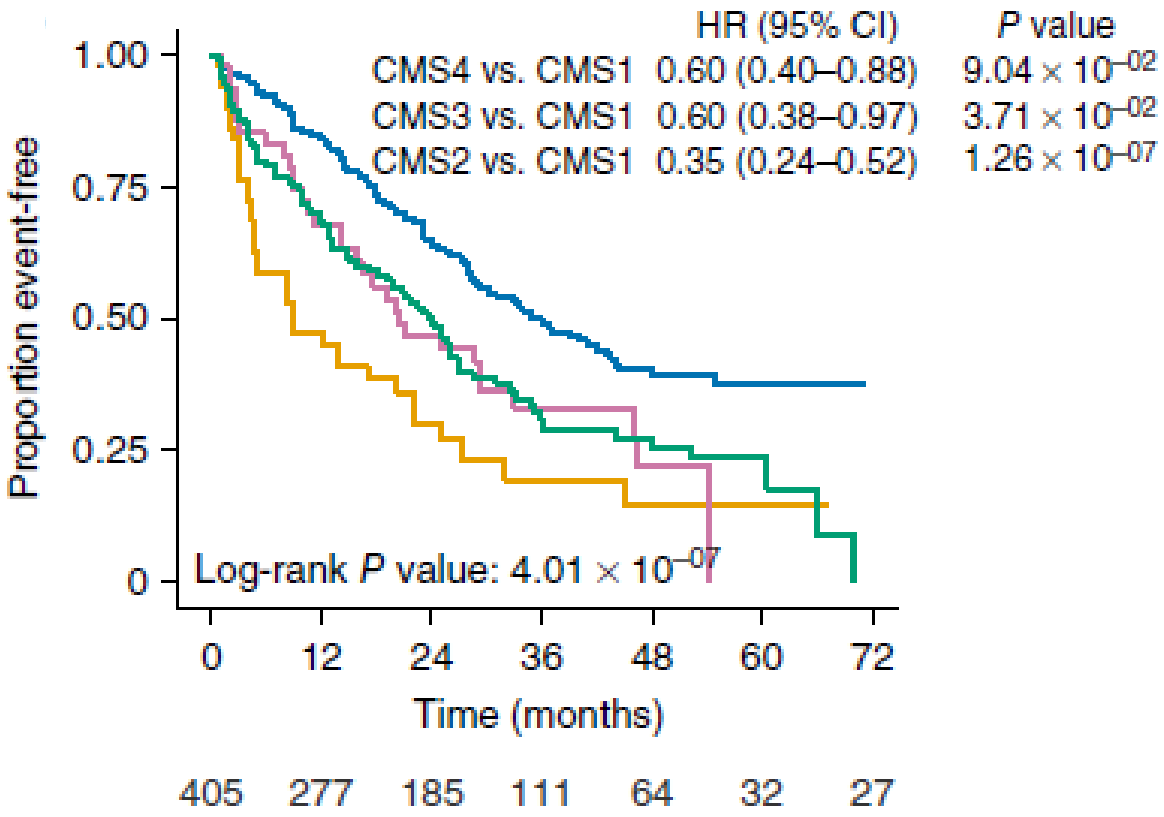
Guinney, Dienstmann et al, Nat Med 2015

Relapse-free survival



Guinney, Dienstmann et al, Nat Med 2015

Survival after relapse



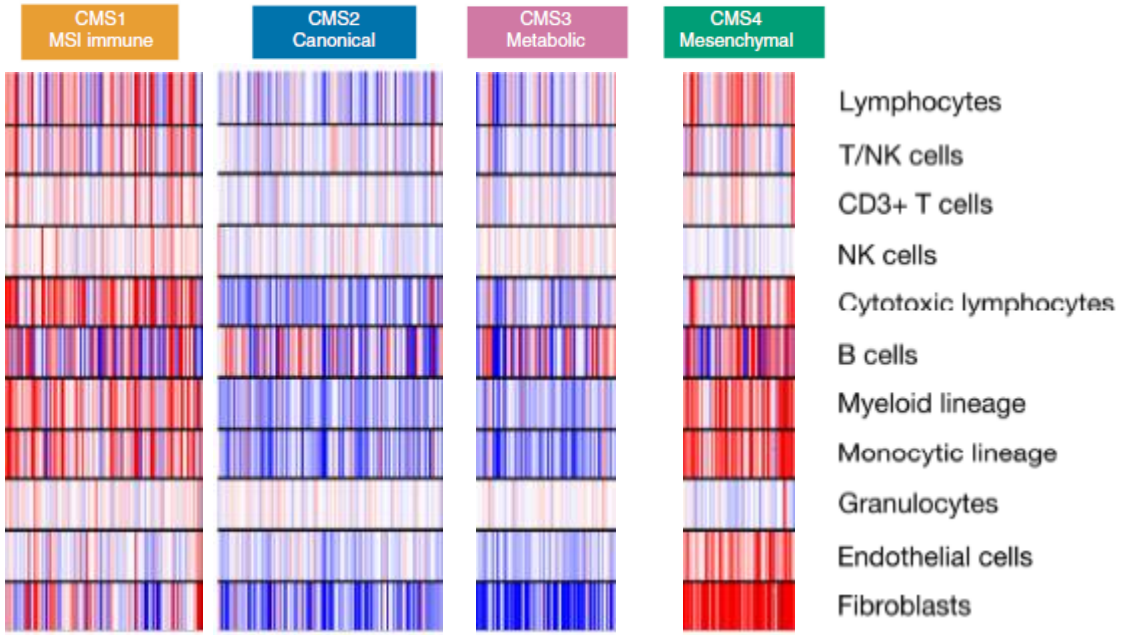
Guinney, Dienstmann et al, Nat Med 2015

Consensus molecular subtypes of Colorectal Cancer

CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

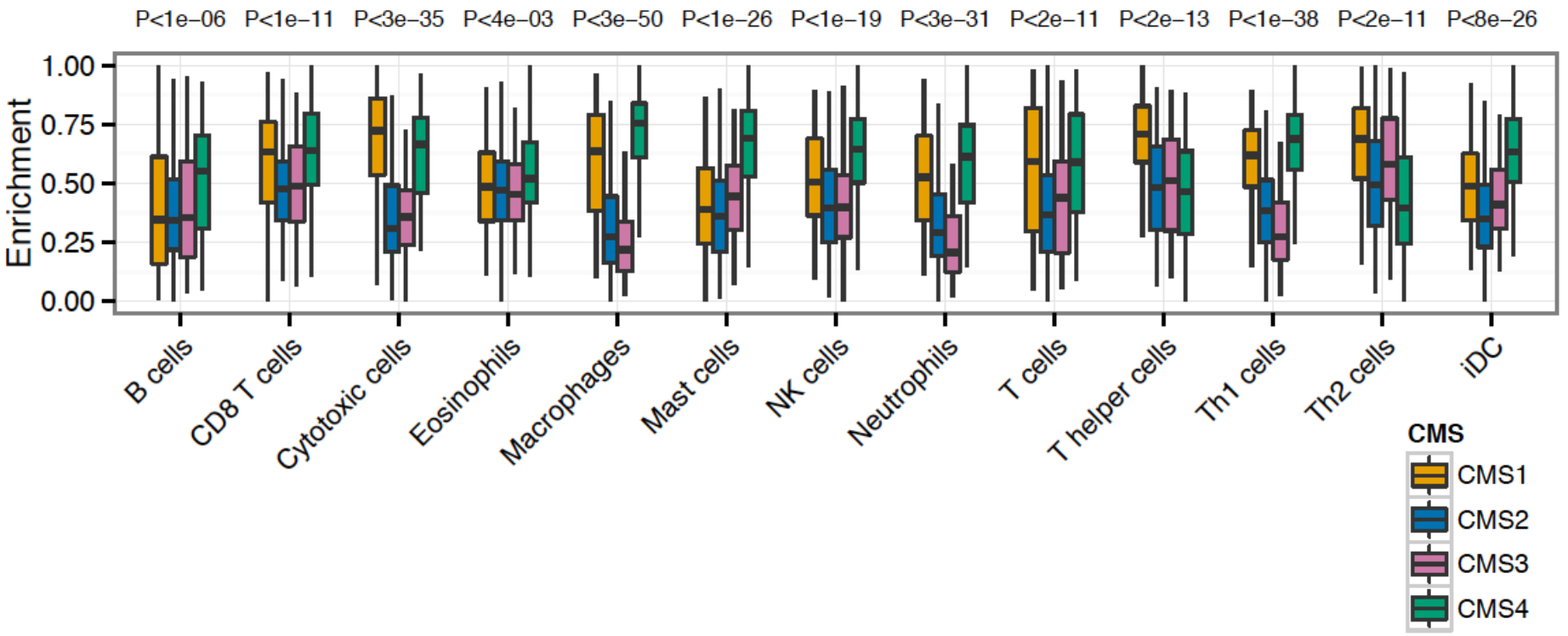
Guinney, Dienstmann et al, Nat Med 2015

Supervised immune infiltration analysis (immunophenotype)



Adapted from Becht et al, Oncoimmunology

Supervised immune infiltration analysis (immunophenotype)



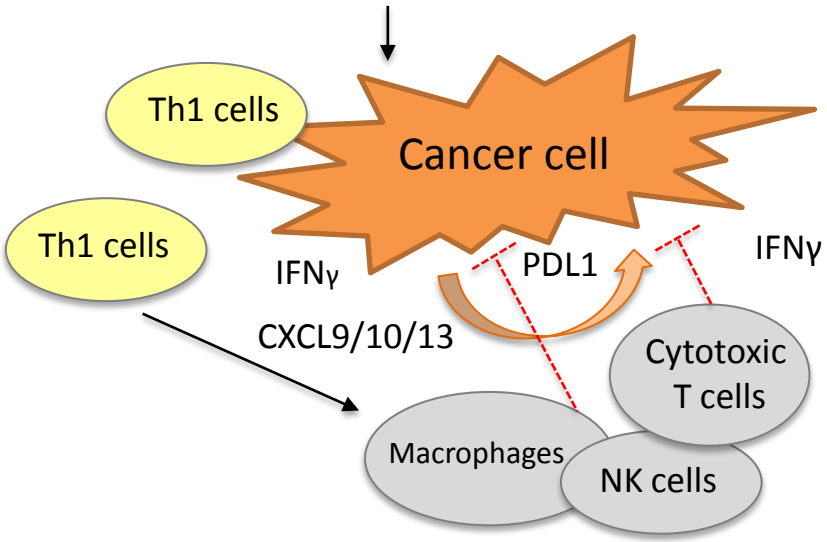
Unpublished

Consensus molecular subtypes of Colorectal Cancer

Immune-activated

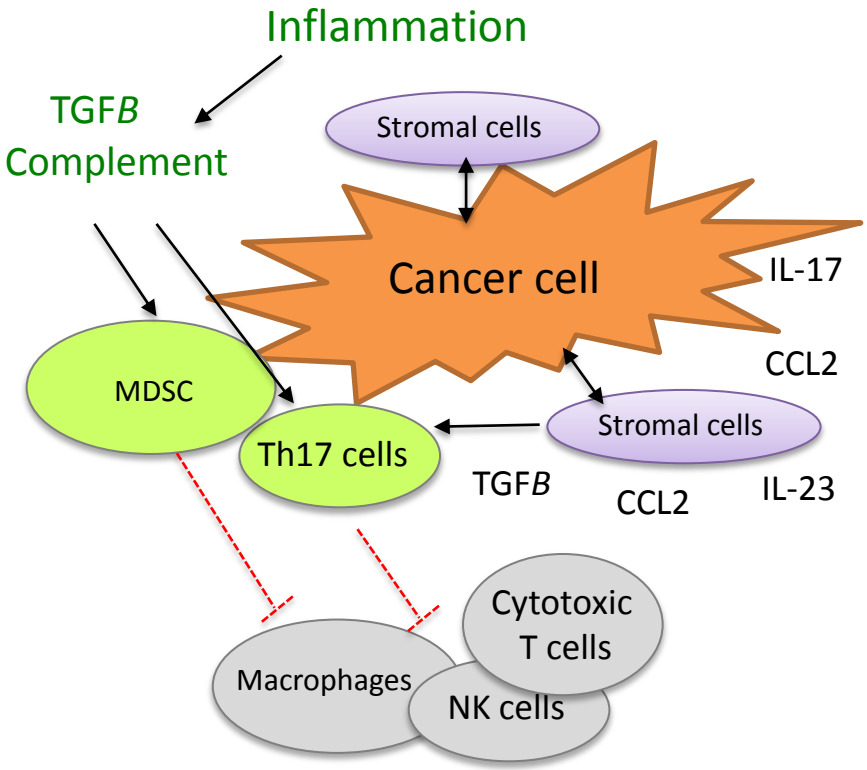
CMS1
MSI immune

dMMR – MSI
Hypermutation



Immune-tolerant

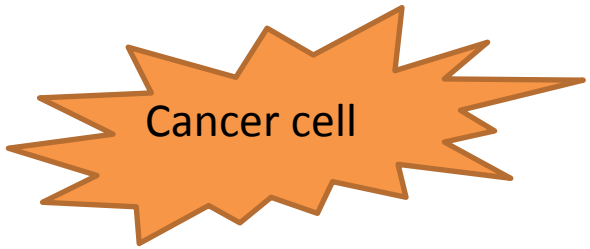
CMS4
Mesenchymal



Immune-ignorant

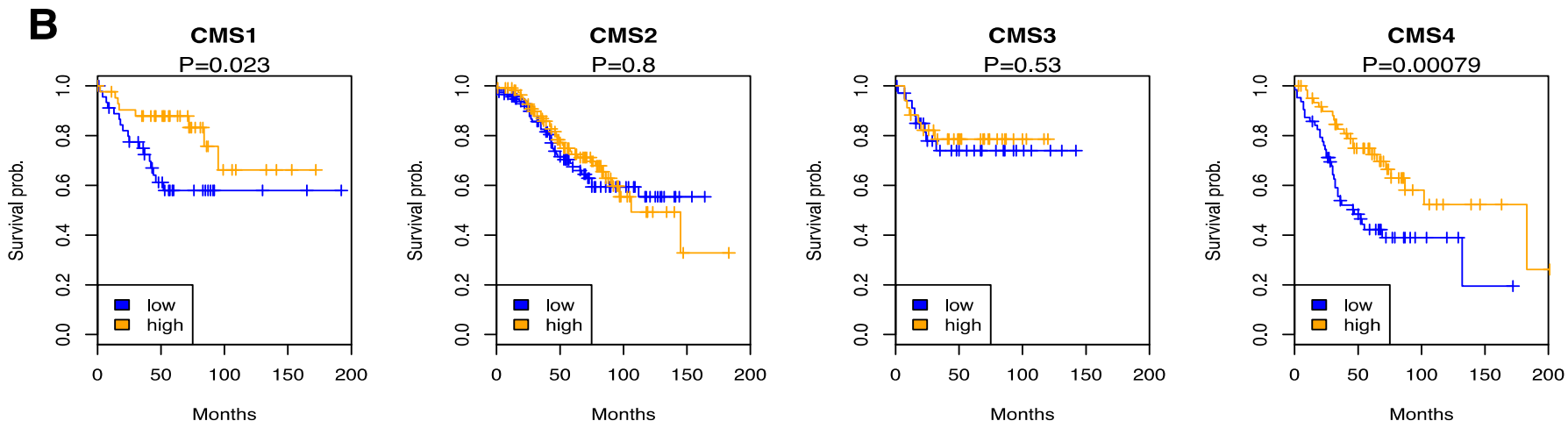
CMS2
Canonical

CMS3
Metabolic



GSE39582

Intra-CMS prognosis according to NK cell activation signature



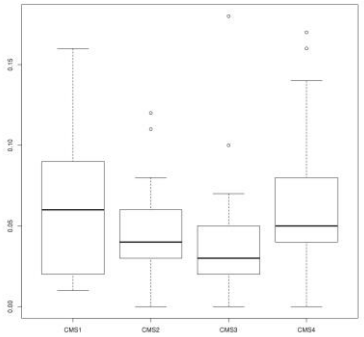
Unpublished

MECC cohort

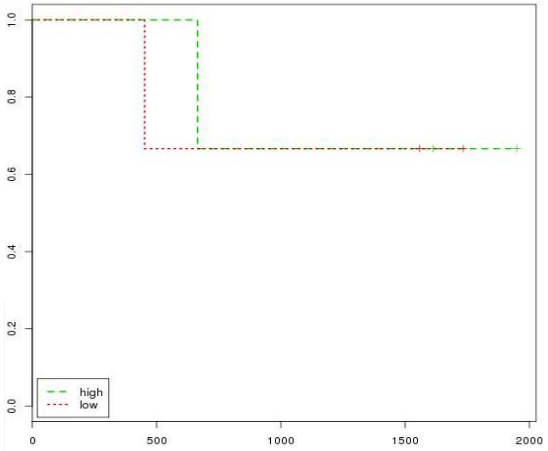
Intra-CMS prognosis according to tumor infiltrating lymphocytes (TILs)

ICO Institut Català d'Oncologia

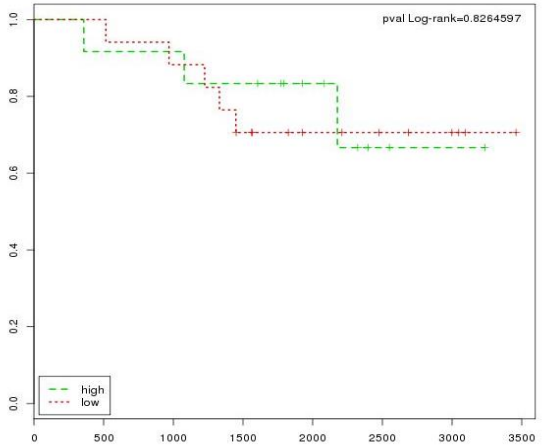
%TIL



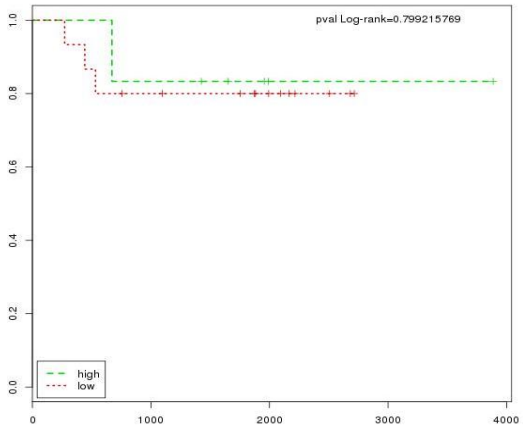
CMS1



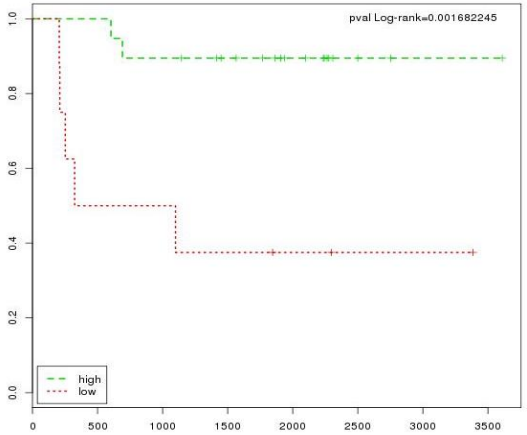
CMS2



CMS3



CMS4



high
low

Unpublished

TAKE-HOME MESSAGES 1:

Even being enriched for key clinicopathological, genomic and epigenomic markers, the striking biological differences of the four CMS groups are only evident when looking at cancer cell pathway activation level and tumor microenvironment.

Guinney, Dienstmann et al, Nat Med 2015

TAKE-HOME MESSAGES 2:

Prognostic differences in unsupervised gene expression signatures confirm the clinical relevance of biological processes implicated in each CMS group.

BUT… predictive value is key for clinical translation!

Guinney, Dienstmann et al, Nat Med 2015

LETTER

doi:10.1038/nature16967

Mutant *Kras* copy number defines metabolic reprogramming and therapeutic susceptibilities

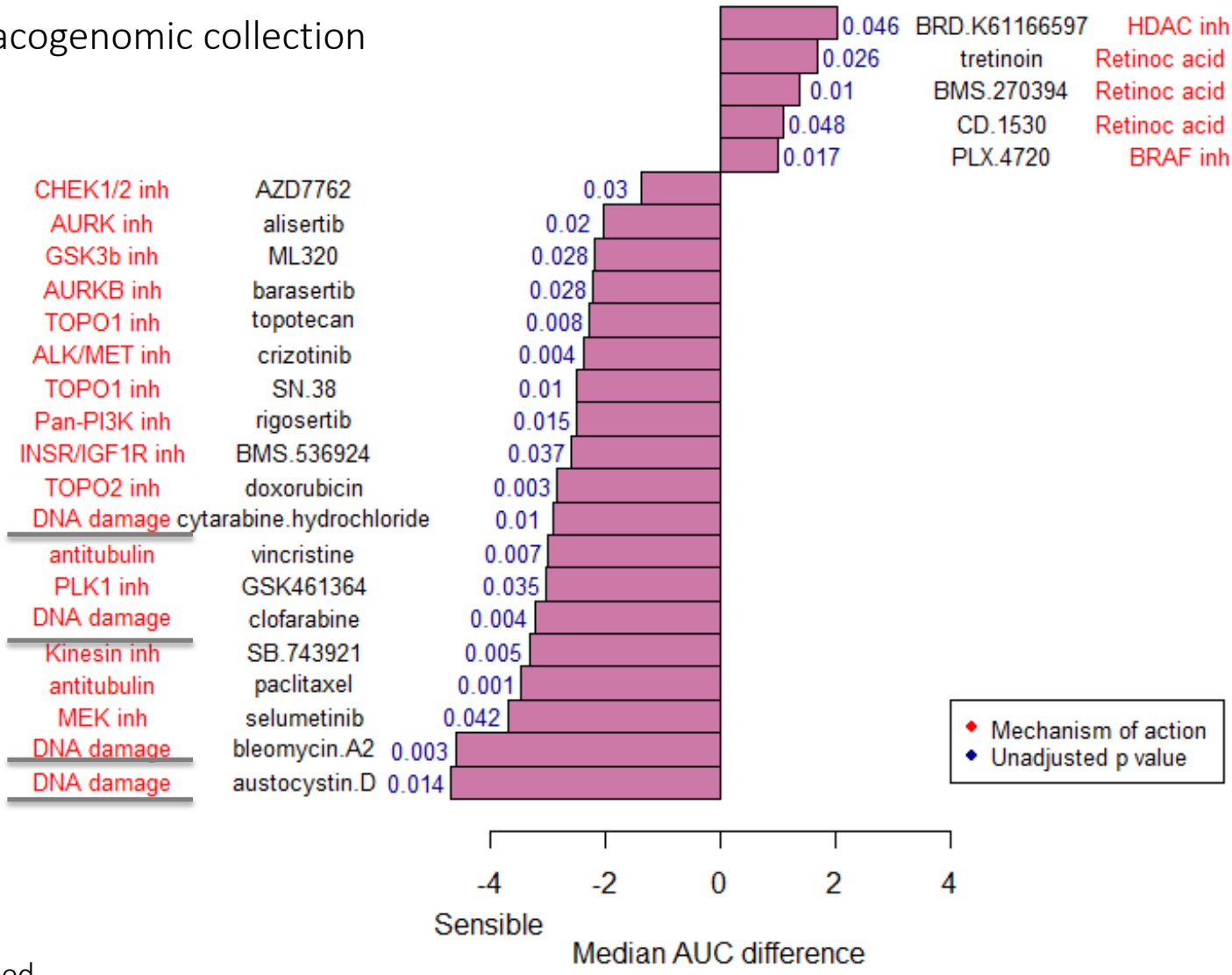
Emma M. Kerr[1], Edoardo Gaude[1], Frances K. Turrell[1], Christian Frezza[1] & Carla P. Martins[1]

Low glucose + glutathione biosynthesis inhibitor = Redox/ROS – DNA damage

Nature 2016 epub

6 cells

Broad Institute
Pharmacogenomic collection



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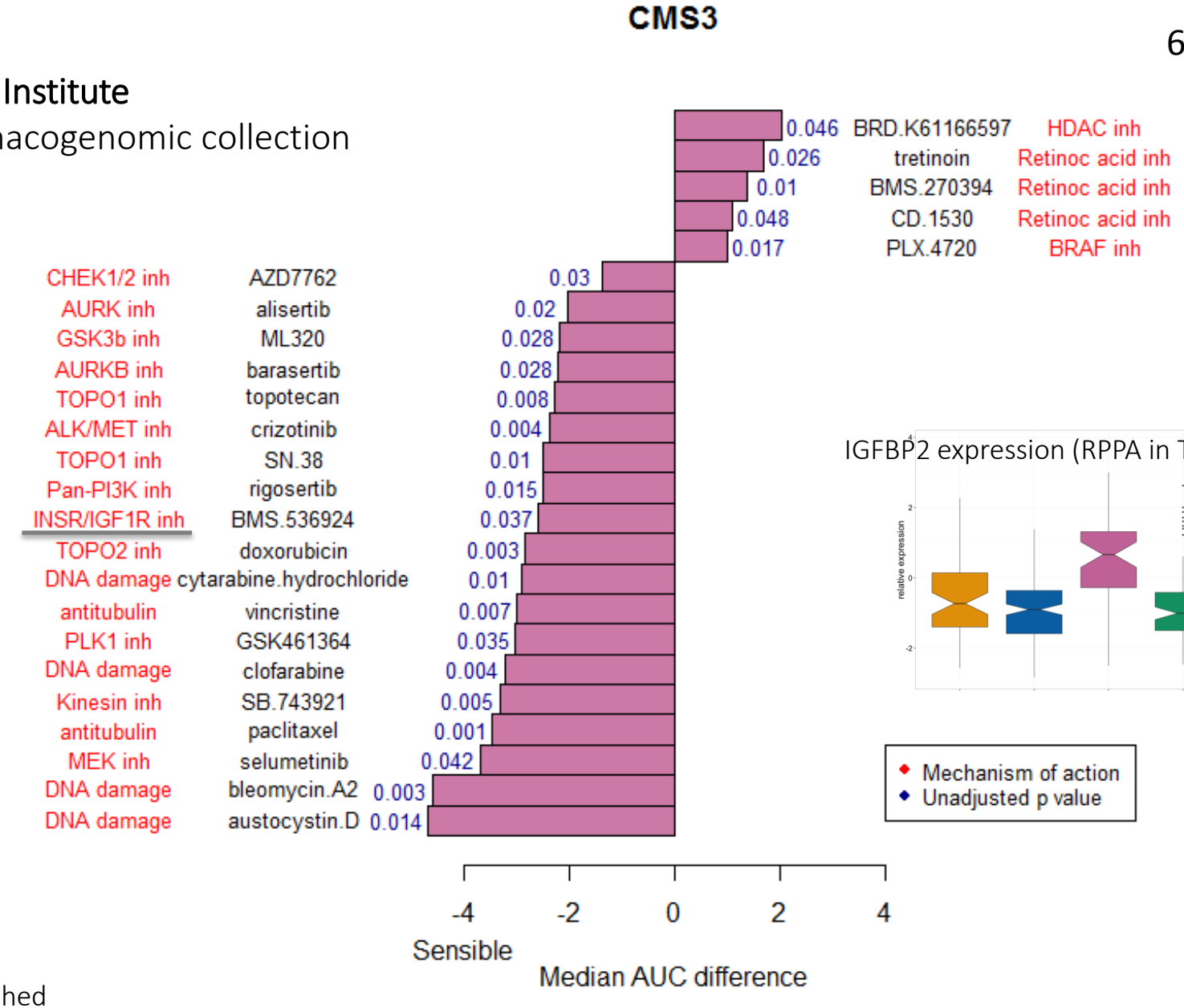
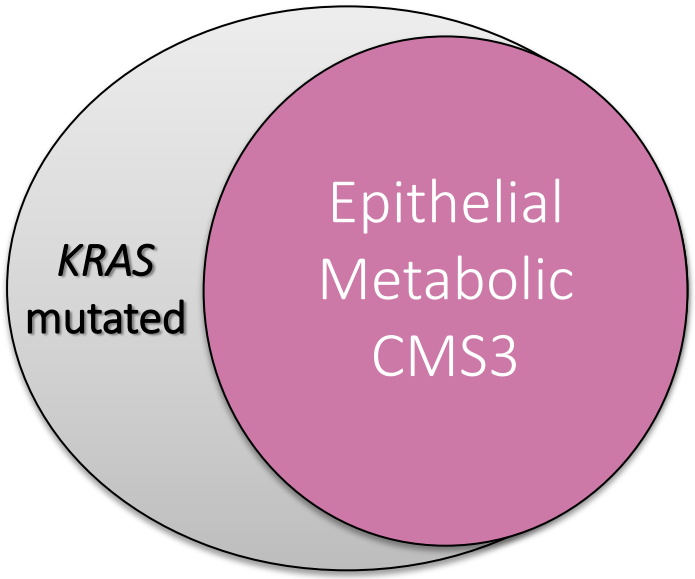
Broad Institute
Pharmacogenomic collection

6 cells



Unpublished

Predictive value – *hypotheses targeted therapies*

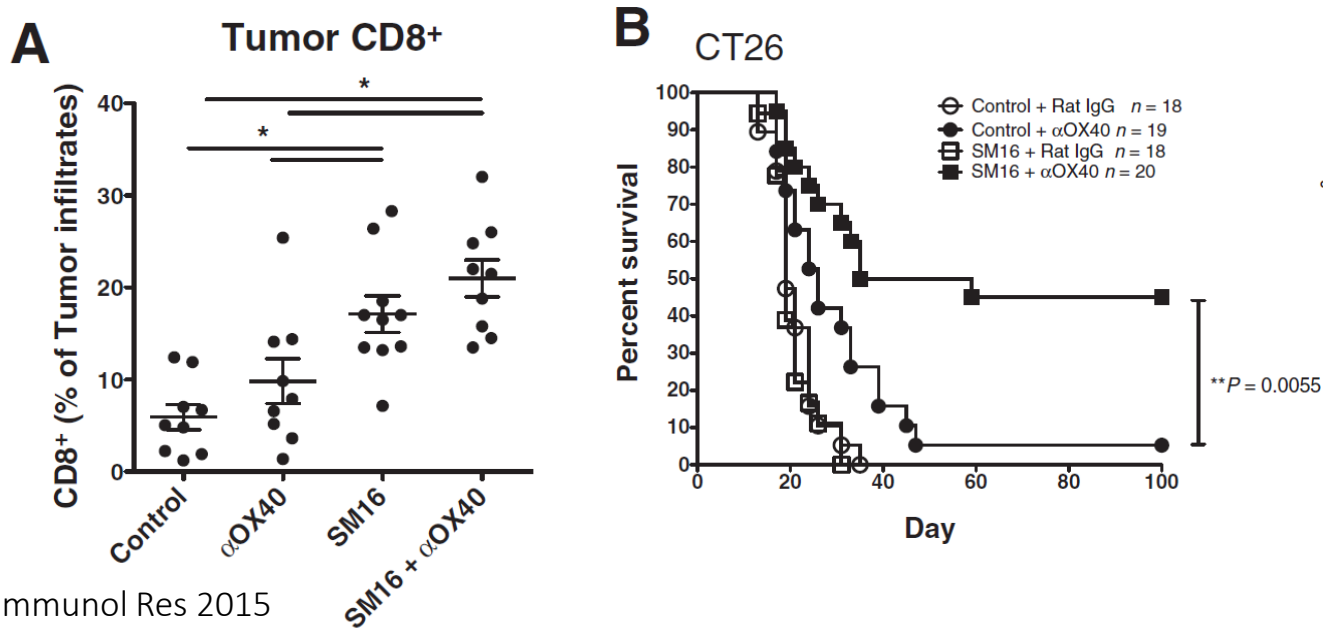


Strategy: combination of DNA damage agents, pan-RAF inhibitors, metabolic enzyme inhibitors

STAT3 Signaling Is Required for Optimal Regression of Large Established Tumors in Mice Treated with Anti-OX40 and TGFβ Receptor Blockade

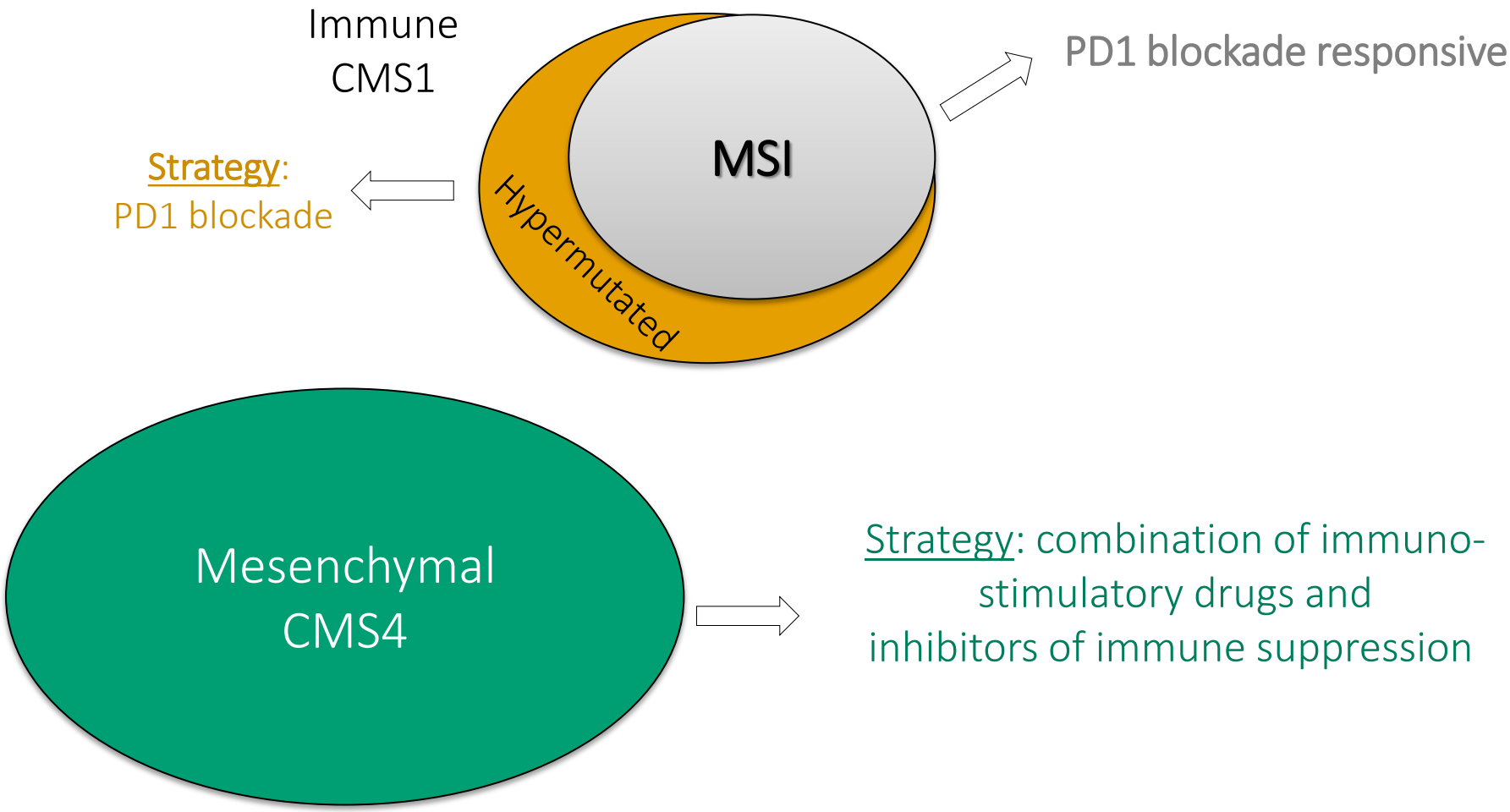
Todd A. Triplett[1,2], Christopher G. Tucker[1], Kendra C. Triplett[1], Zefora Alderman[1], Lihong Sun[3], Leona E. Ling[3], Emmanuel T. Akporiaye[1,2], and Andrew D. Weinberg[1,2]

OX40 agonist + TGFBR inhibitor in CMS4 *in vivo* model



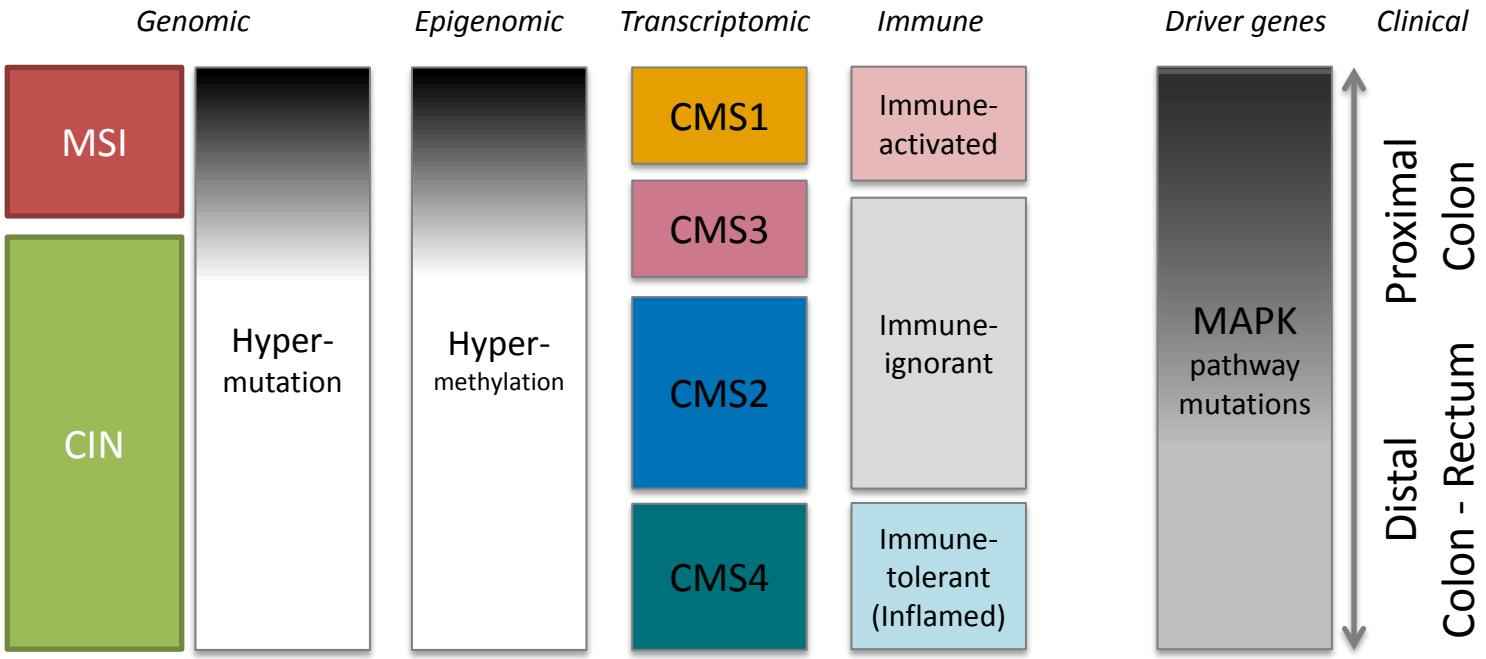
Triplett et al, Cancer Immunol Res 2015

Predictive value – *hypotheses immune therapies*



Consensus molecular subtypes of Colorectal Cancer

PRESENT:



TAKE-HOME MESSAGES 3:

The CMS groups provide the foundation for further disease stratification.

Qualitative and clinically relevant disease subtyping takes time and multiple resources.

TAKE-HOME MESSAGES 4:

Still unknown what combination of genomic features (mutation + MSI + gene expression + immune) will provide will provide the best prediction of drug response.

VHIO

Fiorella Ruiz, Ariadna Garcia, Marta Vilaro, Josep Tabernero

SAGE

Justin Guinney

ICO

Susanna Aussó, Rebeca Sanz, Victor Moreno, Ramon Salazar