Harnessing the Power of Genomics in Correlative Studies

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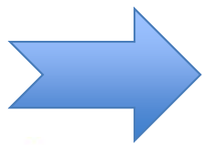
Cancer vs. Genomics

- Cancer specimens present a number of challenges for genomics:
  - % tumor nuclei/cellularity
  - small biopsies/specimens
  - FFPE
  - availability of matched normal
  - data interpretation challenges



These challenges can largely be addressed

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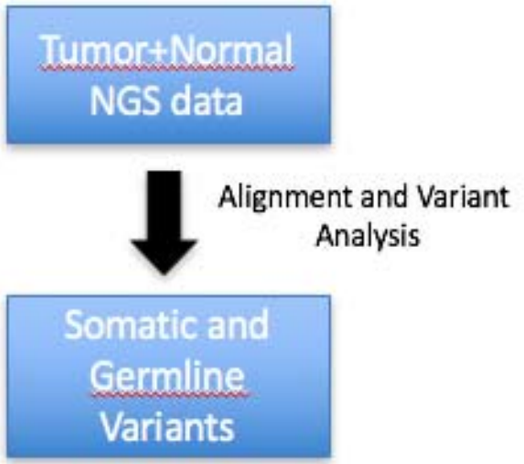
Clinical Applications of Cancer Genomics



Somatic Variants:

- Pathogenic driver mutations (targeted therapy)
- Gene fusion drivers (targeted therapy)
- Amplified cancer driver genes (targeted therapy)
- Calculate mutational load (immunotherapy)
- Neoantigen prediction (immunotherapy incl. vaccine)

Germline Variants:

- Pathogenic cancer susceptibility mutations (Genetic counseling)
- Microsatellite instability (Immunotherapy)
- BRCA1/2, other HRD genes (PARP inhibitors)
- Pol E (treatment considerations)

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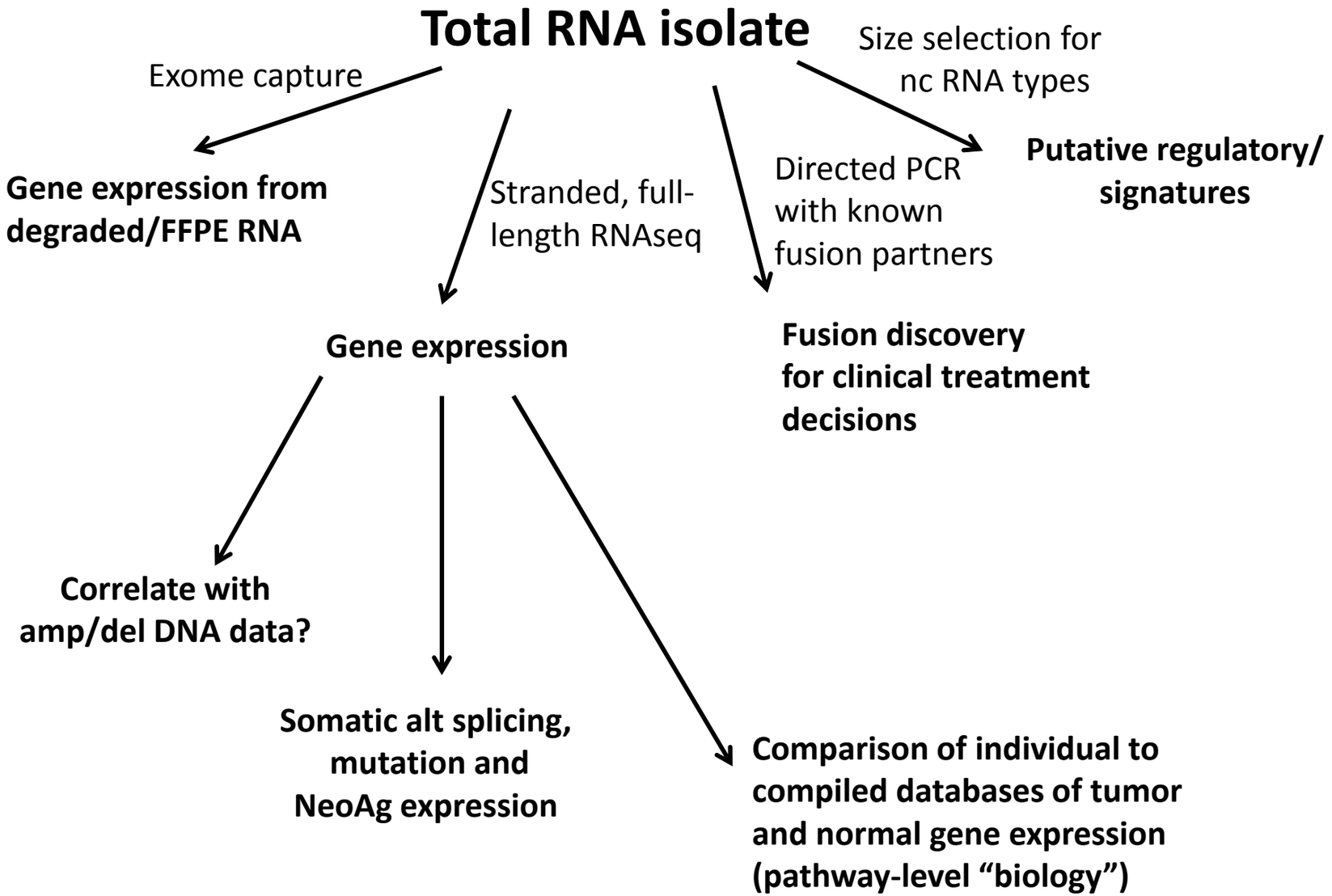
Applying RNA Sequencing to Cancer



Correlative Genomics of Clinical Trial Samples

Correlating Genotype to Outcome

Genomics to Mechanisms

ARTICLE

doi:10.1038/nature11143

Whole-genome analysis informs breast cancer response to aromatase inhibition

Matthew J. Ellis[1,2,3]*, Li Ding[4,5]*, Dong Shen[4,5]*, Ji
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Tammi L. Vickery[4,5], Adnan Elhammali[8,9,10], Helen
David J. Dooling[4,5], David Ota[23], Li-Wei Chang[3,14],
Joshua M. Stuart[11], Richard K. Wilson[2,4,5] & Elaine

nature COMMUNICATIONS

Approaching unknown mechanisms of treatment response/resistance requires banking and collecting clinical data for many pre- and post-treatment samples obtained under a similar treatment regimen…

…and requires both DNA and RNA sequencing data to provide an integrated evaluation of how the genome and it's interpretation changes.

ARTICLE

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Aromatase inhibition remodels the clonal architecture of estrogen-receptor-positive breast cancers

Christopher A. Miller[1,2], Yevgeniy Gind
Jeremy Hoog[3], Tiandao Li[1], David E. La
Jacqueline Snider[3], Thomas Walsh[9], G
Elaine R. Mardis[1,3,4,5] & Matthew J. Ell

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 1070–1077, 2017
doi:10.1093/annonc/mdx048
Published online 21 February 2017

ORIGINAL ARTICLE

Genomic characterization of HER2-positive breast cancer and response to neoadjuvant trastuzumab and chemotherapy—results from the ACOSOG Z1041 (Alliance) trial

R. Lesurf[1], O. L. Griffith[1,2,3,4], M. Griffith[1,2,3,4], J. Hundal[1], L. Trani[1], M. A. Watson[5], R. Aft[3], M. J. Ellis[1,2,6], D. Ota[7], V. J. Suman[8], F. Meric-Bernstam[9], A. M. Leitch[10], J. C. Boughey[11], G. Unzeitig[12], A. U. Buzdar[9], K. K. Hunt[9] & E. R. Mardis[13,14]*

Clinical Trial Samples Inform Late Relapse ER+ Breast Cancer

Large-scale genomic discovery in breast cancer has identified new genes and driver alterations, but little in the way of prognostic markers, especially in ER+ late relapse disease

Prior studies have identified GOF mutations and translocations into ESR1 in late relapse ER+ disease, likely due to long-term estrogen suppression

A more comprehensive approach to connect somatic alterations to outcomes requires large sample numbers, uniform treatment and long-term outcome data

By definition, these samples must come from old-age FFPE tumor samples

Study Design: Informed by Large-Scale Discovery

- We identified 83 genes from large-scale genomic studies that were frequently mutated in ER+ breast cancer and designed a panel for hybrid capture (IDT ultramers)
- Three clinical trials were identified with desired attributes: ER+ disease, uniform treatment and long-term follow-up
- Due to lack of matched normal blood, we developed a computational approach to identify somatic variants in the 83 genes
- Results were compared to TCGA and then evaluated in context of patient outcomes (BCSS and RFS)

Clinical Trial Samples

TAM Series:

- average age of 67 at diagnosis (range: 40-89+), primarily postmenopausal, grade 2 or 3 ductal histology, all clinically ER+, at least 88.6% were clinically HER2-
- treated with five years of adjuvant tamoxifen, median follow-up of 10 years
- **625** of 632 (98.8%) patient samples that fully met study criteria, **and** passed a minimum sequencing quality cutoff of at least 80% of targeted bases covered at greater than 20X

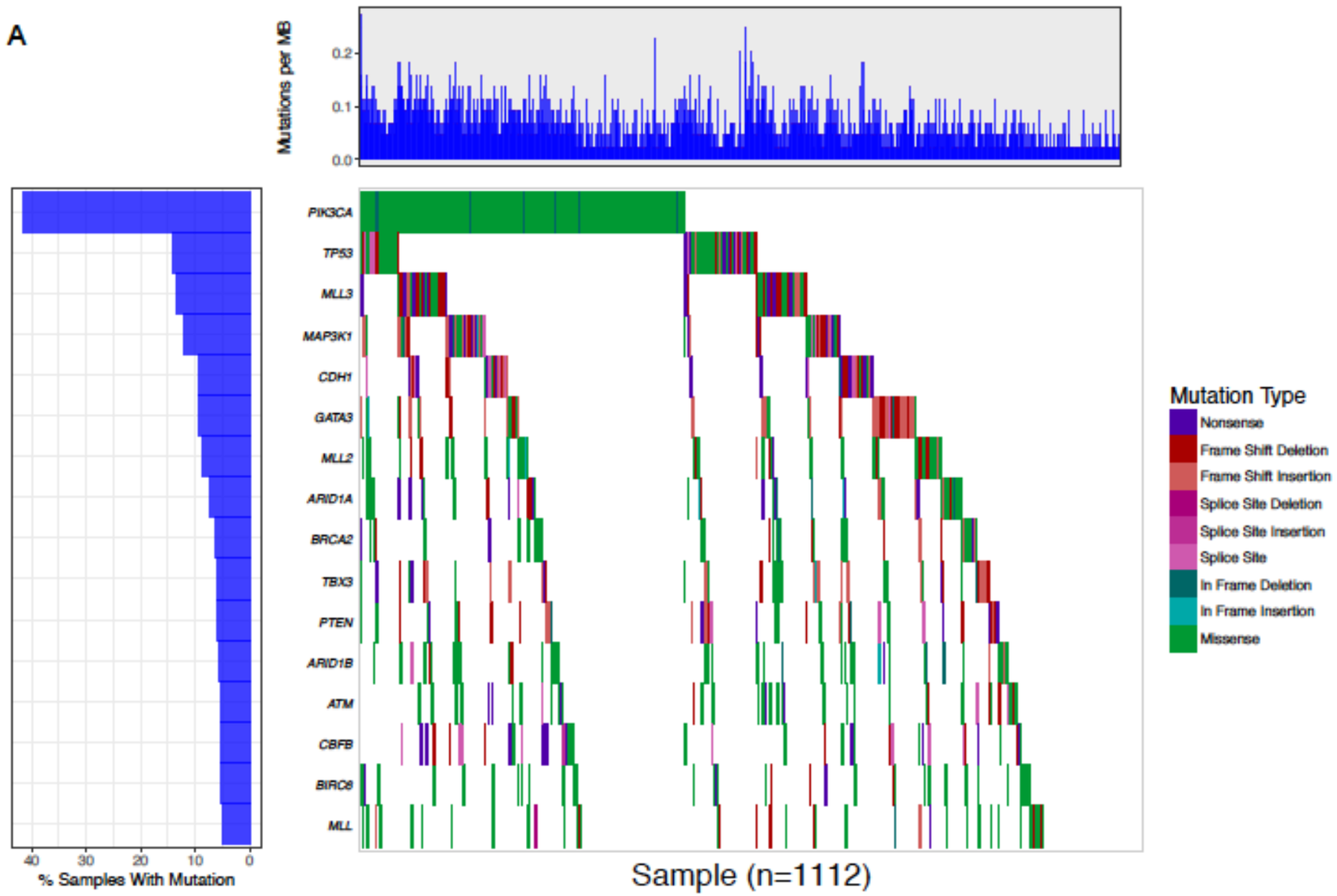
POLAR Series:

- case-control study of ER+ breast tumors, with 91 cases (48 late relapse, >5 yr) and 84 controls (all pts. w/o relapse)
- All received adjuvant endocrine therapy (and/or chemotherapy)
- **175**/194 pts. passed data coverage thresholds

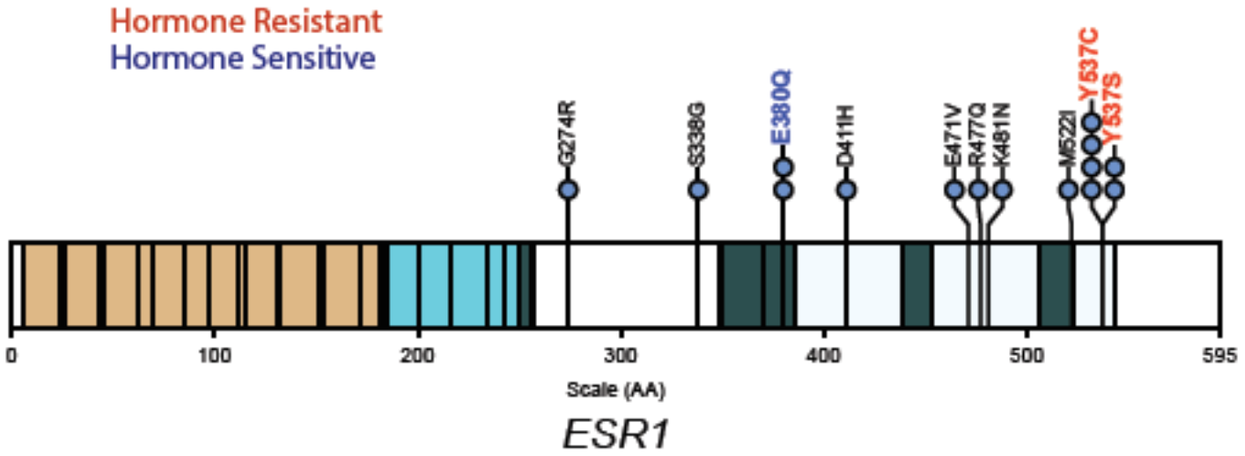
MA12 Series:

- Ductal ER+ disease in pre-menopausal pts. (mean age 45 yr)
- All patients received chemotherapy, and 48% were treated with 5 years of adjuvant tamoxifen
- **328** patient samples passed the data coverage thresholds

Mutation Spectrum in Late-Relapse ER+ Disease

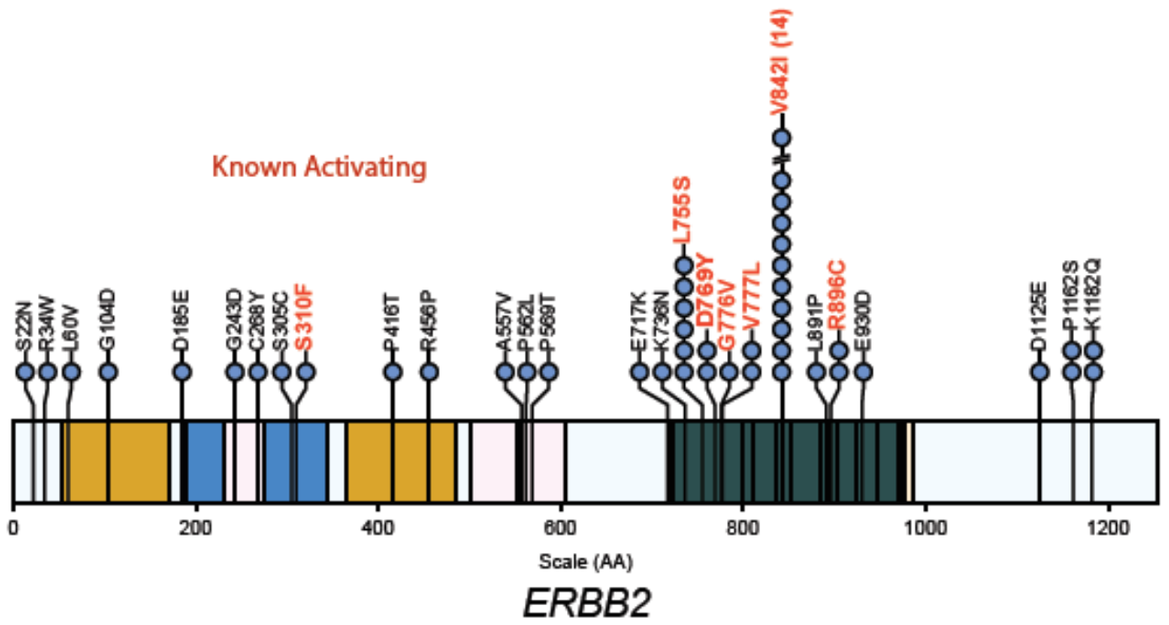


Increased Prevalence of ESR1 and ERBB2 Mutations

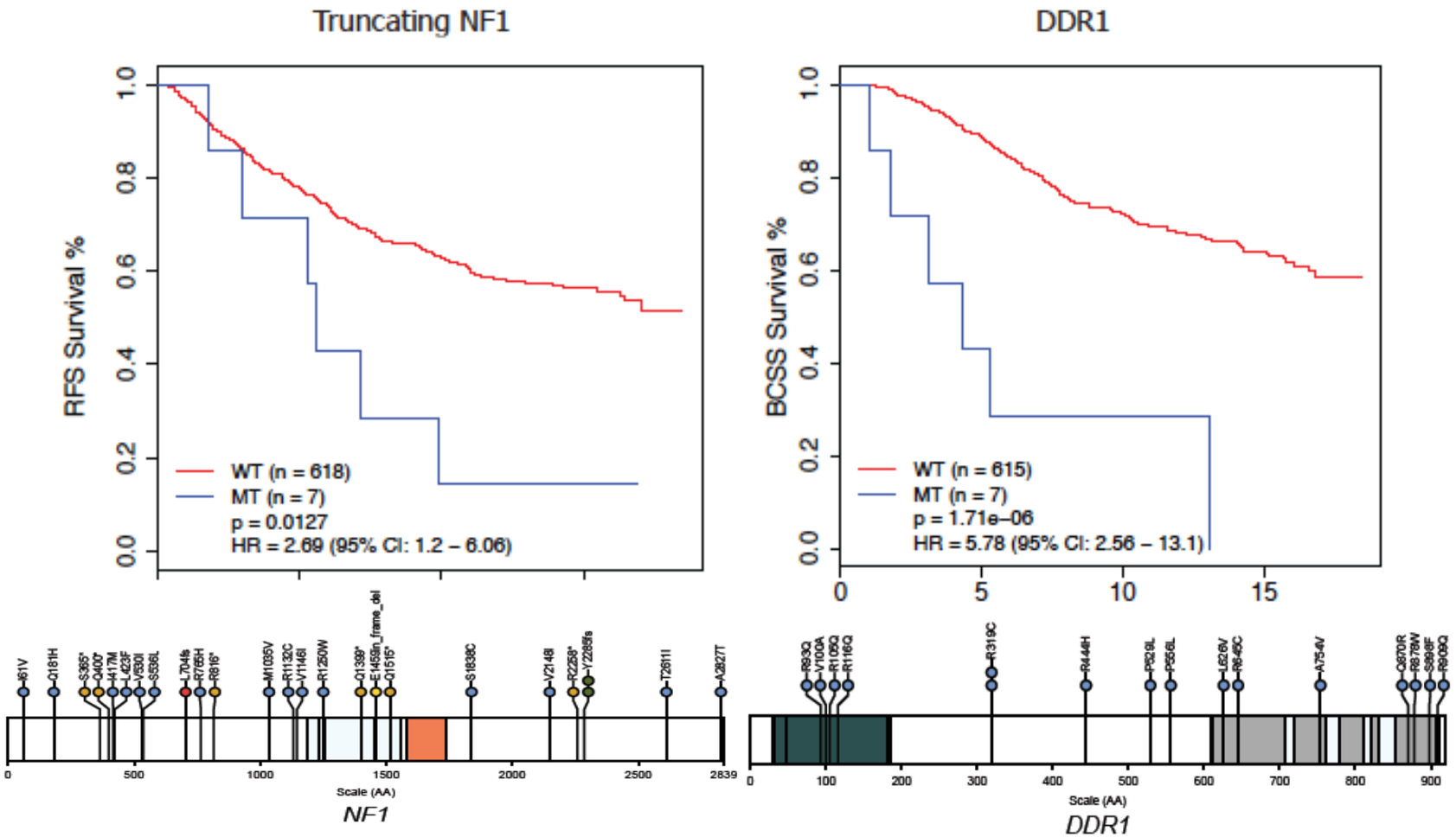


2.1% mutated

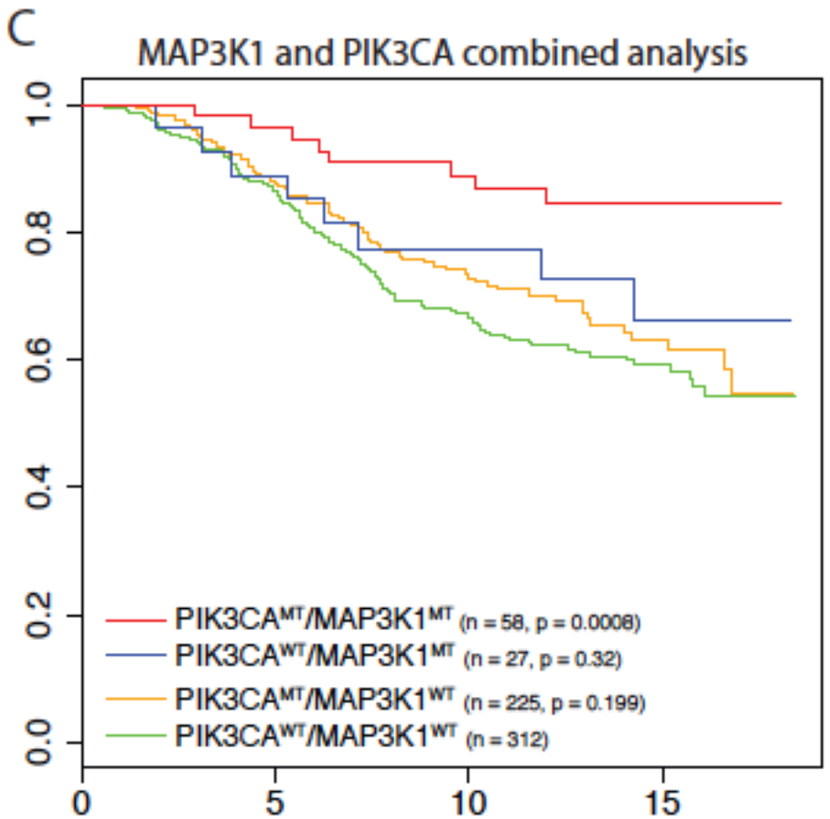
5.0% mutated



Non-silent DDR1 and Truncating NF1 Mutations : Outcomes



Combined Prognostic PIK3CA and MAPK31 Mutations

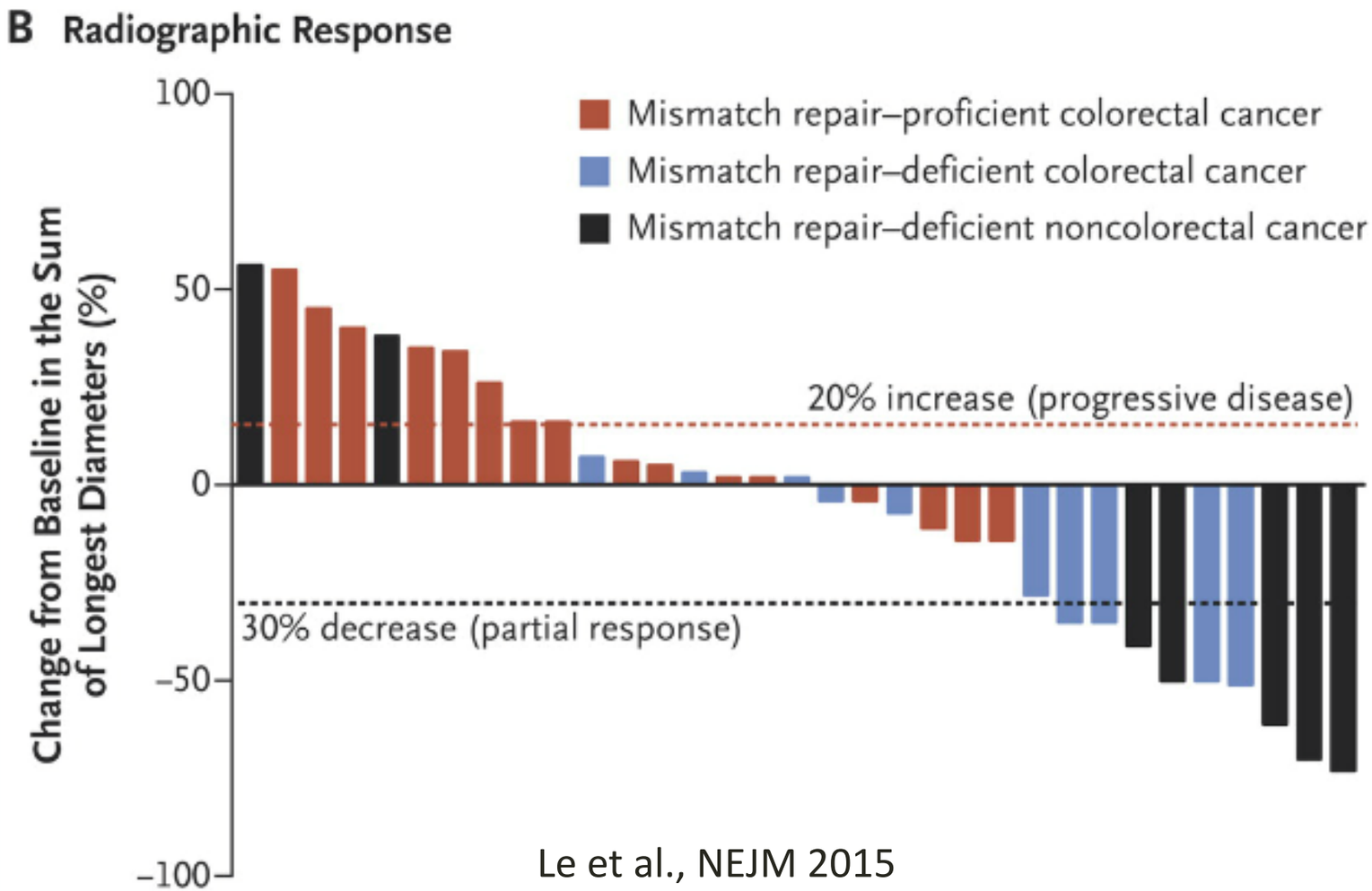


- Restricting to *PIK3CA* mutant cases, *MAP3K1* mutant patients showed favorable prognosis versus MAP3K1 wild-type
- In contrast, in *MAP3K1* wild-type cases, *PIK3CA* was not prognostic

Immunogenomics in Clinical Trials

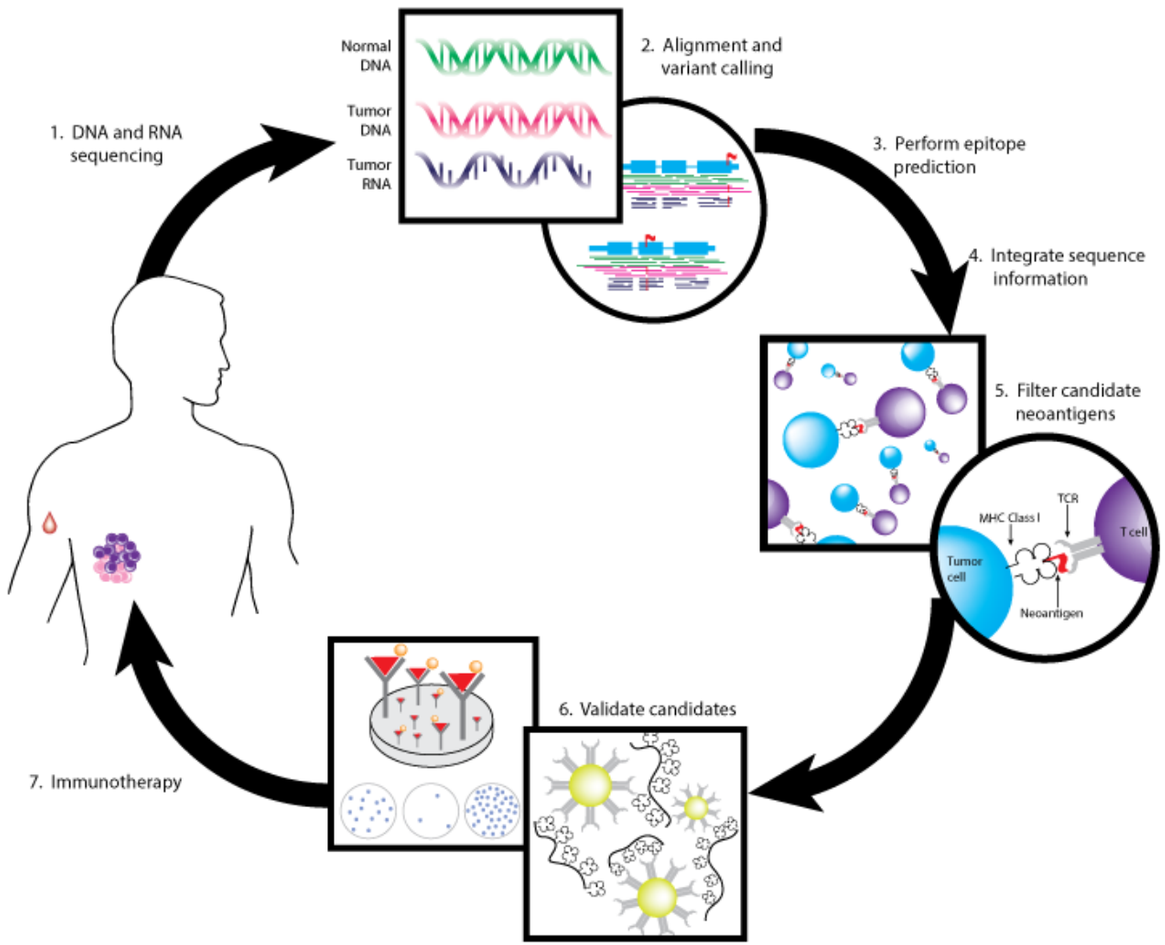
Neoantigens to Immune Correlates

Mismatch Repair Defects and Checkpoint Blockade Response



Le et al., NEJM 2015

Genome-guided Neoantigen Prediction



To design a vaccine or predict neoantigen load for a specific tumor, we need:

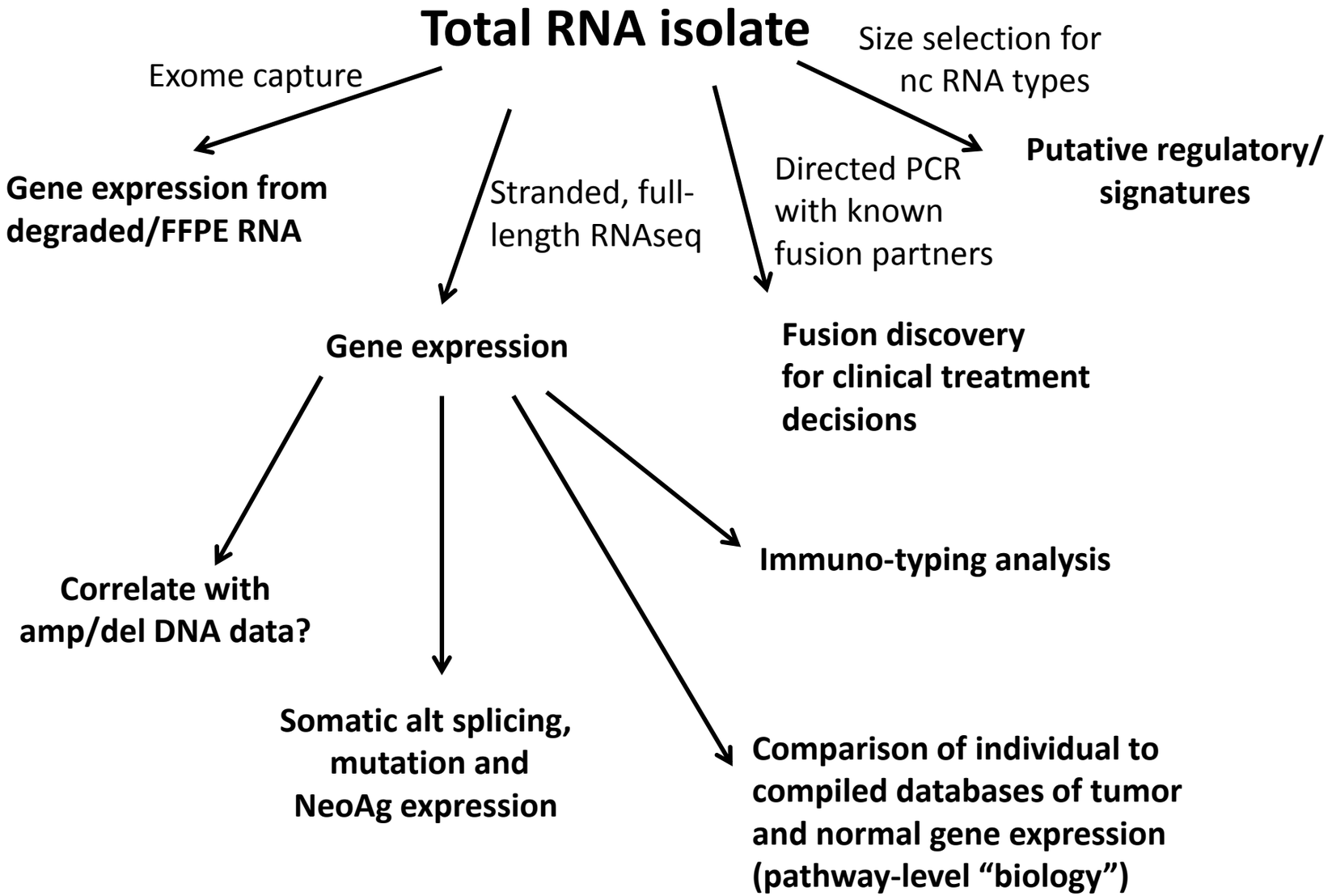
- NGS to compare cancer and normal exomes and identify mutations
- the HLA haplotypes of the patient
- RNA sequencing data from the cancer cells

Algorithms then model the binding of mutant peptides to the HLA proteins and predict neoantigens

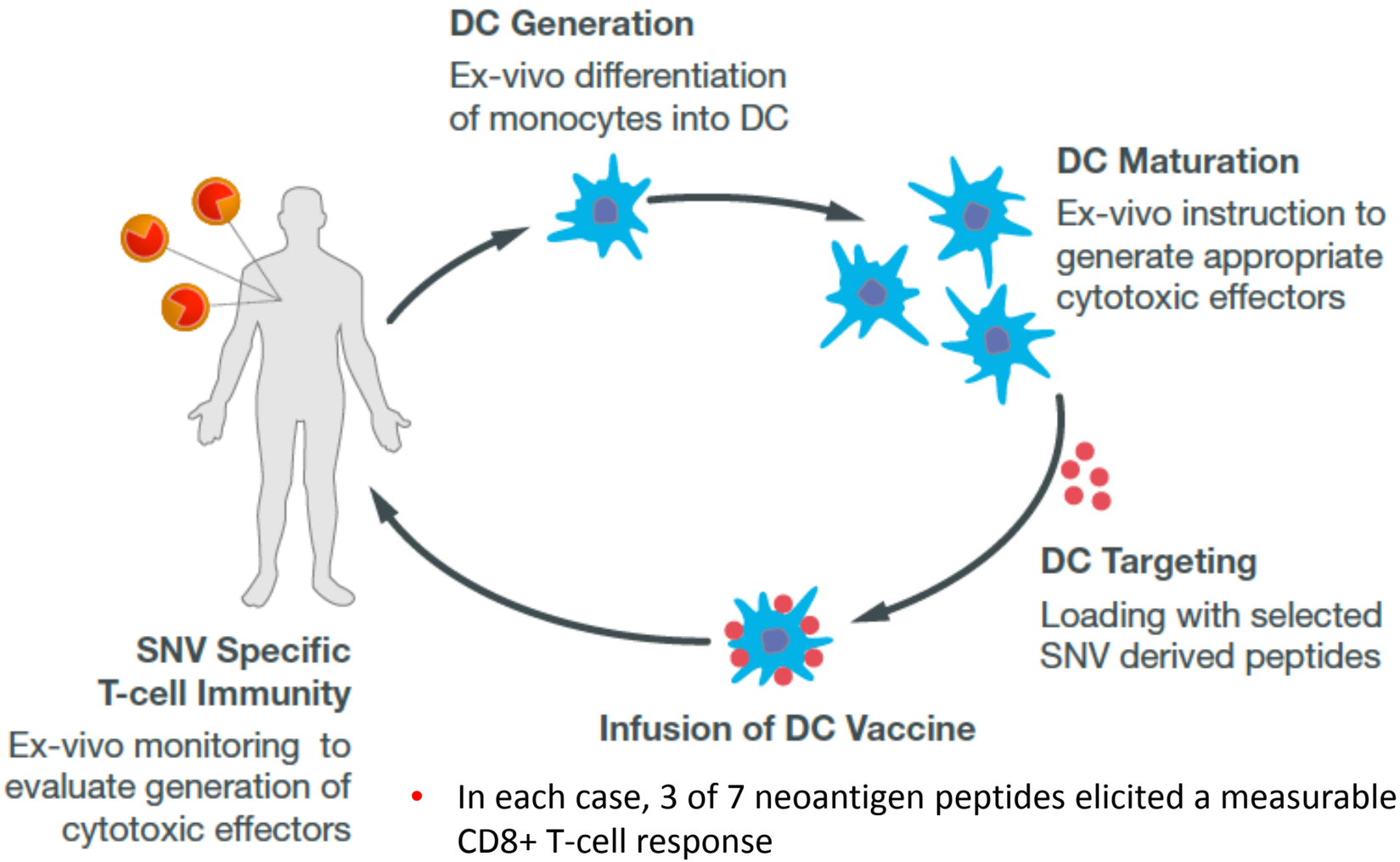
RNA data tells us which mutants are expressed

Hundal et al., Genome Medicine 2016

Applying RNA Sequencing to Cancer



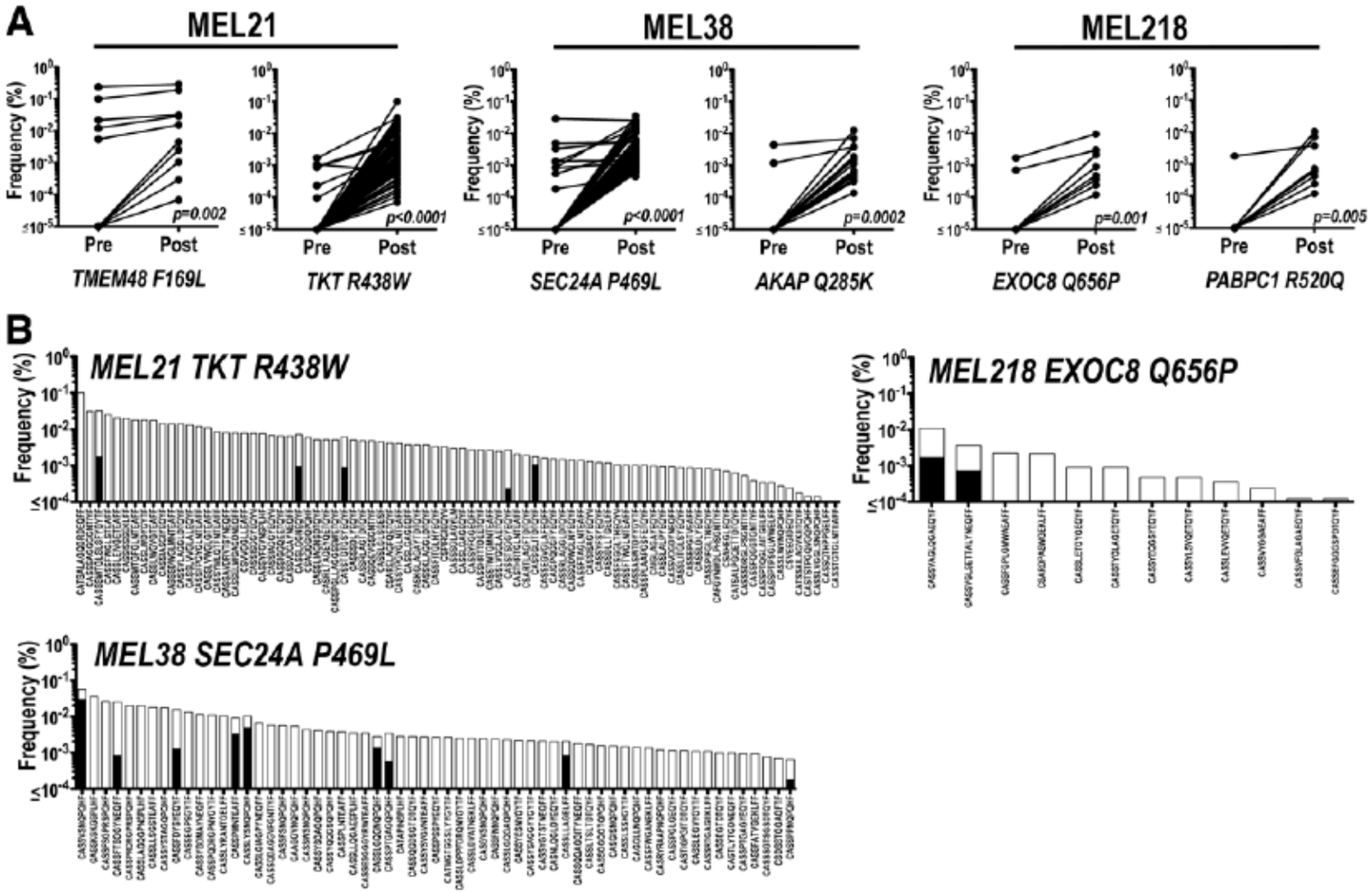
Genome-guided cancer vaccine trial: melanoma



- In each case, 3 of 7 neoantigen peptides elicited a measurable CD8+ T-cell response
- No severe adverse events were reported

Carreno et al., Science 2015

Genomics Evaluates TCR Diversity in the Tumor and Peripheral Circulation



TCRβ clonotypes in CD8+ T cell populations isolated from PBMC before and after vaccination

Urothelial Cancer and Atezo: Correlative Immunogenomics

- Clinical trial of Atezolizumab in urothelial cancer patients with locally advanced or metastatic disease at MSKCC

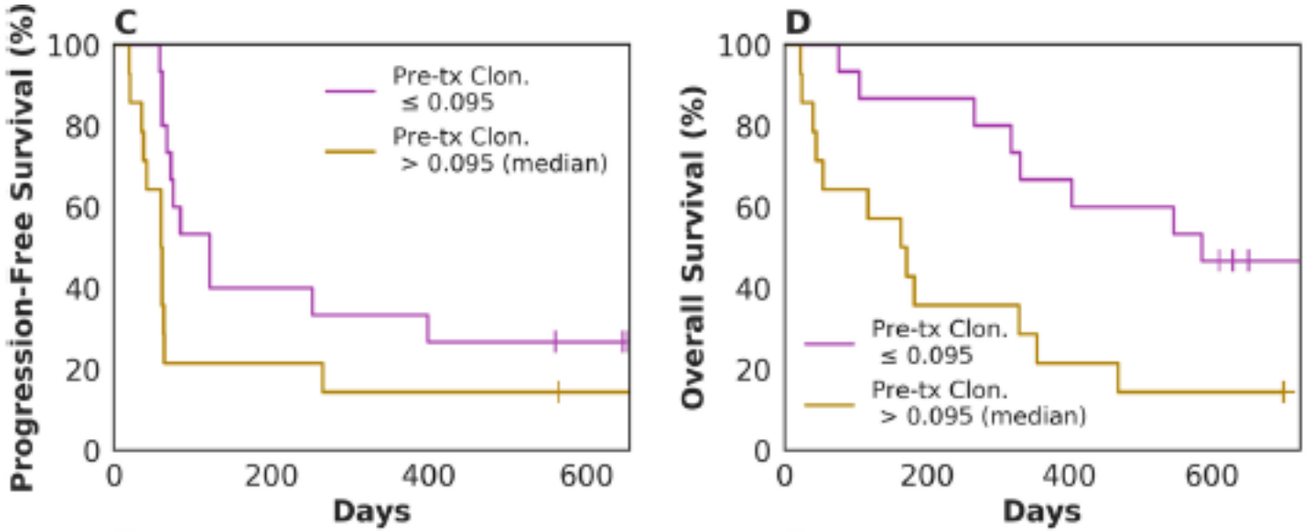
- Study goals:
  - determine the association of mutational or neoantigen load to therapeutic benefit
  - determine whether intratumoral and peripheral blood TCR clonality inform clinical outcomes

- All patients had PD-L1 positive TIL evaluated in the microenvironment (IC)
- Whole exome sequencing of tumor/normal plus RNAseq of tumor
- TCRseq of pre-treatment biopsies plus TCRseq of blood pre- and post-treatment with Atezo

  - All parameters evaluated with durable clinical benefit (DCB) defined as progression-free survival (PFS) >6 months and overall survival (OS)

A. Snyder et al., PLoS Medicine 2017

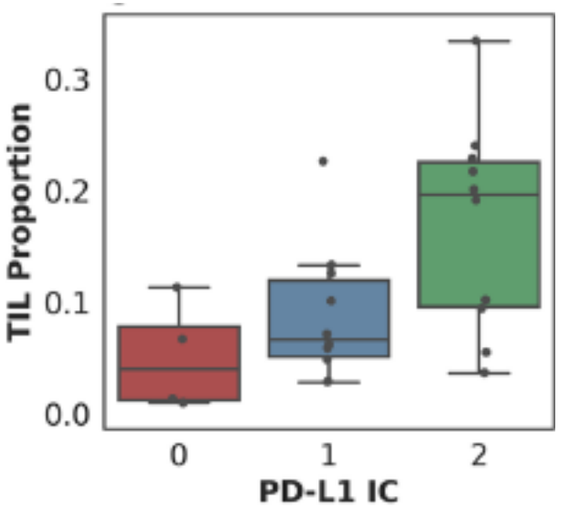
Comparing NGS Profiling to Outcome



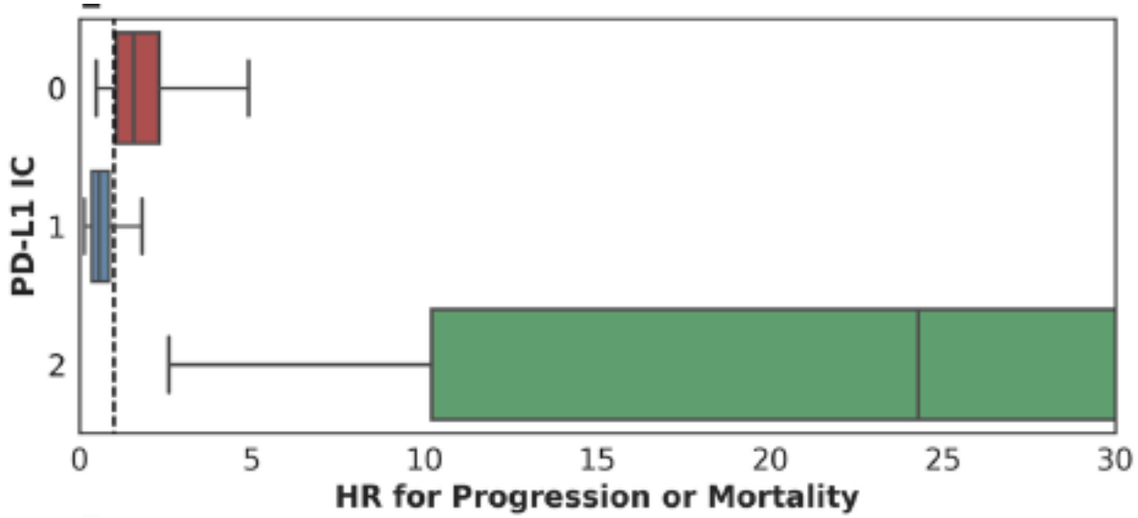
What measures associated with Durable Clinical Benefit??

- TCR clonality below the median in peripheral blood: implies an important relationship between circulating and intratumoral immunity upon PD-L1 blockade
  - Increases the likelihood of harboring one or more clones capable of tumor recognition
- Peripheral blood expansion of TCRs 3 weeks after treatment initiation: underscores the continuity of tumor and blood compartments
- Higher TIL proportion: reported in past studies

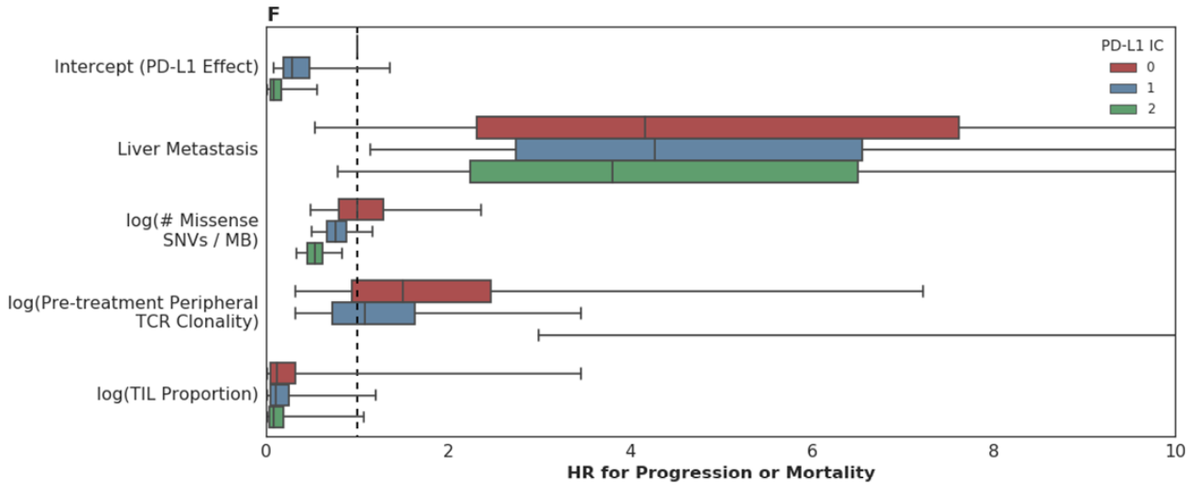
Association between Immune and Clinical Variables



TIL proportion estimated from TCRseq was associated with PD-L1 IC staining

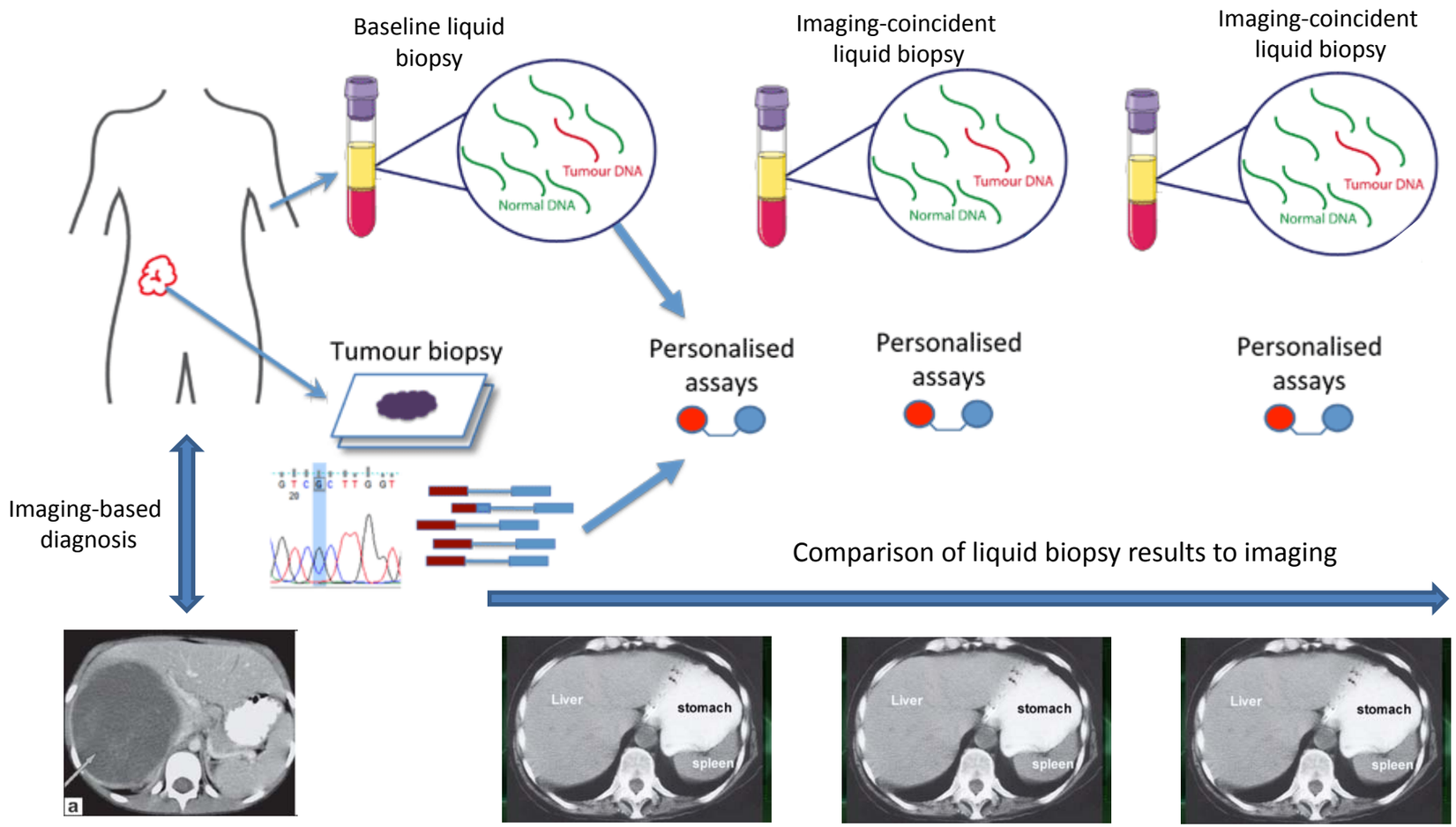


Hazard associated with progression or mortality as a function of PD-L1 IC



Multivariate survival analysis of various clinical, peripheral and intratumoral biomarkers for association with time to disease progression or mortality (PFS)

Genomics Enables Liquid Biopsy



Personalized assays can be mutation-directed or immune marker-directed, or both
Clinical utility of liquid biopsy compared to imaging is underway!

Conclusions

Genomics is playing an increasing role in cancer diagnosis and treatment and by extension, can be incorporated into prospective or retrospective correlative studies of clinical trials

Immunogenomics has the capability to personalize cancer therapy and to contribute to evaluating the likelihood of therapeutic response, as well as to response monitoring

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Late Relapse Breast Cancer Study

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Our patients and their families