NEOANTIGEN SPECIFIC THERAPIES (NESTs), PUSHING BOUNDARIES WHILE TOEING THE LINE!

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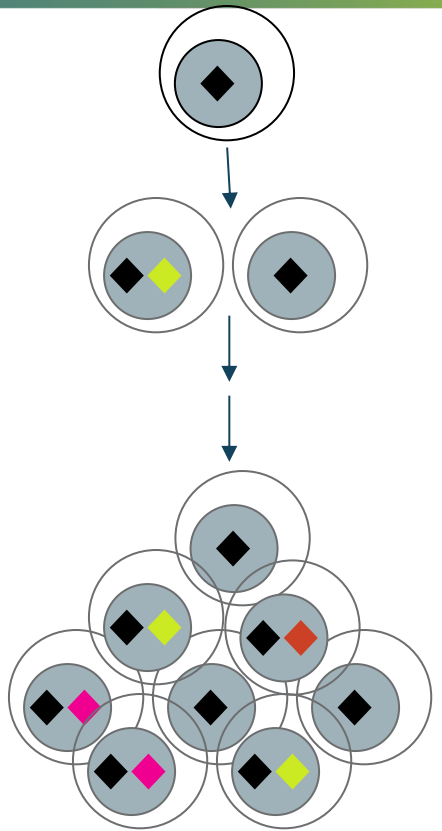
What Are Neoantigens?

- Mutations in key oncogenes or tumor suppressors can cause cancers. These are driver mutations (◆).
- Driver mutations are often clonal/truncal and present in majority of the cancer cell population as they divide.
- Targeted therapies can be directed against cancer driver mutations (e.g. Tyrosine Kinase inhibitors).
- As the cancer cells evolve they accumulate mutations. These mutations can occur anywhere in the genome and are often sub-clonal, these are called passenger mutations (◆◆◆).
- Some cancer mutations can be translated to novel antigens that can be targeted by the immune system. These are called **Neoantigens** and are potential therapeutic targets.



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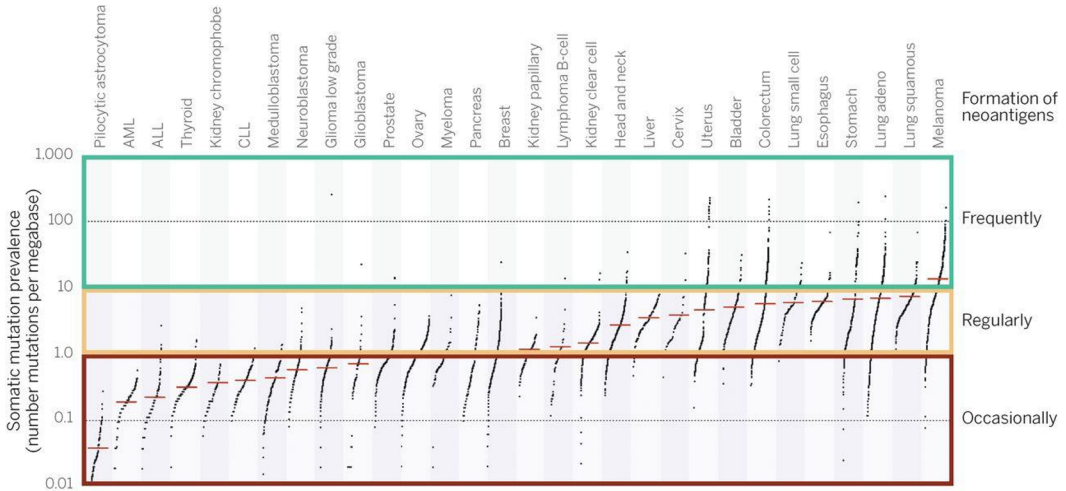
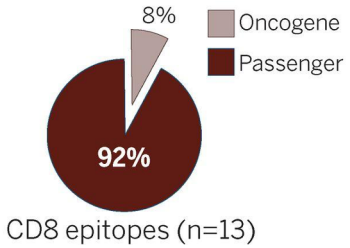
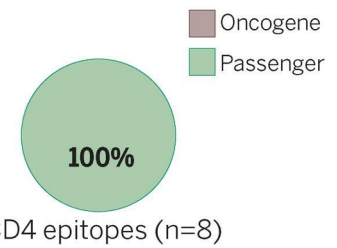
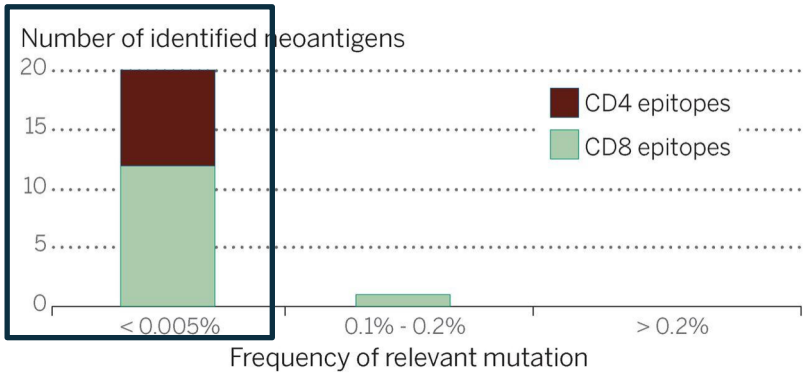
Neoantigens are Private and Predominantly Derived from Passenger Mutations









- Higher Tumor Mutational Burden (TMB) correlates with formation of higher number of neoantigens.
- A large fraction of neoantigens are derived from passenger mutations.
- Shared neoantigens are very rare in patient populations, so we have developed an individualized E2E manufacturing process that targets patient specific neoantigens.

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Schumacher et al., DOI: 10.1126/science.aaa4971

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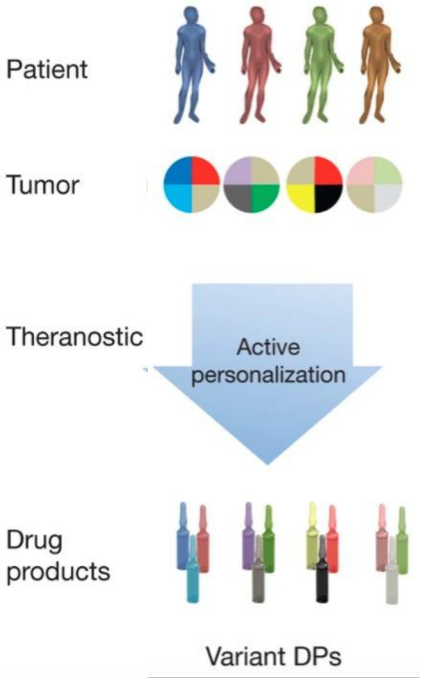
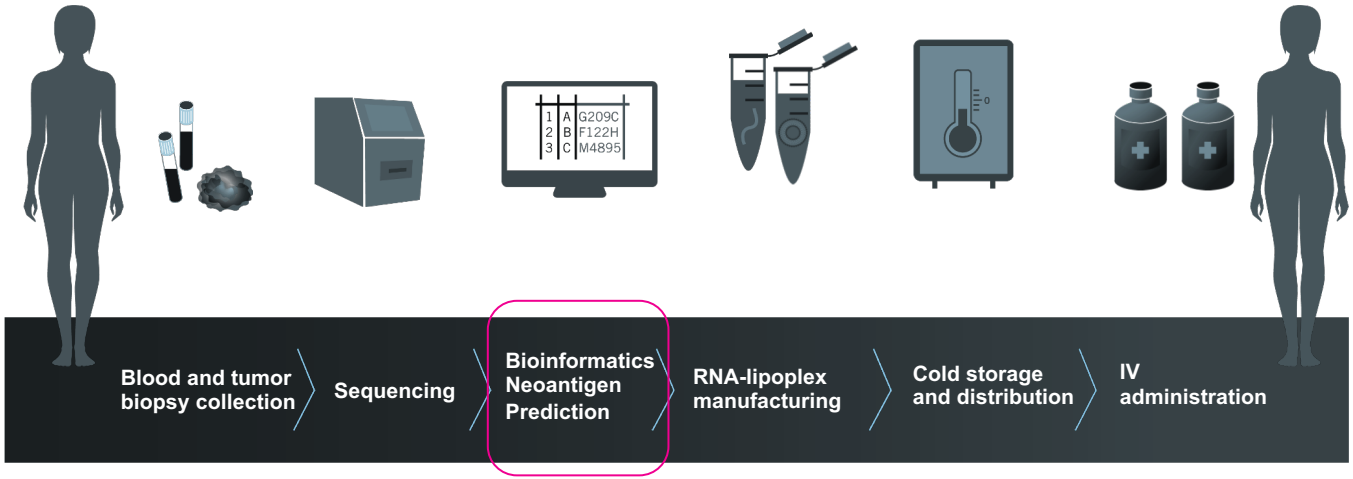
Autogene Cevumeran, An Individualized NEST

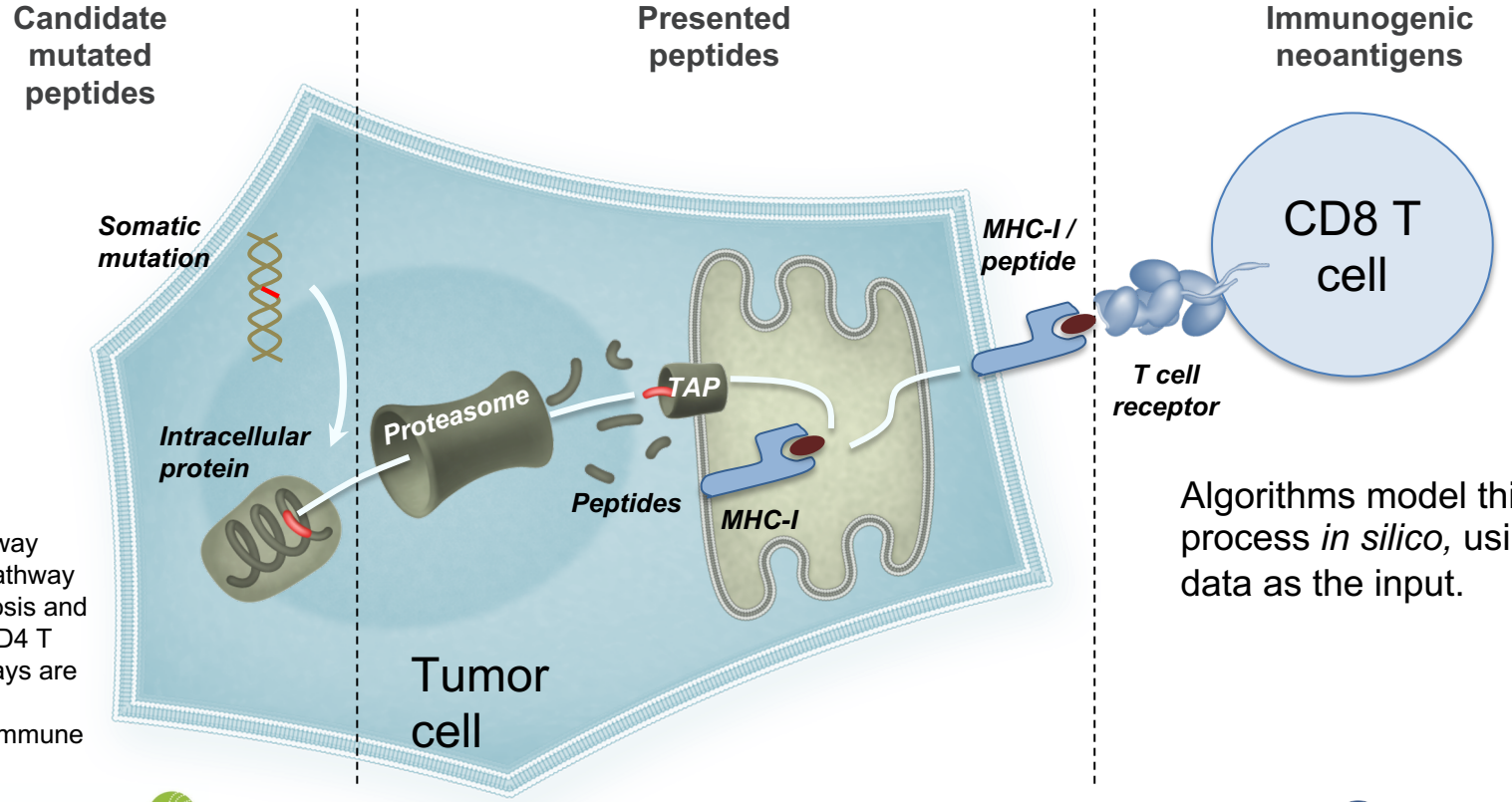




- A fully individualized workflow, where each patient gets their own batch of drug product.
- A complex End to End manufacturing process that incorporates computational algorithms to enable selection of potent neoantigens.

Britten, C., *et al. Nat Biotechnol* 31, 880–882 (2013)

The Pathway of a DNA Mutation To an Immunogenic Peptide (Neoantigen)



Only MHC-I pathway shown, MHC-II pathway involves endocytosis and presentation to CD4 T cells, both pathways are involved in a complete/robust immune activation.

Algorithms model this entire process *in silico,* using NGS data as the input.

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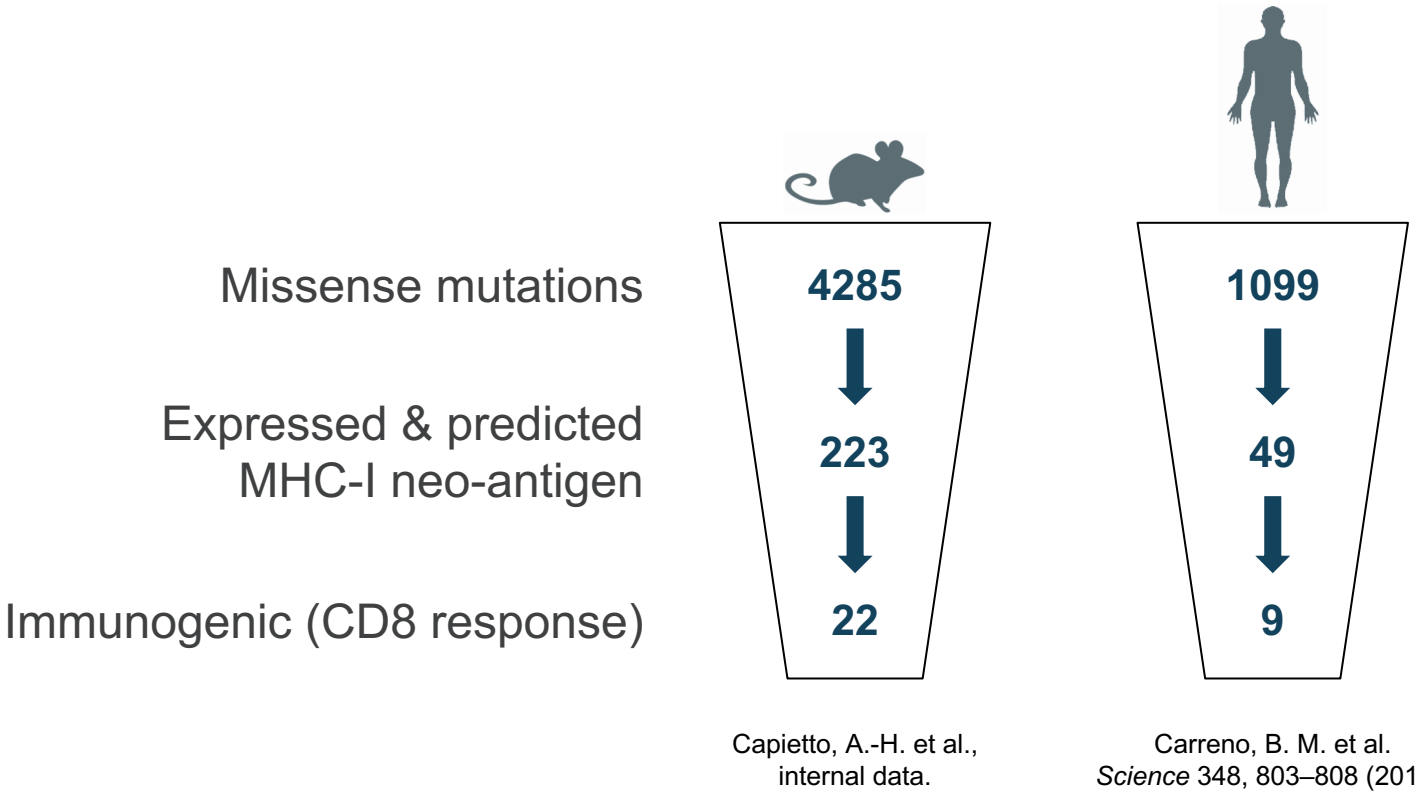
Most Missense Mutations Do Not Become Neoantigens



Capietto, A.-H. et al., internal data.

Carreno, B. M. et al. *Science* 348, 803–808 (2015).

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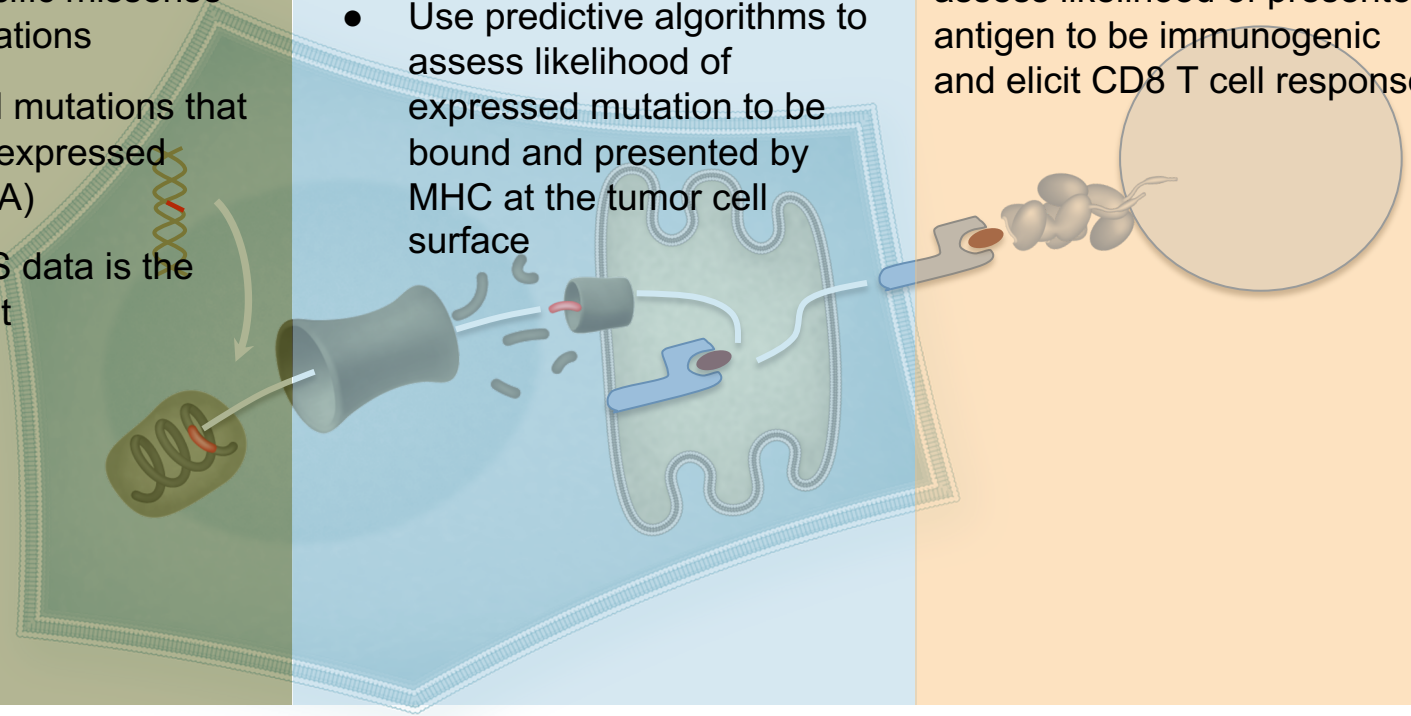
Computational Modeling For Neoantigen Identification

- Identify tumor specific missense mutations
- Find mutations that are expressed (RNA)
- NGS data is the input

- Identify HLA type
- Use predictive algorithms to assess likelihood of expressed mutation to be bound and presented by MHC at the tumor cell surface

Use predictive algorithms to assess likelihood of presented antigen to be immunogenic and elicit CD8 T cell response



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Identify Tumor Specific, Expressed, Missense Mutations

Tumor (FFPE)

Normal (blood)

Exome (normal and tumor) and RNA (tumor) alignment

Somatic mutation calling (SNVs, indels, fusions)

Filtering for expressed protein-altering mutations

Protein

Peptides

MHC genotype

Genome

Short reads

Tumor exome

Normal exome

DNA

RNA

Protein

Binding/Presentation Prediction AI/ML models

Tabulation of all criteria for peptide ranking

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Rank Neoantigens

Selection criteria

- Predicted MHC-I binding
- Predicted MHC-II binding
- Mutant vs. wild type MHC-I difference
- Tumor gene expression
- Variant allele frequency in tumor DNA
- Variant allele frequency in tumor RNA
- Estimated mutation clonality

Exclusion criteria & safety filters

- Target protein is linked to autoimmunity in critical organs (brain, heart etc)
- Neoantigen linker suture has homology to known protein

- Current ranking modules are empirical, where different criteria are weighted based on expert knowledge.
- Complex AI/ML models (with appropriate interpretability) may be useful.

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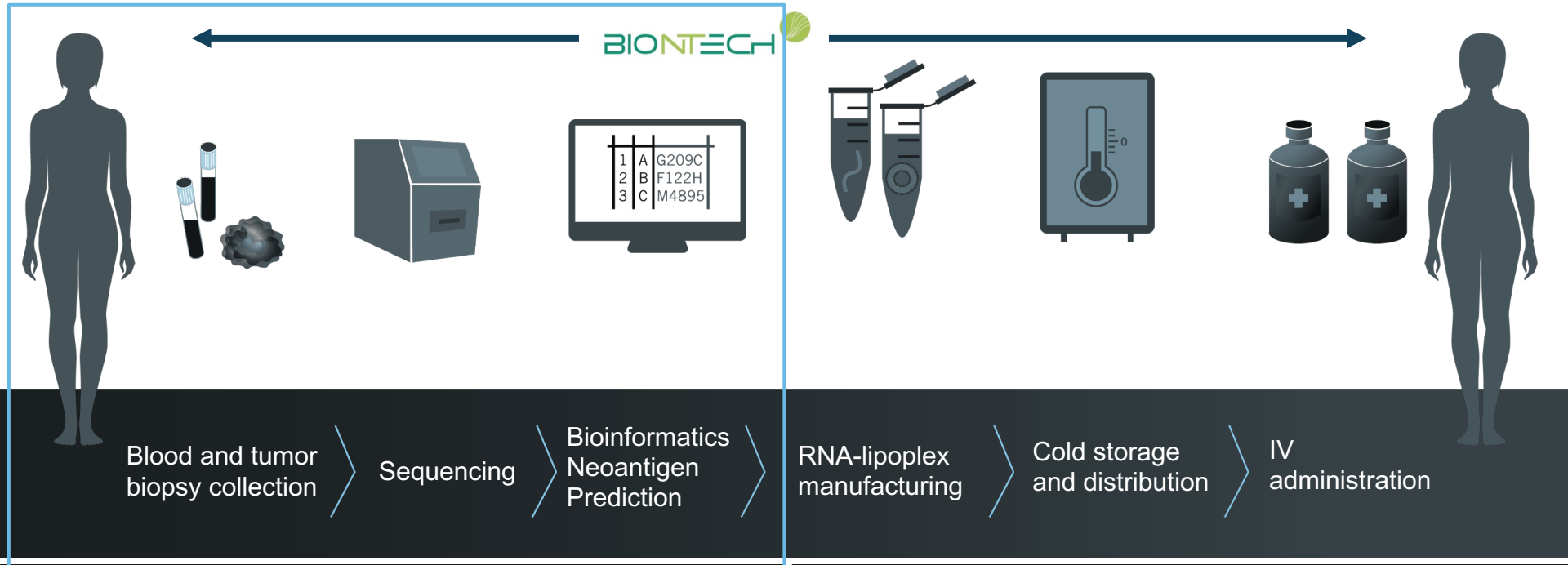
Individualized End to End Manufacturing Process



Identify tumor specific mutations and predict immunogenic neoantigens.***Upstream Process (GCLP)***

Encode immunogenic neoantigens in RNA-LPX drug product and administer. ***Downstream Process (GMP)***

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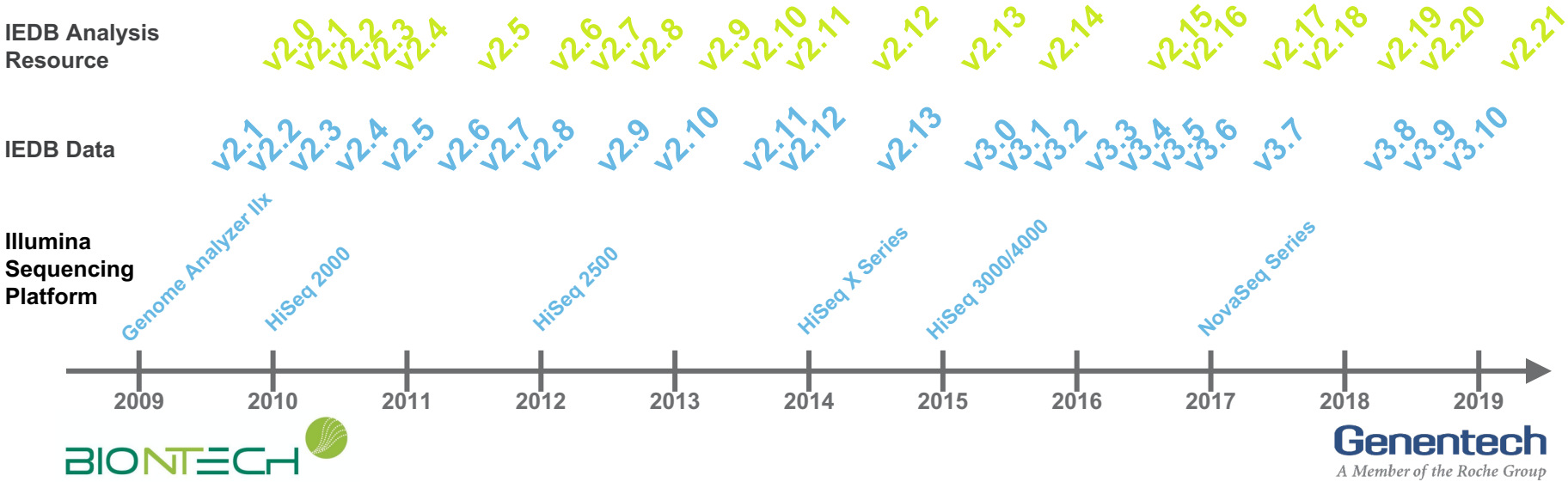
Rapid Progression of NGS Technologies and Neoantigen Prediction Algorithms

The Immune Epitope Database (IEDB): 2018 update

Randi Vita[1], Swapnil Mahajan[1], James A. Overton[2], Sandeep Kumar Dhanda[1], Sheridan Martini[1], Jason R. Cantrell[3], Daniel K. Wheeler[3], Alessandro Sette[1,4] and Bjoern Peters[1,4,*]

[1]La Jolla Institute for Allergy and Immunology, Division of Vaccine Discovery, La Jolla, CA 92037, USA, [2]Knocean Inc., Toronto, Ontario M2P 2T3, Canada, [3]Leidos Health, LLC, San Diego, CA 92121, USA and [4]University of California San Diego, Department of Medicine, La Jolla, CA 92093, USA



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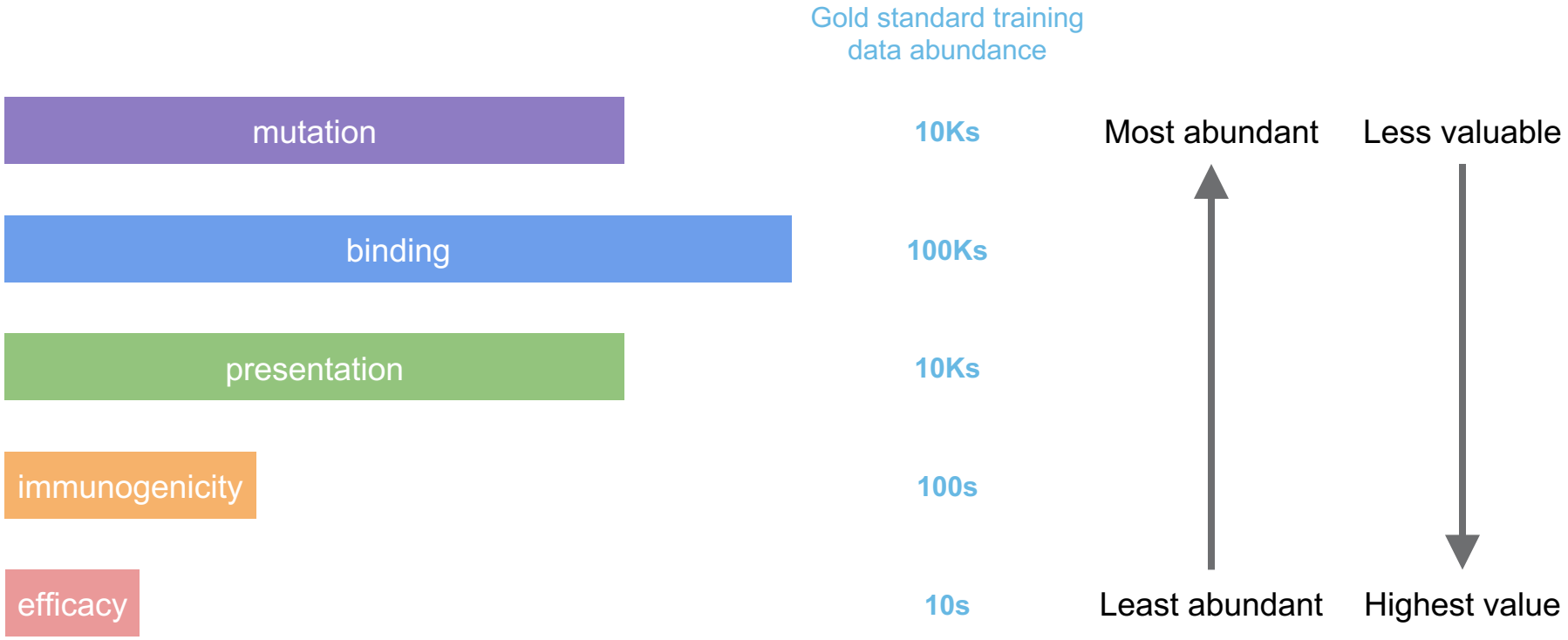
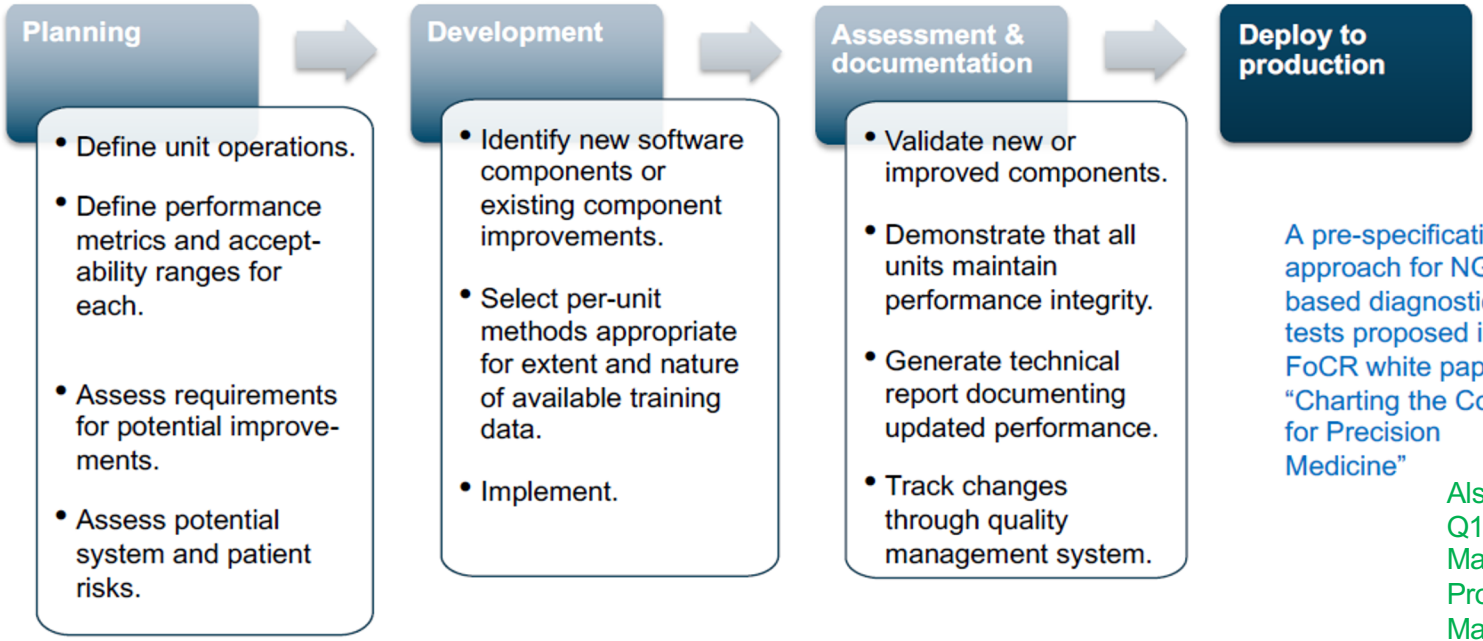
Improvements to Algorithms are Driven by Availability of Training Data



Enabling Timely Improvements While Providing Transparency to Regulators



A **pre-determined change control plan** (PCCP) proposed in FDA Action Plan: AI/ML for Software as a Medical Device (SaMD) (Jan 2021)

A pre-specification approach for NGS-based diagnostic tests proposed in FoCR white paper "Charting the Course for Precision Medicine"

Also consistent with ICH Q12 Change Management Protocols & Product Lifecycle Management

Updates in genome sequencing and bioinformatics should be based on *performance metrics*, rather than product comparability

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Summary and Outlook

- Immunogenic neoantigens can arise from patient-specific passenger mutation/MHC allele combinations, requiring bioinformatics prioritization.
- NGS and bioinformatics technologies for neoantigen selection processes will continue to make significant advances in technological capability.
    - Incorporation of improvements across the workflow enables increased accuracy of mutation detection, immunogenicity prediction and ultimately an effective anti-tumor response.
    - It is in the best interest of the patient to keep our knowledge, algorithms and databases up-to-date.
- We propose a novel performance metric and risk-based regulatory framework, that enables scientific and technical advances while simultaneously ensuring product quality and patient safety.

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