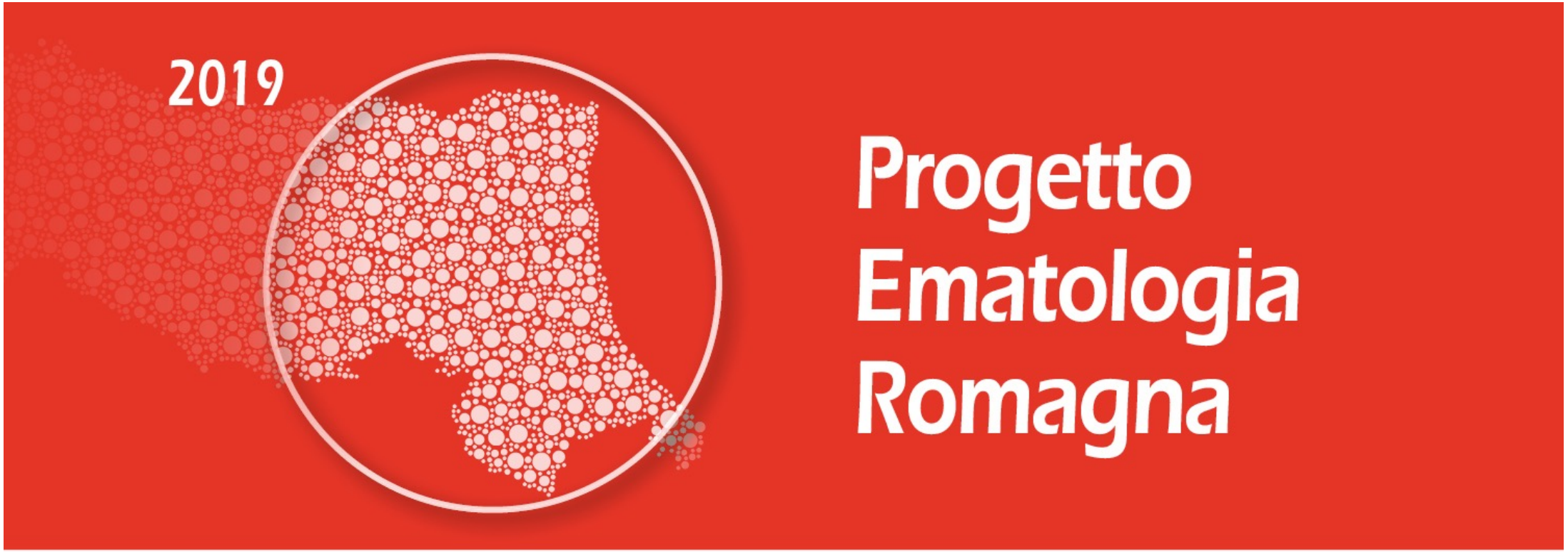


LA MULTICLONALITÀ DELLE MALATTIE ONCOEMATOLOGICHE E LA LORO EVOLUZIONE CLONALE: DA MGUS A MIELOMA MULTIPLO

Niccolò Bolli

Clonal evolution: not a new concept

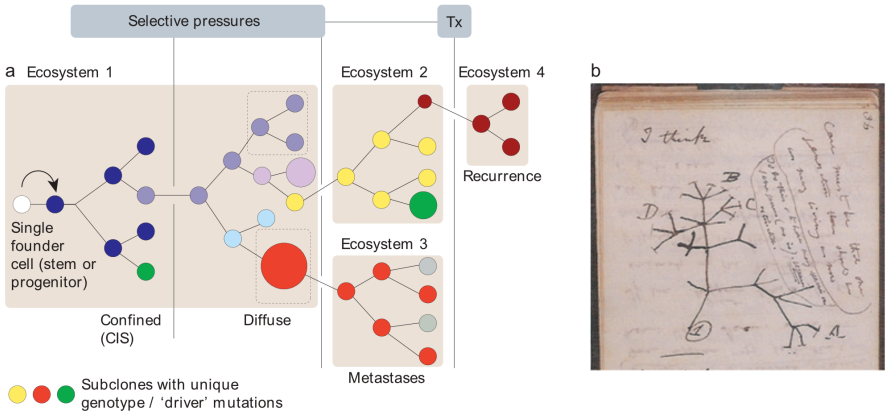
This Week's Citation Classic®

Nowell P C. The clonal evolution of tumor cell populations. *Science* 194:23-8, 1976.
[School of Medicine, University of Pennsylvania, Philadelphia, PA]

REVIEW

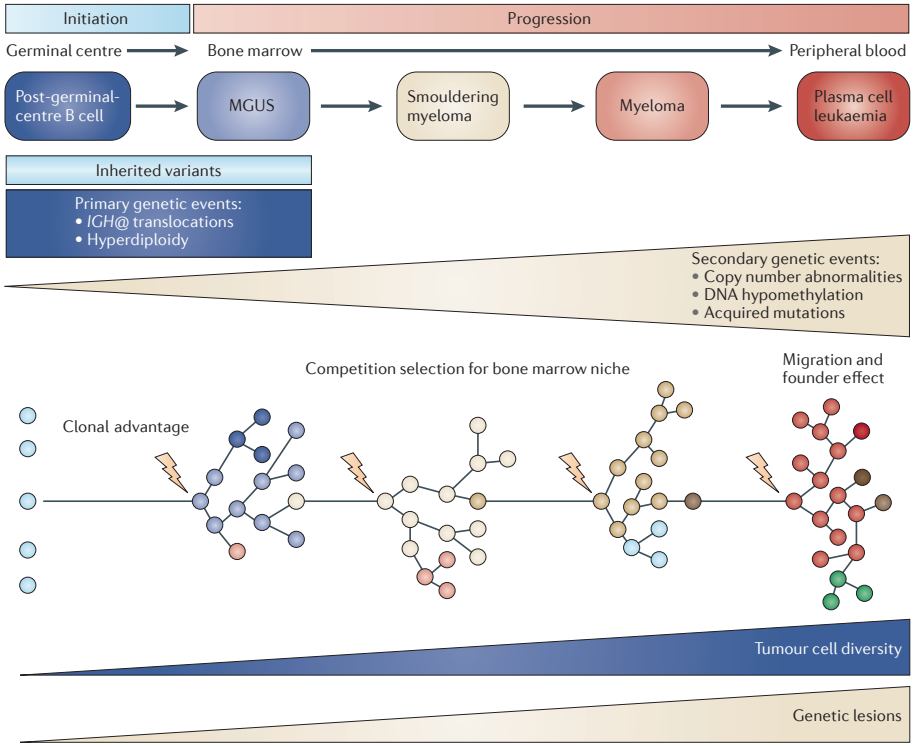
doi:10.1038/nature10762

Clonal evolution in cancer



Greaves and Maley, Nature 2012

Myeloma evolves in discrete steps that are clinically (and biologically?) recognizable



Morgan et al, Nat Rev cancer 2012

Consequently, myeloma is heterogeneous

ORIGINAL ARTICLE

Intraclonal heterogeneity is a critic
development of myeloma and precedes th
symptoms

Walker[1,6], CP Wardell[1,6], L Melchor[1], A Brioli[1,2], DC Johnson[1], MF Kaiser[1],
NC Gutiérrez[3], R Garcia-Sanz[3], J San Miguel[3], FE Davie

nature COMMUNICATIONS

ARTICLE

Received 18 Jul 2013 | Accepted 25 Nov 2013 | Publis

Heterogeneity of genc
profiles in multiple myelom

Niccolo Bolli[1,2], Hervé Avet-Loiseau[3,4], David
Inigo Martincorena[1], Kevin J. Dawson[1], Frances
Jonathan W. Hinton[1], Yilong Li[1], Jose M.C. Tubio
Jon W. Teague[1], Laura Mudie[1], Elizabeth Anderson
Adam S. Sperling[8], Mariateresa Fulciniti[8], Paul G. Ri
Stephane Minvielle[11,12], Philippe Moreau[13], Michel At
Kenneth C. Anderson[8], Peter J. Campbell[1,2] & Nikhil C

Review

The Impact of Tumor Heterogeneity on Diagnostics and Novel Therapeutic Strategies in Multiple Myeloma

Leo Rasche [1,2,*], K. Martin Kortüm [1], Marc S. Raab [3] and Niels Weinhold [2,3]

1 Department of Internal Medicine 2, University Hospital of Würzburg, 97080 Würzburg, Germany; Kortuem_M@ukw.de
2 Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA
3 Department of Internal Medicine V, University Hospital of Heidelberg
Marc.Raab@med.uni-heidelberg.de (M.S.R.); Niels
* Correspondence: Rasche_L@uk

Cancer Cell
Article

Widespread Genetic Heterogeneity in Myeloma: Implications for Targeted

Jens G. Lohr,[1,2,10] Petar Stojanov,[1,2,10] Scott L. Carter,[1,10] Peter Cruz-Gordillo,[1] Michael S. Lawrence,[1] Carrie Sougnez,[1] Birgit Knoechel,[1,2,3] Joshua Gould,[1] Gordon Saksena,[1] Kristian Cibulskis,[1] Aaron McKenna,[1] Michael A. Chapman,[4] Ravid Straussman,[1] Joan Levy,[5] Louise M. Perkins,[5] Jonathan J. Keats,[6] Steven E. Schumacher,[1] Mara Rosenberg,[1] The Multiple Myeloma Research Consortium,[11] Gad Getz,[1,7,12] and Todd R.

DOI: 10.1038/s41467-017-00296-y OPEN

blood

2012 120: 1077-1086
Prepublished online May 9, 2012;
doi:10.1182/blood-2012-03-412981

Intraclonal heterogeneity and distinct molecular mechanisms characterize the development of t(4;14) and t(11;14) myeloma

Brian A. Walker, Christopher P. Wardell, Lorenzo Melchor, Sanna Hulkki, Nicola E. Potter, David C Johnson, Kerry Fenwick, Iwanka Kozarewa, David Gonzalez, Christopher J. Lord, Alan Ashworth, Faith E. Davies and Gareth J. Morgan

www.impactjournals.co

Target, Advance Publications 2015

Spatial genomic heterogeneity in multiple myelom
revealed by multi-region sequencing

L. Rasche[1], S.S. Chavan[1], O.W. Stephens[1], P.H. Pat
S. Deshpande[1], C. Wardell[1], T. Ru
J. Epstein[1], F.E. Da

ARTICLES

https://doi.org/10.1038/s41591-018-0269-2

nature medicine

Single cell dissection of plasma cell heterogeneit
in symptomatic and asymptomatic myeloma

Guy Ledergor[1,2,22], Assaf Weiner[1,22], Mor Zada[1], Shuang-Yin Wang[1], Yael C. Cohen[3,4], Moshe E. Gatt[5], Hila Magen[4,8], Maya Koren-Michowitz[4,9], Katrin Herzog-Tzarfati[4,9], Hadas Keren-Shaul[1,10], Ido Yofe[1], Eyal David[1], Venkata Yellapantula[11,12], Sigalit Kay[3], Lev Shvidel[6,13], Avi Orr-Urtreger[4,14], Jesus San-Miguel[17], Bruno Paiva[17], Amos Tanay[20,21] and Ido Amit[1*]

Whole-exome sequencing of primary plasma cell leukemia discloses heterogeneous mutational patterns

Ingrid Cifola[1,*], Marta Lionetti[2,3,*], Eva Pinatel[1], Katia Todoerti[4], Eleonora Mangano[1], Alessandra Pietrelli[1], Sonia Fabris[2,3], Laura Mosca[2,3], Vittorio Simeon[4], Maria Teresa Petr[illegible]to Morabito[6], Massimo Offidani[7], Francesco Di Raimondo[8], Anto[illegible] Caravita[10], Cristina Battaglia[1,11], Gianluca De Bellis[illegible][13], Antonino Neri[2,3]

Genetics of multiple myeloma: another heterogeneity level?

Jill Corre,[1,2] Nikhil Munshi,[3,4] and Hervé Avet-Loiseau[1,2]

[1]Unit for Genomics in Myeloma, L'Institut Universitaire du Cancer de Toulouse-Oncopole, Centre Hospitalier Universitaire
Recherche en Cancérologie de Toulouse Institut National de la Santé et de la Recherche Médicale U1037
Center, Dana–Farber Cancer Institute, Harvard Medical School, Boston, MA; and [4]

P[illegible]a, 21 settembre 2019

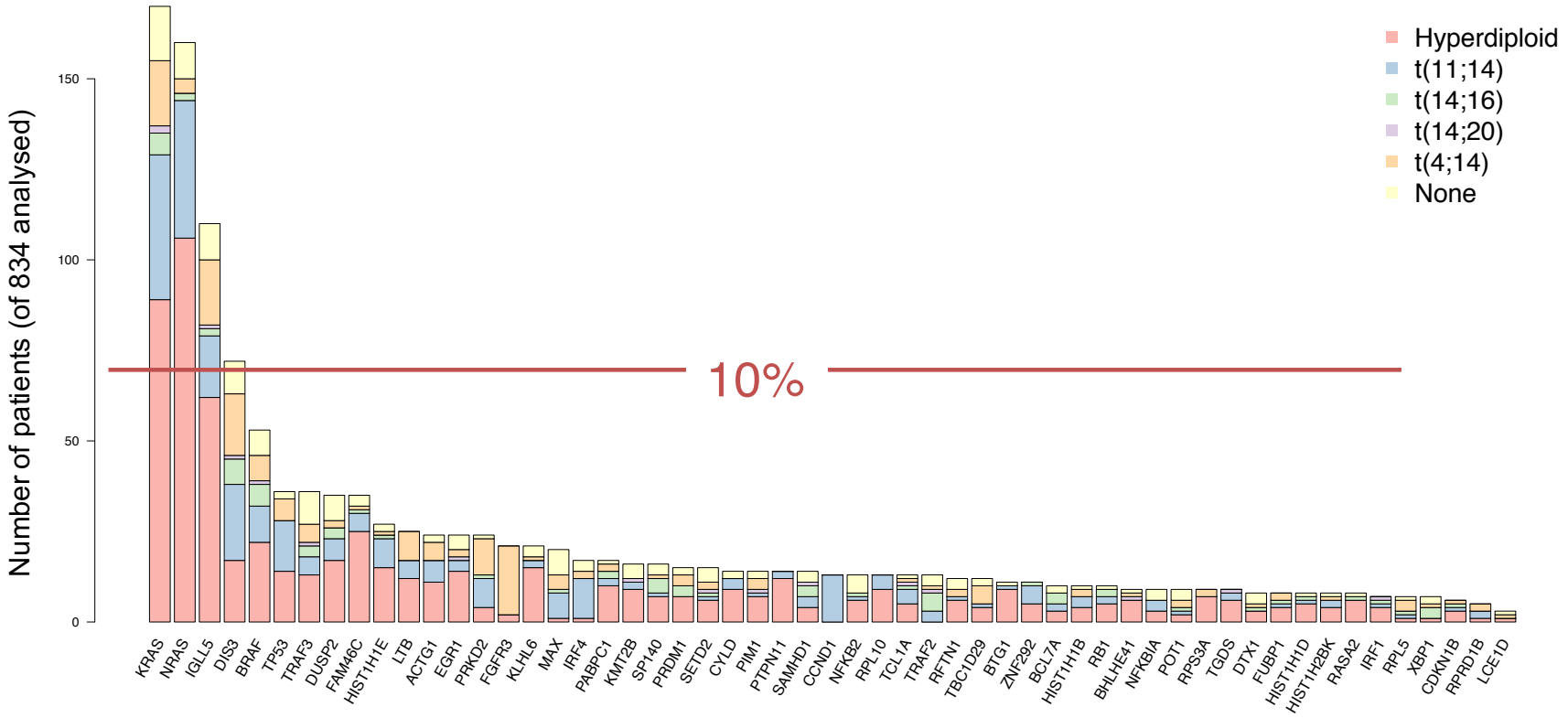
Recent acquisitions in myeloma "evolutionary biology" that support heterogeneity

Heterogeneity in SPACE and TIME of the disease:

- Frequency of recurrence of driver mutations across patients
- Number of cells carrying a driver mutation
  - Mutations are often "late" events and present only in a fraction of cells
- Confounding effect of additional mutations carried by
  - The same cells
  - Different cells in the tumor
- Tumors evolve
  - Spontaneously (*in situ* or in different locations)
  - After treatment

Keats Blood 2012
Egan Blood 2012
Walker Blood 2012
Bolli Nat Comms 2014
Lohr Cancer Cell 2014
Melchor Leukemia 2014
Walker Leukemia 2014
Corre et al Blood 2015
Rasche Nat Comms 2017
Bolli Leukemia 2018
Bolli Nat Comms 2018
Ledergor Nat Med 2018
Rasche Int Journ Mol Sci 2019

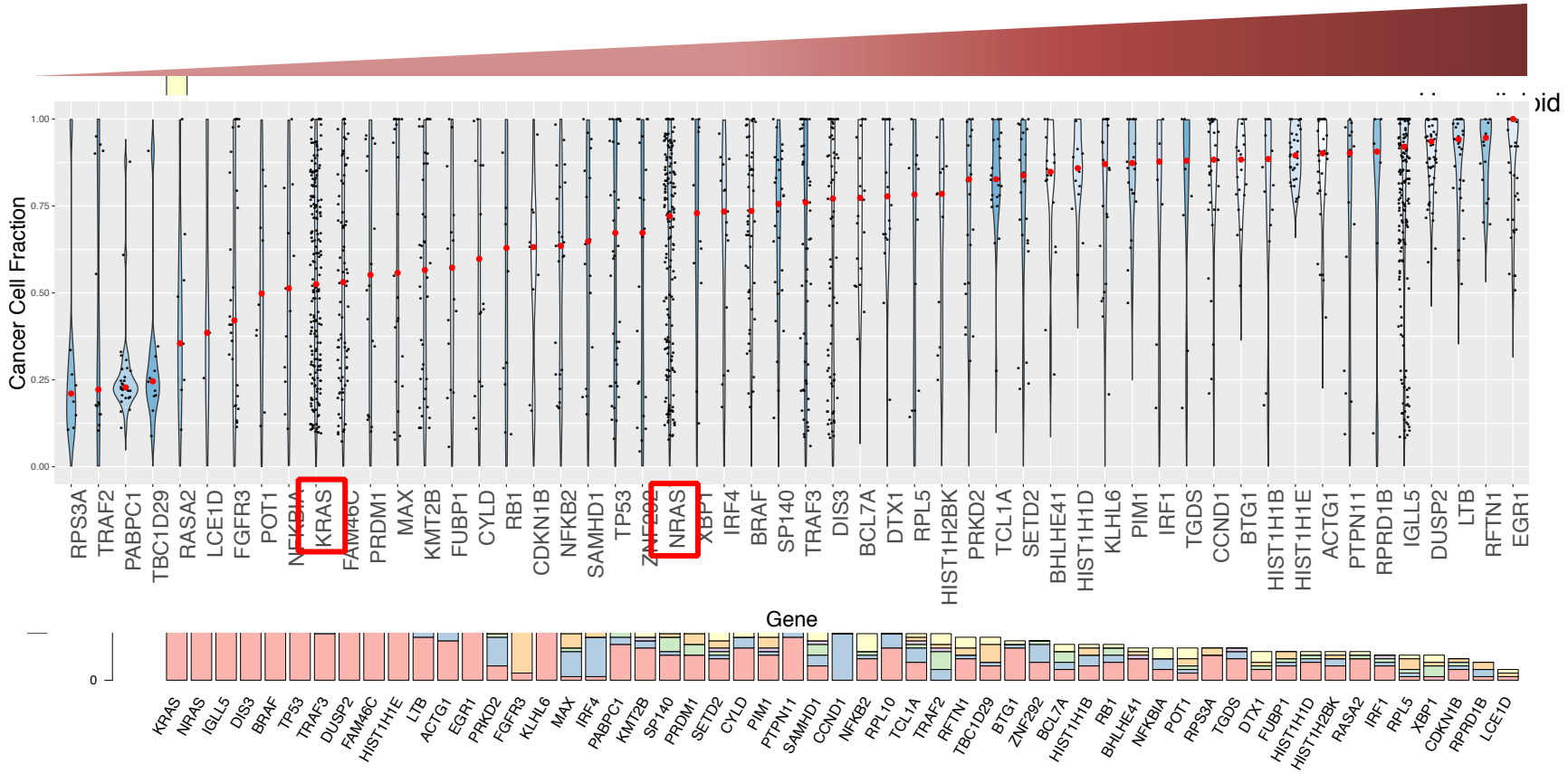
Driver mutations show low recurrence and low cancer cell fraction



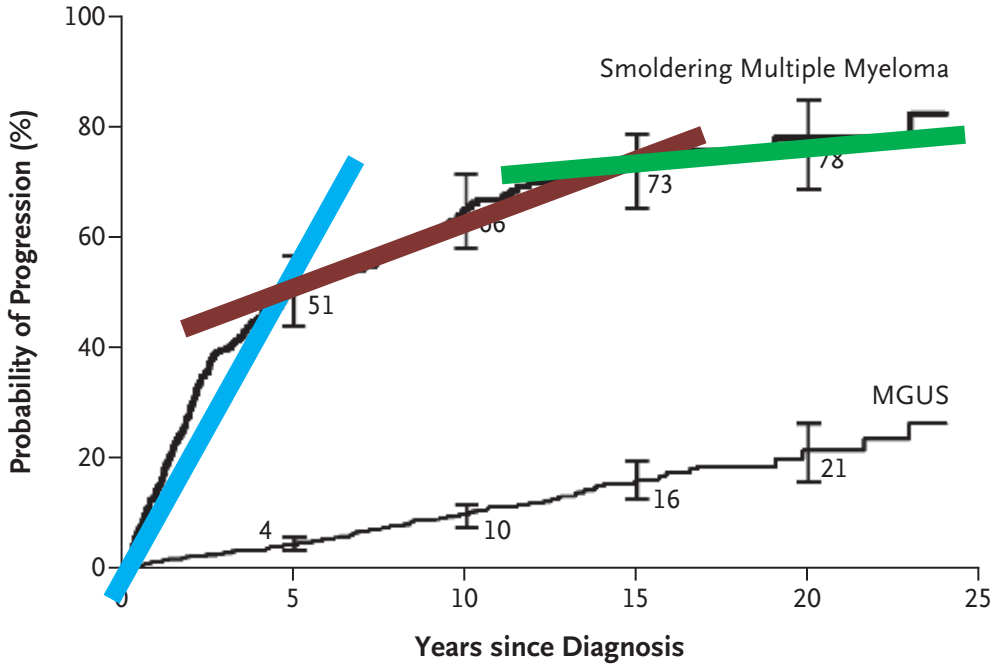
CoMMpass release IA9 at
https://research.themmrf.org

Maura et al., Nat Comms 2019

Driver mutations show low recurrence and low cancer cell fraction



Clinical question: can genomics help predict the outcome of SMM at diagnosis?



Kyle et al, NEJM 2007

High risk, probably already myeloma

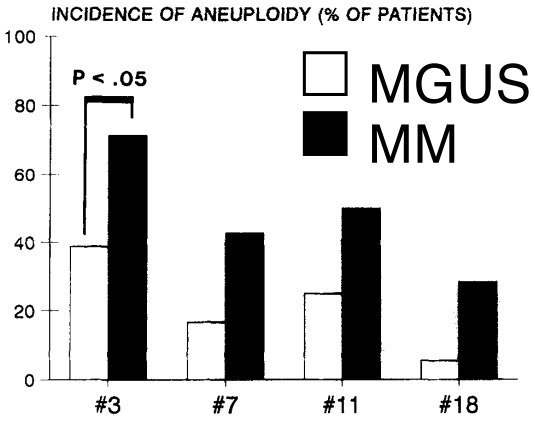
Intermediate risk, needs evolution to progress to myeloma

Low-risk, MGUS-like

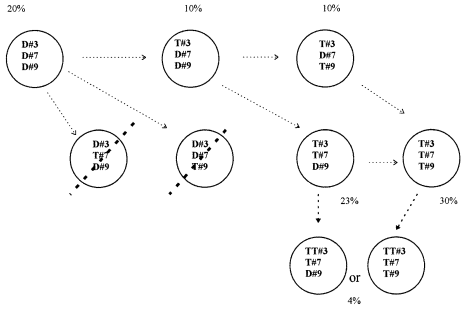
* Perez-Persona et al, Blood 2007
Dispenzieri et al, Blood 2008
Rajkumar et al, Blood 2015

Asymptomatic stages show a lower genomic complexity

FISH

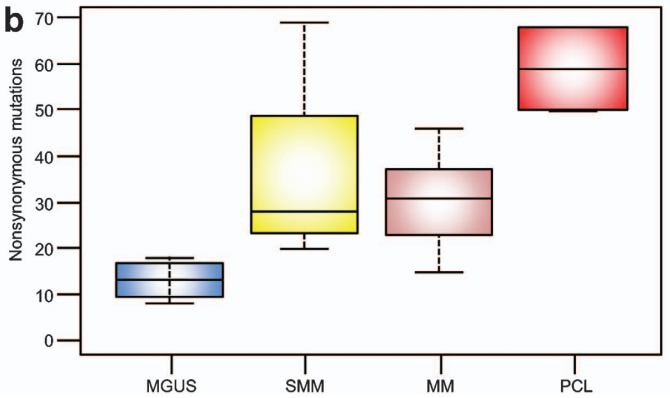


Drach et al, 1995

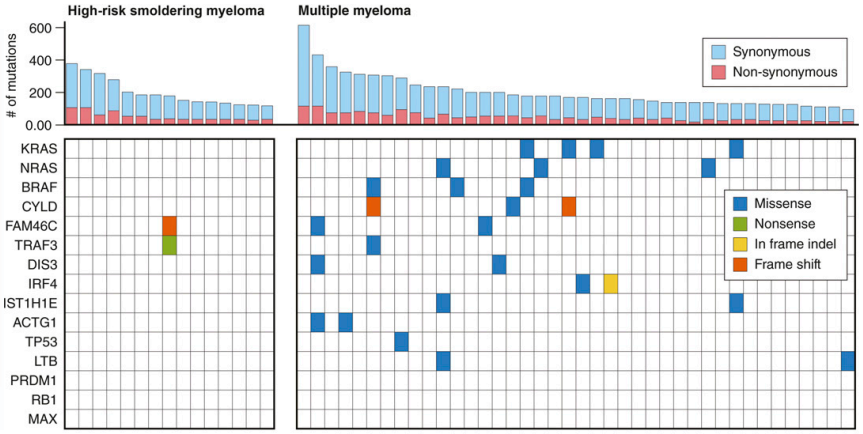


Zandecki et al, 1997

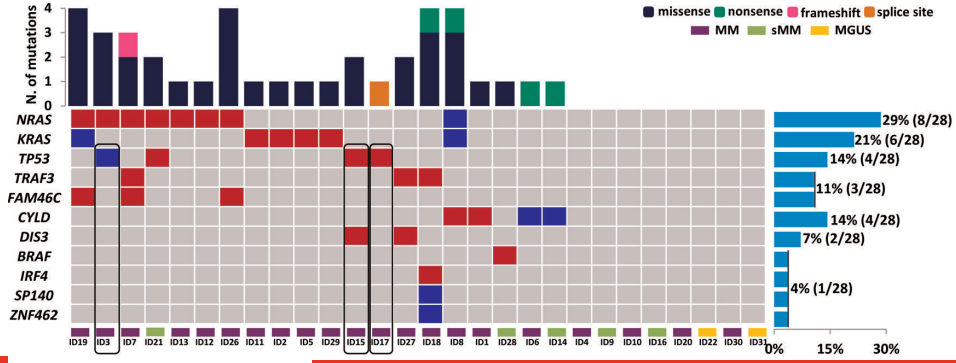
NGS (whole exome, targeted)



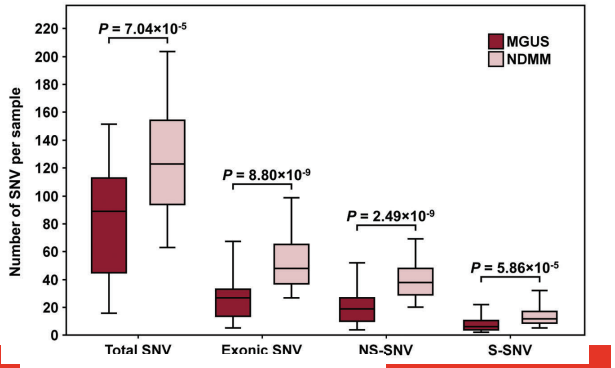
Walker et al, 2014



Mailankody et al, 2017



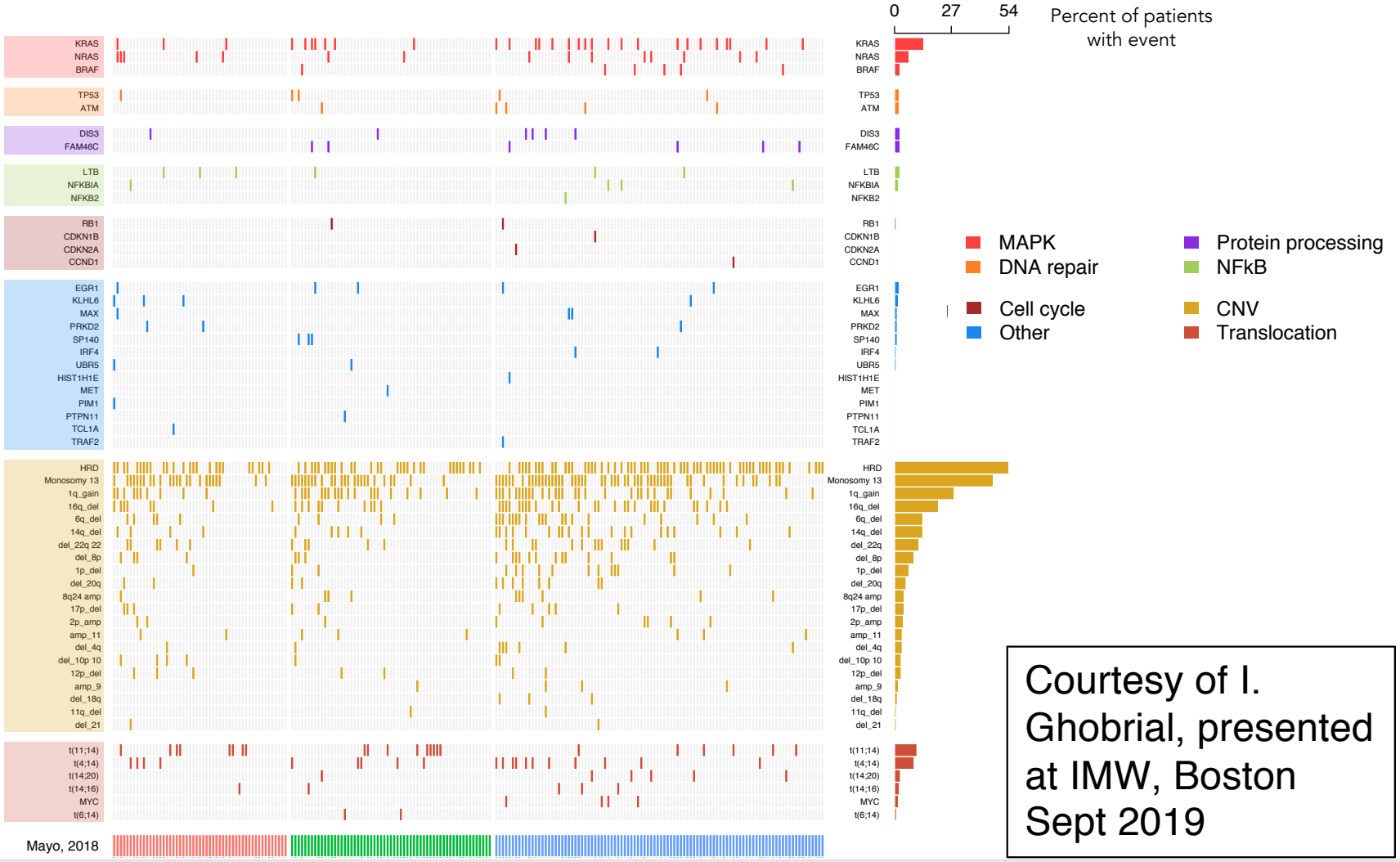
Gerber et al, 2018



Mikulasova et al, 2017

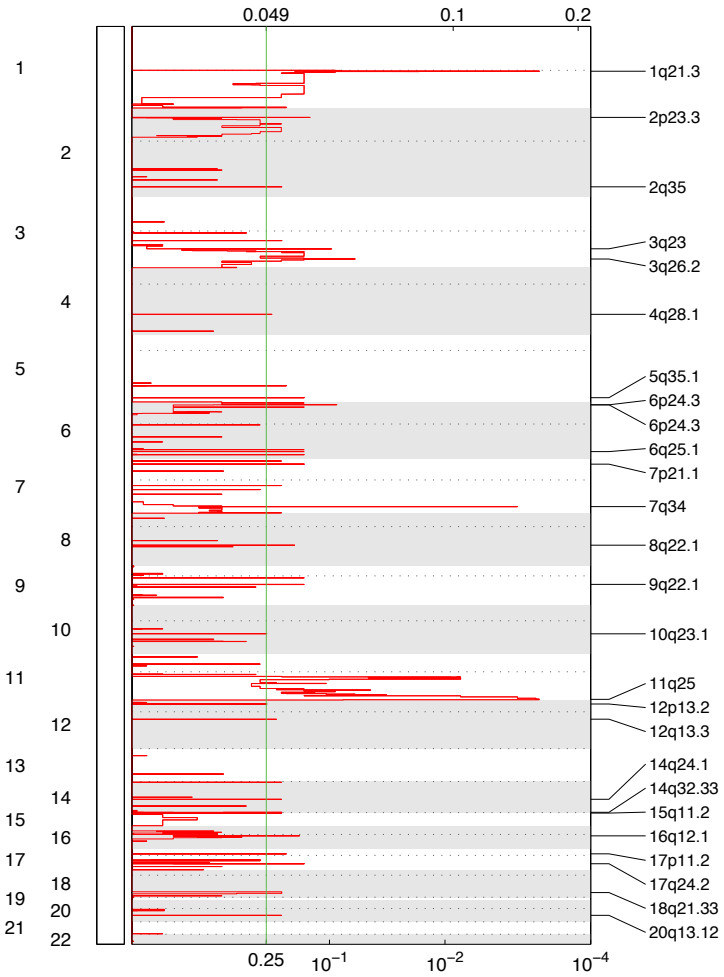
Mutational landscape of SMM (*n*= 214)

80% CNAs,
42% Tx,
36% mutations
- No difference based on the clinical model

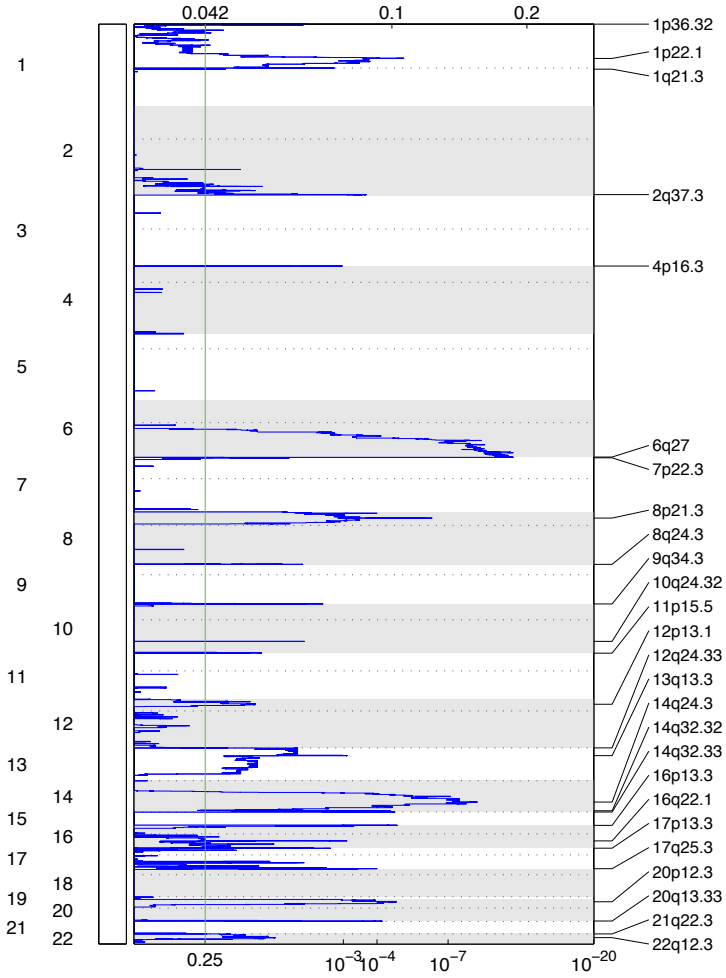


Courtesy of I. Ghobrial, presented at IMW, Boston Sept 2019

Significant arm level and focal CNAs

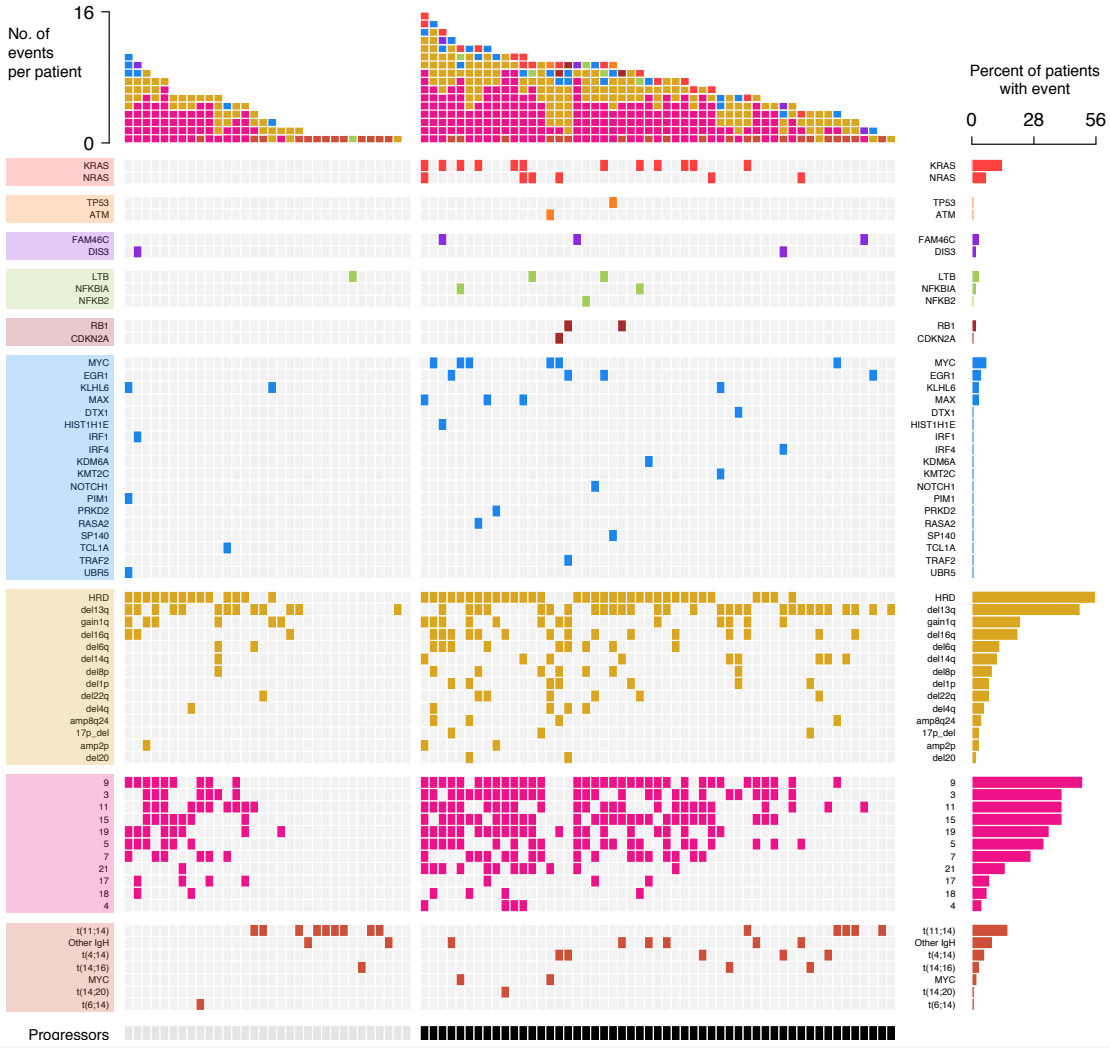


Amplifications



Deletions

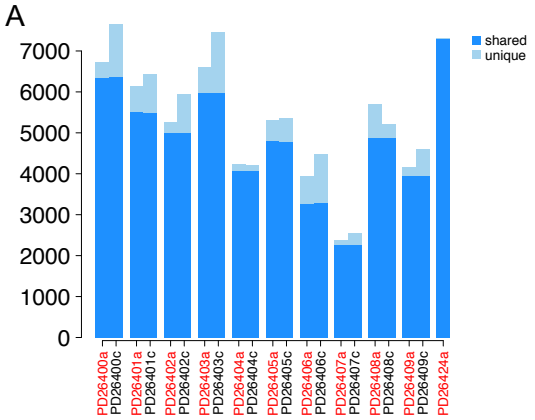
Genomic landscape of progressors *vs* non-progressors (*n* = 85)

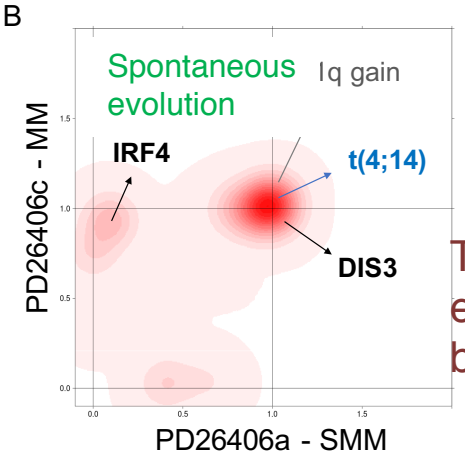


Courtesy of I. Ghobrial, presented at IMW, Boston Sept 2019

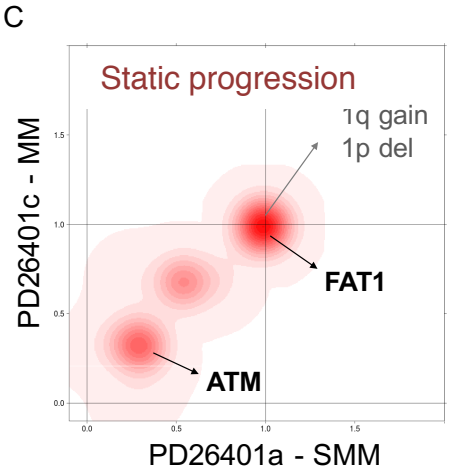
Two genomic routes of evolution from SMM to MM

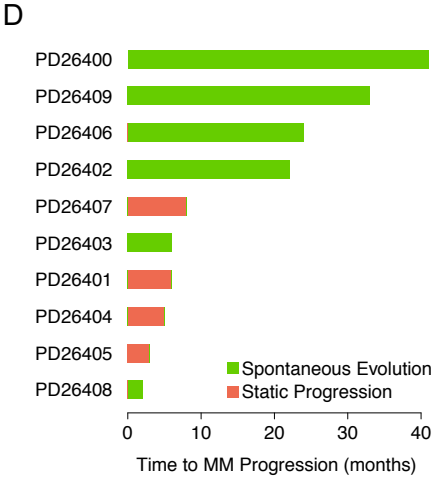
- 10 serial samples
- Short progression time
  - (ultra-HR)
- Whole genome sequencing





These cases need an evolutionary shift to become myeloma



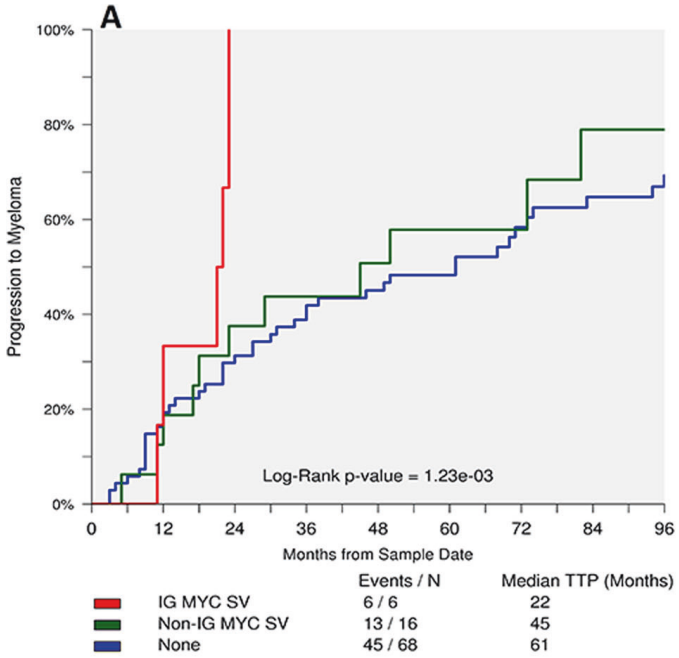


These cases are
- «de facto» MM already?
-dependent on the microenvironment?

Bolli et al, Nat Comms 2018

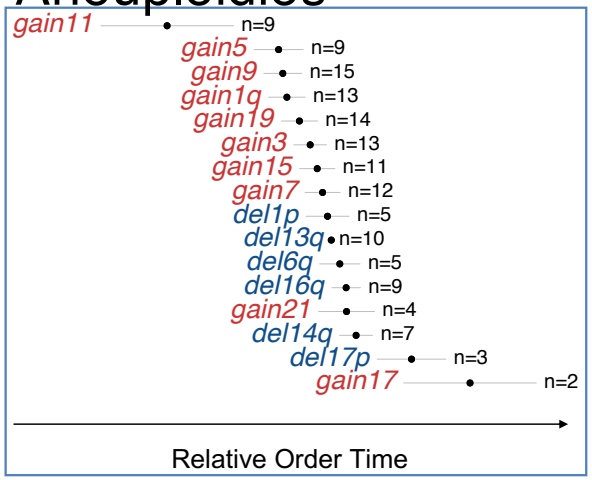
Structural events appear in a somewhat orderly fashion

opportunity to define what's associated with initiation and what with progression

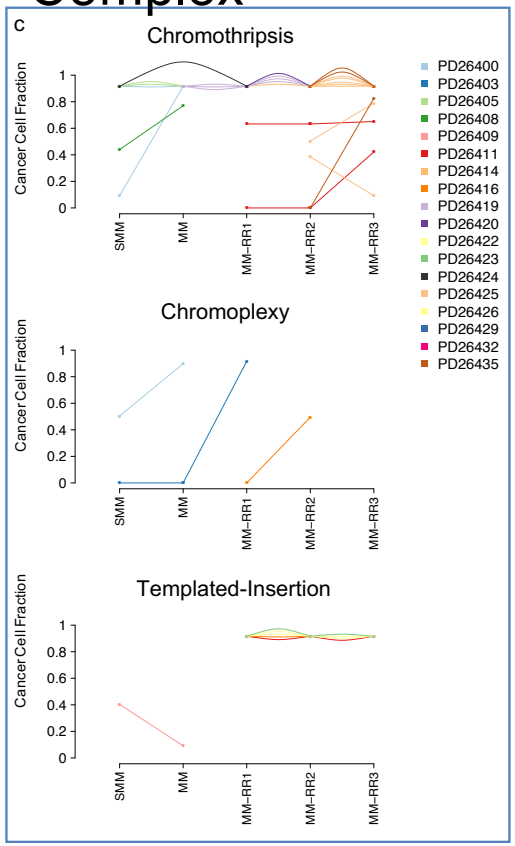


Misund et al, Leukemia 2019

Aneuploidies



Complex



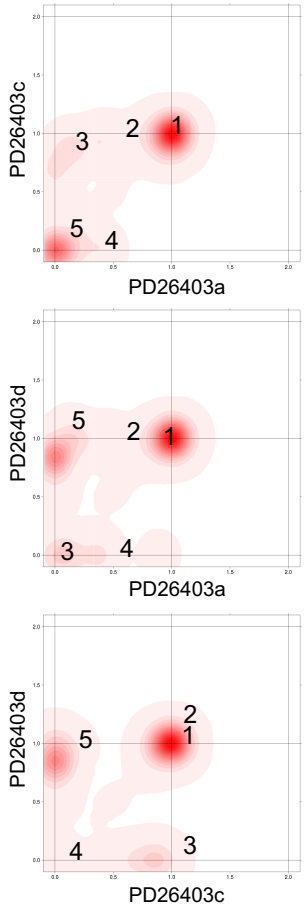
Bolli et al, Nat Comms 2018
Maura et al., Nat Comms 2019

Genomic analysis allows reconstruction of the life history of each case

PD26403a: SMM

PD26403c: NDMM

PD26403d: RRMM



Genomic analysis allows reconstruction of the life history of each case

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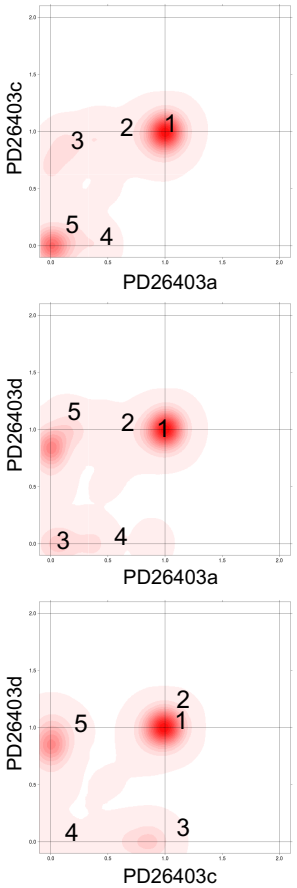

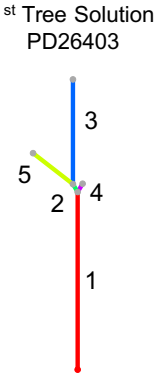

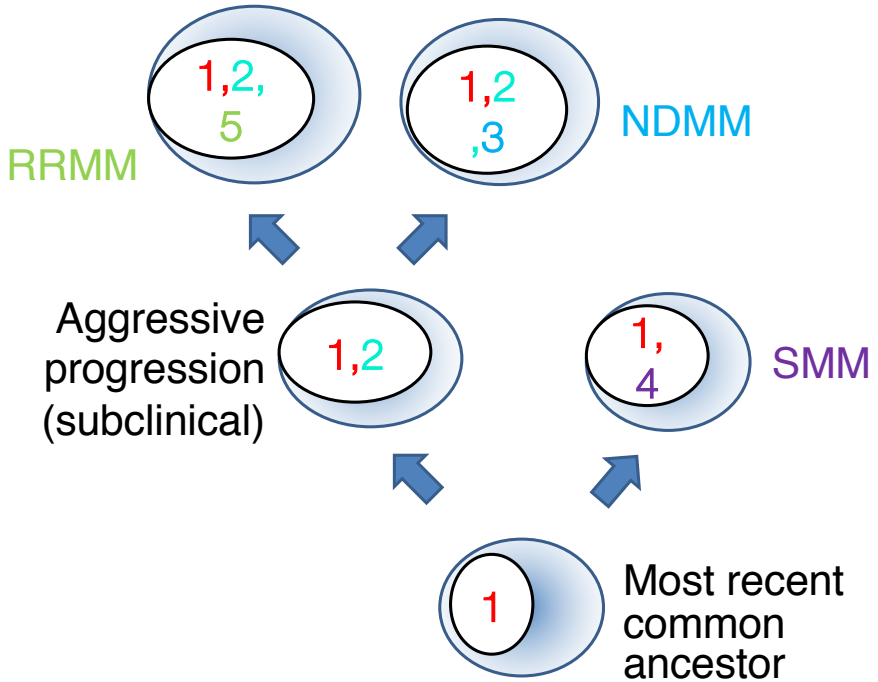

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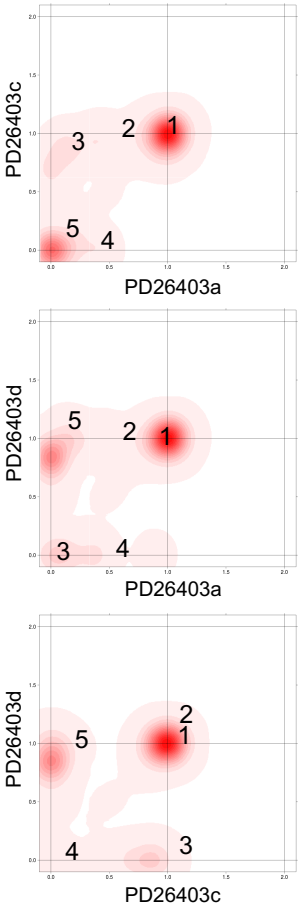
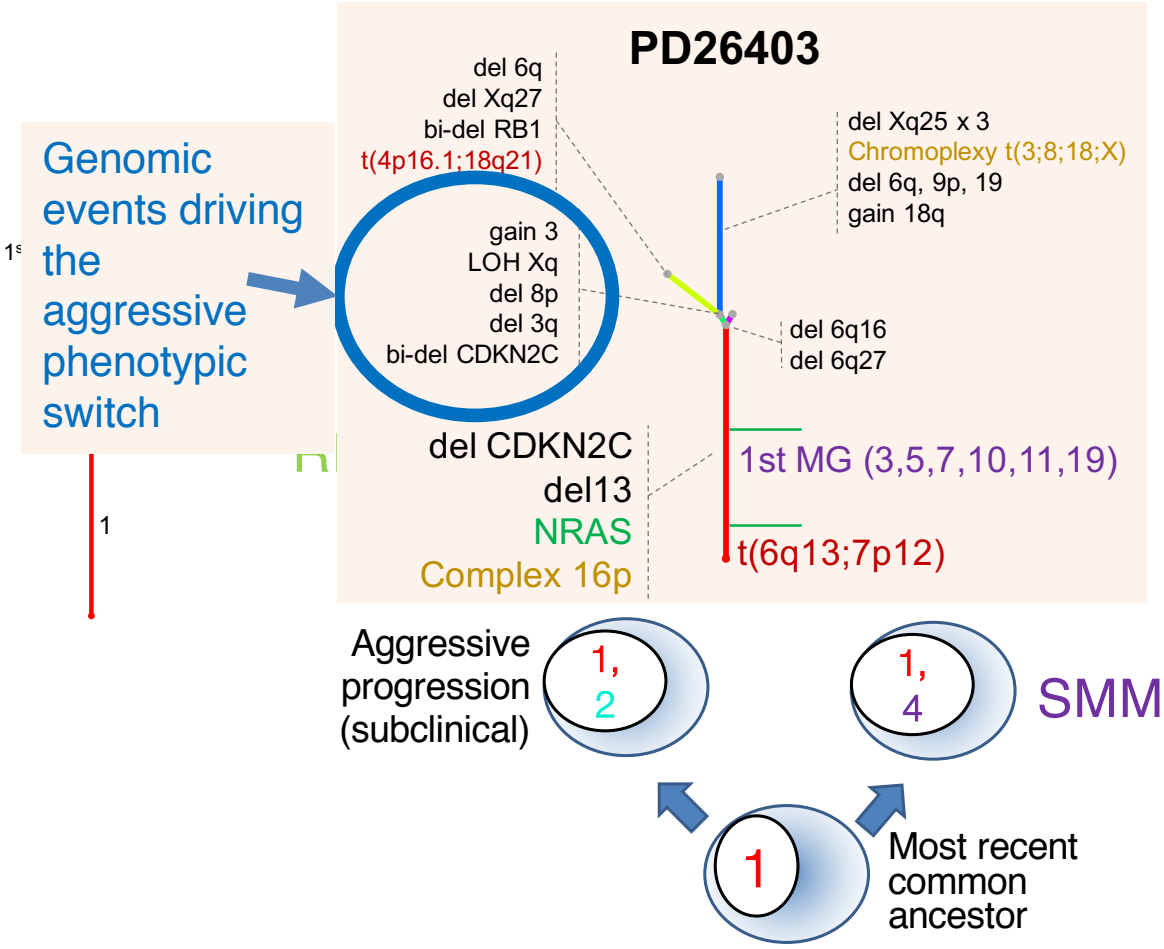
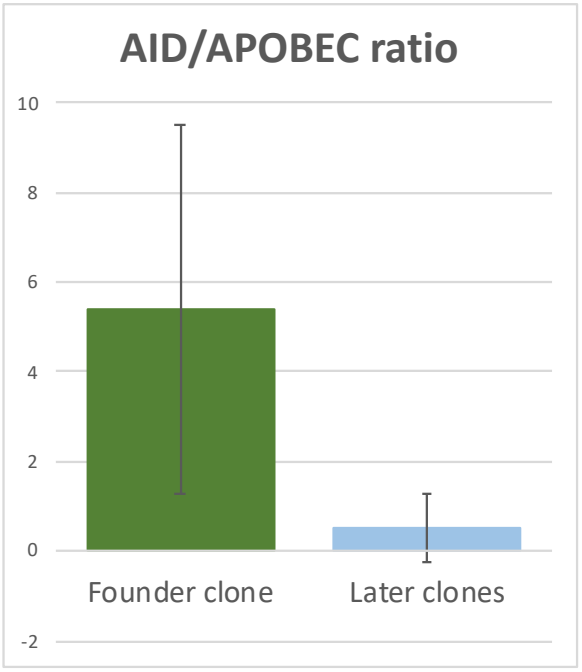
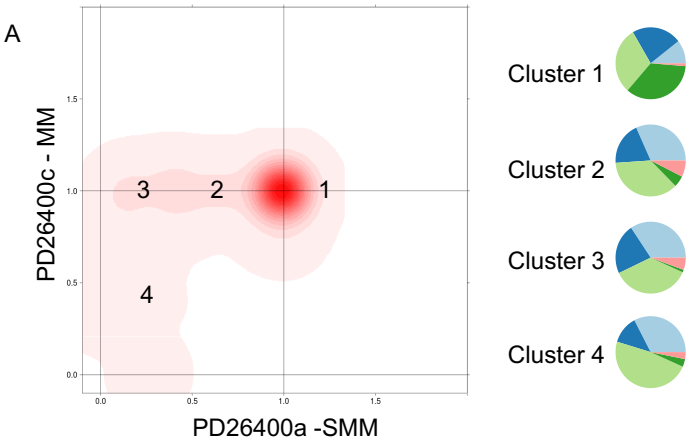


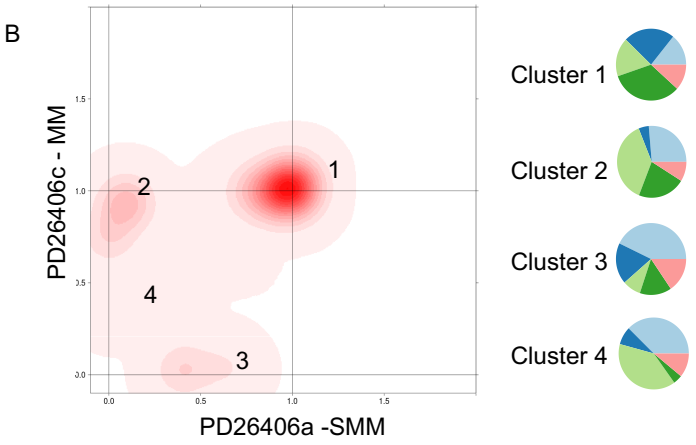
Genomic events driving the aggressive phenotypic switch

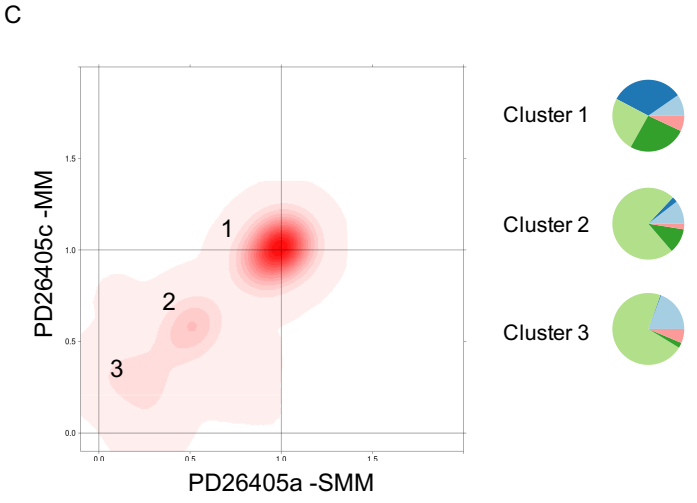


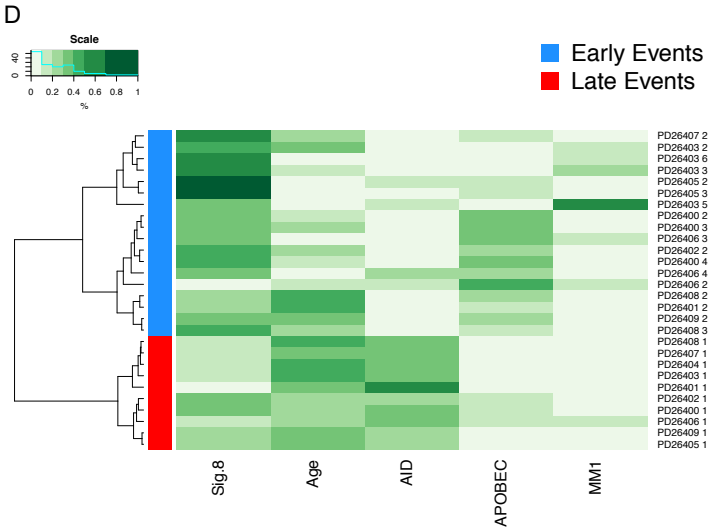
Differential activity of mutational signatures over time



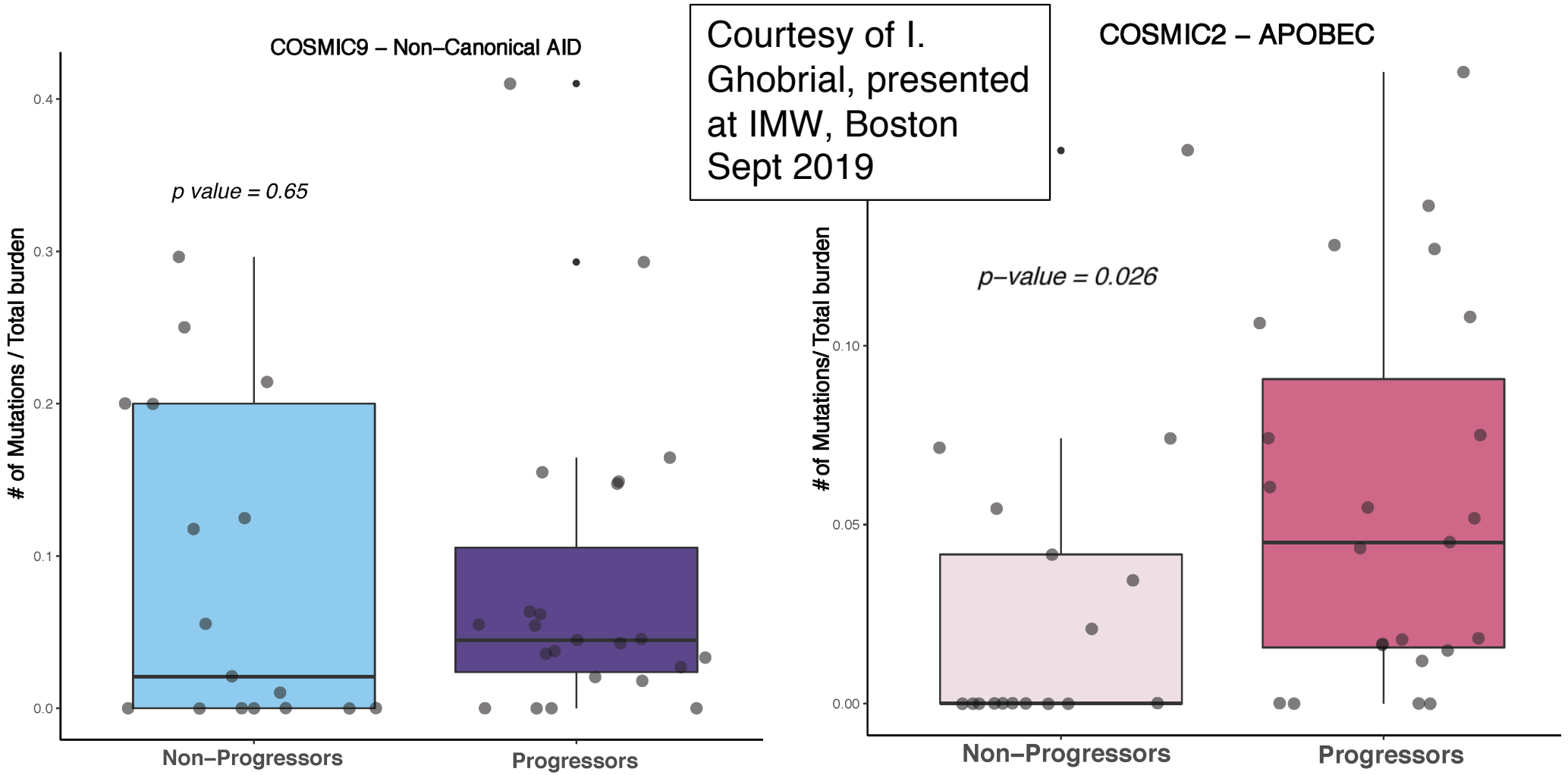




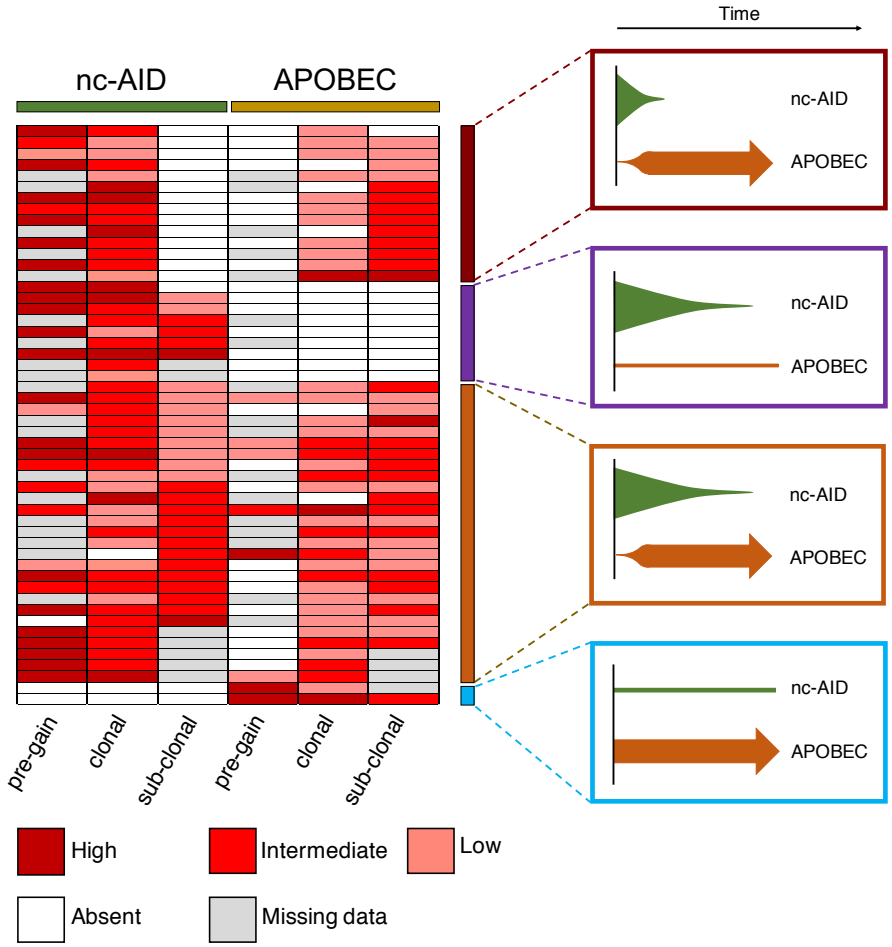


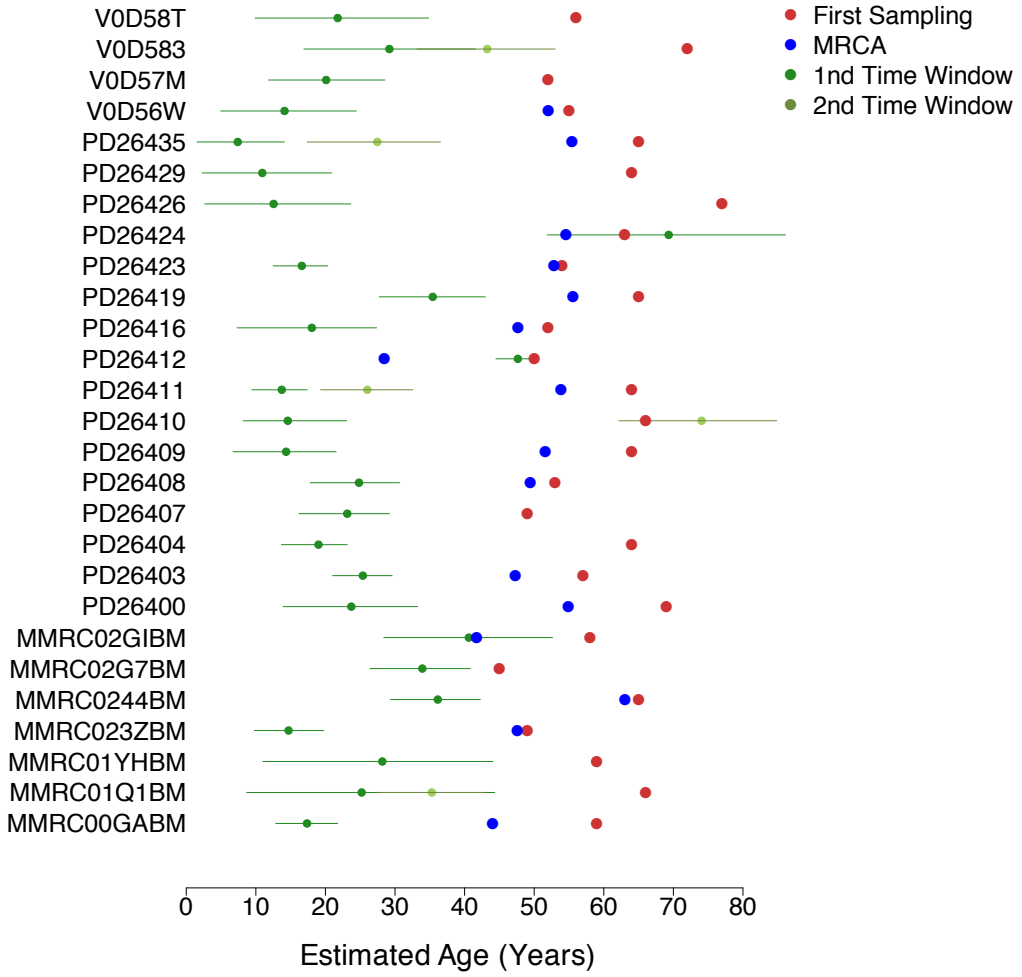


Mutational signatures association with progression



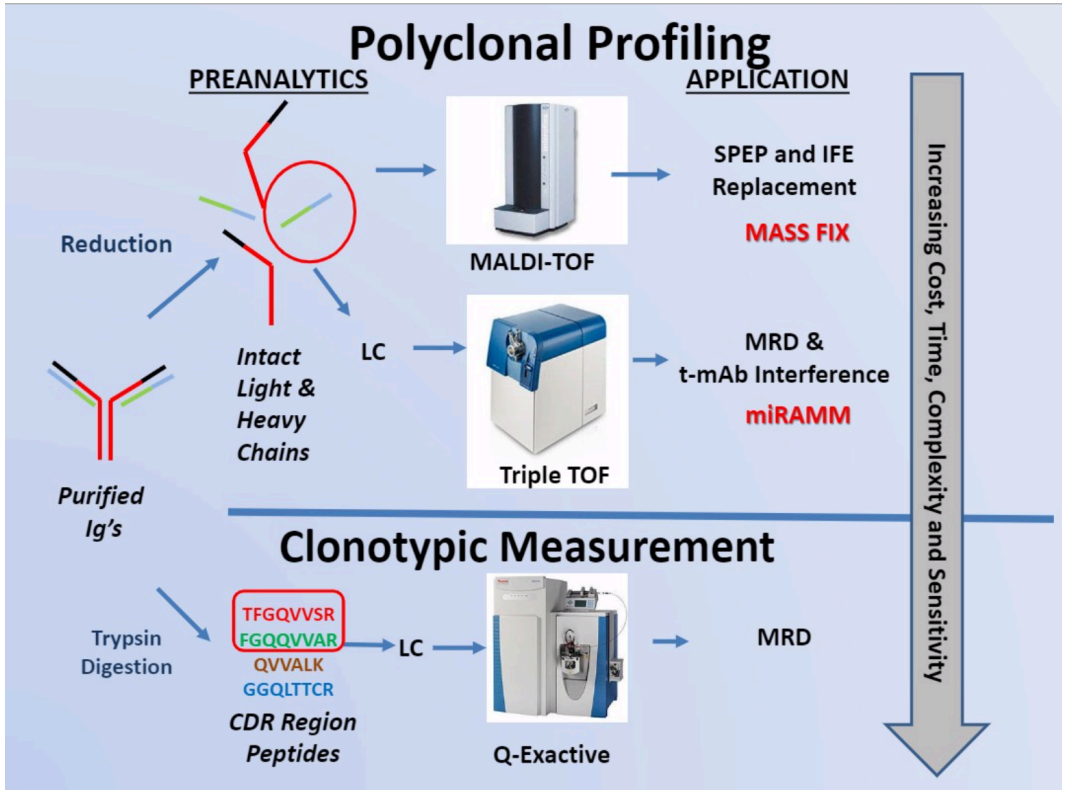
Insights into timing and modality of MM initiation

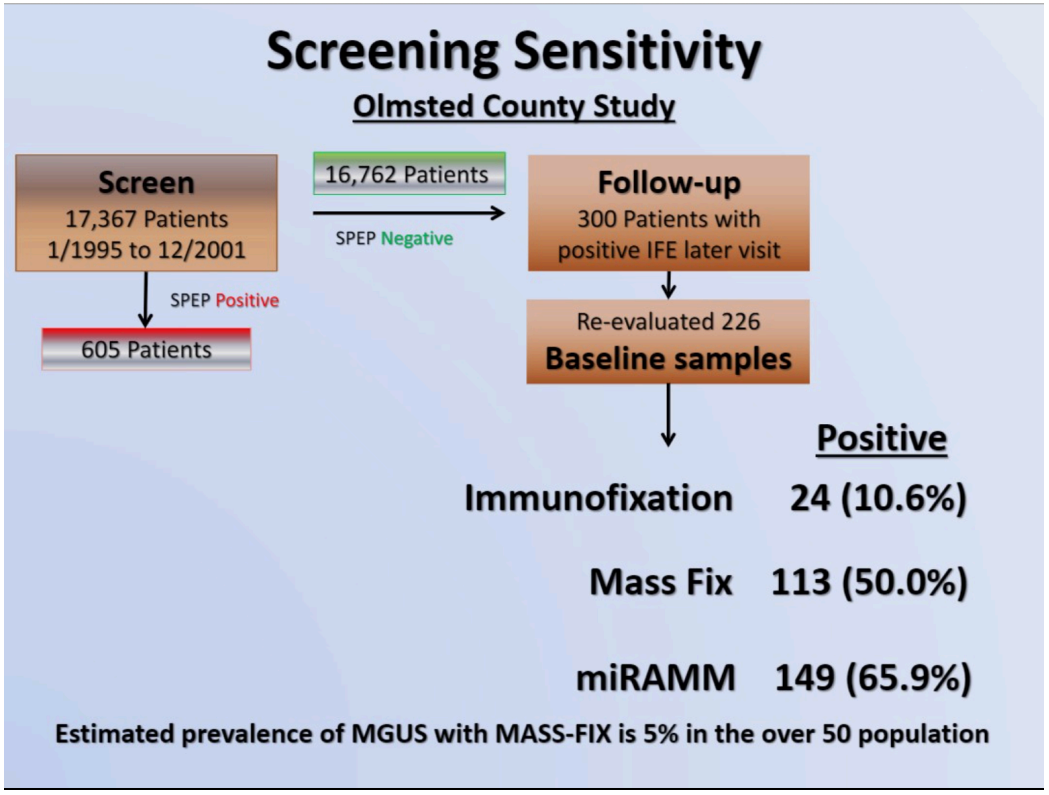




Maura et al, submitted

Mass spectrometry redefines the prevalence of MGUS





Mass spectrometry redefines the prevalence of MGUS

Screening Sensitivity

Olmsted County Study

Screen
17,367 Patients
1/1995 to 12/2001

SPEP Positive → 605 Patients

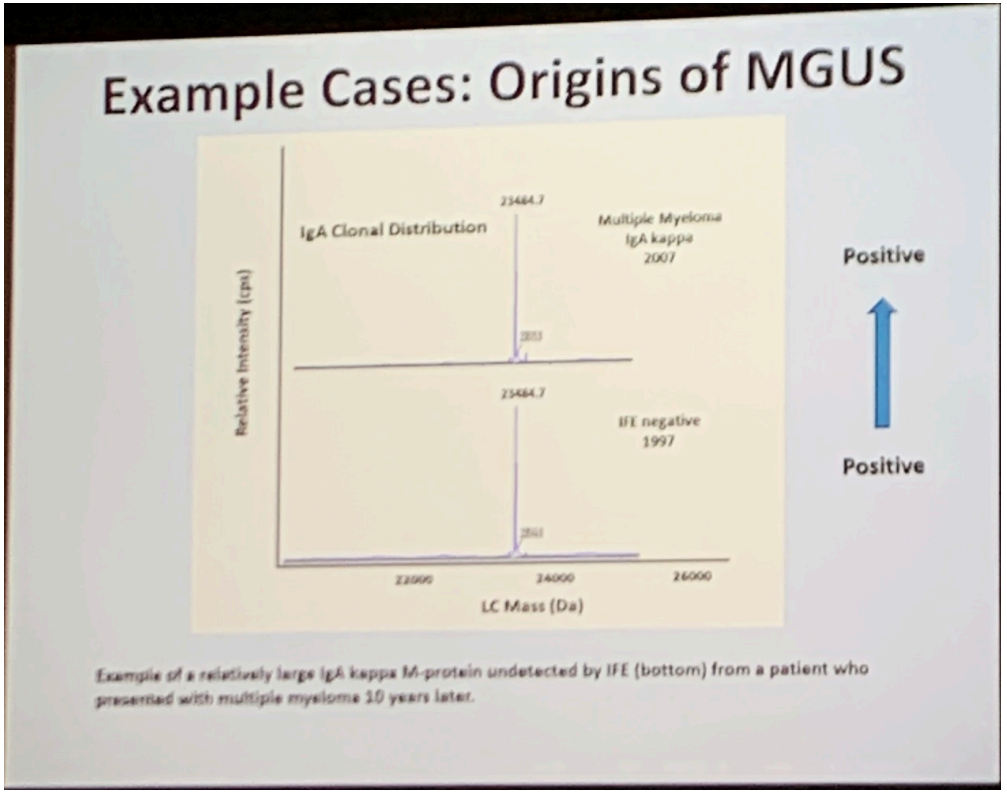
16,762 Patients → SPEP Negative

Follow-up
300 Patients with positive IFE later visit

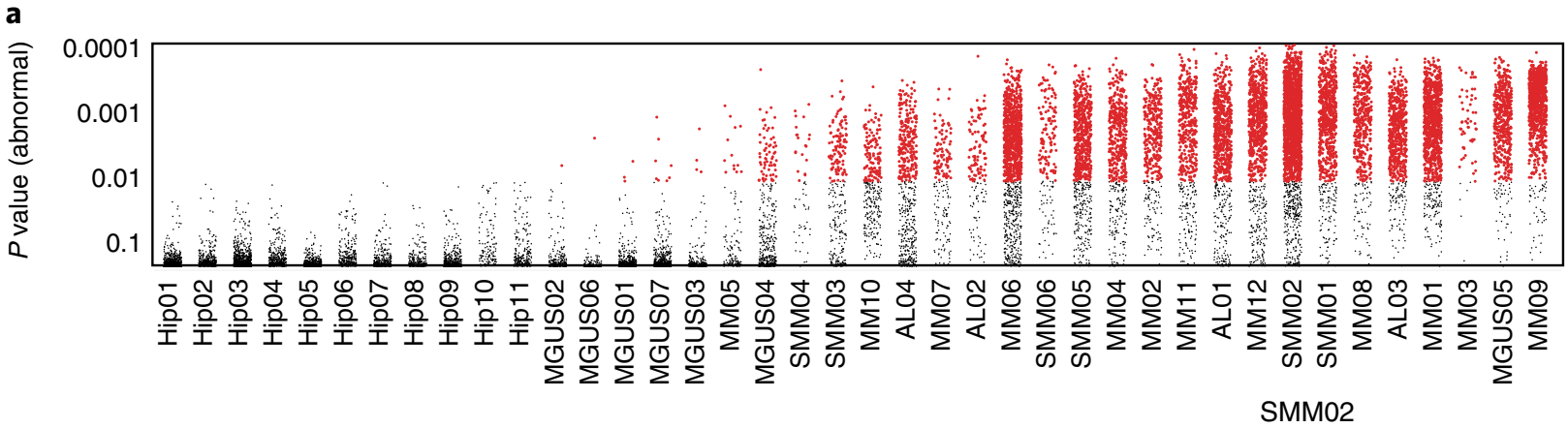
Re-evaluated 226
Baseline samples

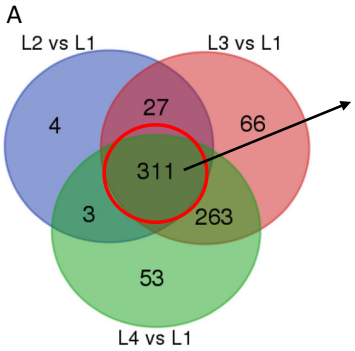
	Positive
Immunofixation	24 (10.6%)
Mass Fix	113 (50.0%)
miRAMM	149 (65.9%)

Estimated prevalence of MGUS with MASS-FIX is 5% in the over 50 population



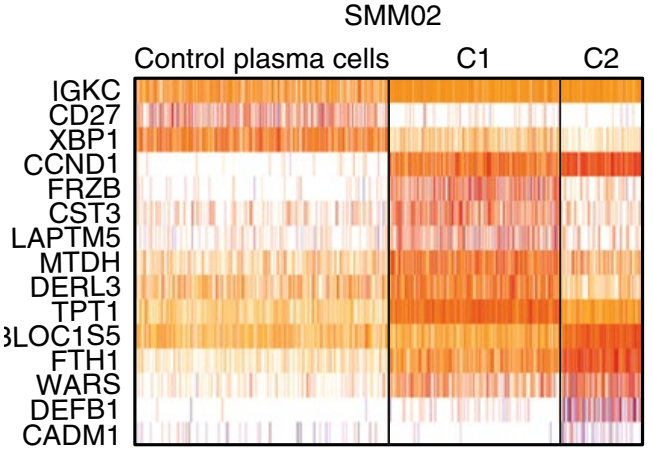
2019 Single cell RNAseq can identify aggressive PCs within an indolent clone





Gene Set Name*	No. of Genes in Overlap	p-value
OXIDATIVE PHOSPHORYLATION	42	$1.42\ e^{-50}$
MYC TARGETS	27	$2.61\ e^{-27}$
MTORC1 SIGNALING	17	$3.15\ e^{-14}$
ANDROGEN RESPONSE	9	$2.5\ e^{-8}$
UNFOLDED PROTEIN RESPONSE	9	$6.66\ e^{-8}$
ADIPOGENESIS	11	$1.06\ e^{-7}$
INTERFERON GAMMA RESPONSE	10	$9.69\ e^{-7}$

* Hallmark gene set database



n = 3,290 single cells

Ledergor et al, Nat Med 2018
Jang et al, BCJ 2019

Conclusions

- Intra-tumor and inter-tumor heterogeneity is higher than anticipated
  - ➢ Need for larger-scale studies and novel (single-cell) technologies to dissect heterogeneity
- Structural events more than gene mutations seem to drive evolution; however, genomic analyses still explain little of the transcriptional variability
  - ➢ Need to integrate genomic studies with epigenetics, immune microenvironment etc
- Discrete steps of *clinical* evolution do not necessarily correlate with stages of *genomic* evolution
  - ➢ Opportunities to re-define risk of progression
- Is it time for clinical translation of these findings?
  - ➢ Probably not yet, but results encourage further research
    - ○ Probability of SMM evolution
    - ○ Risk of NDMM
    - ○ Genomic correlates of drug response

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