

# Sequencing to Synthesis: Innovative Antibody Discovery Workflow Leveraging Biological Intelligence to Prioritize Leads

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## Abstract

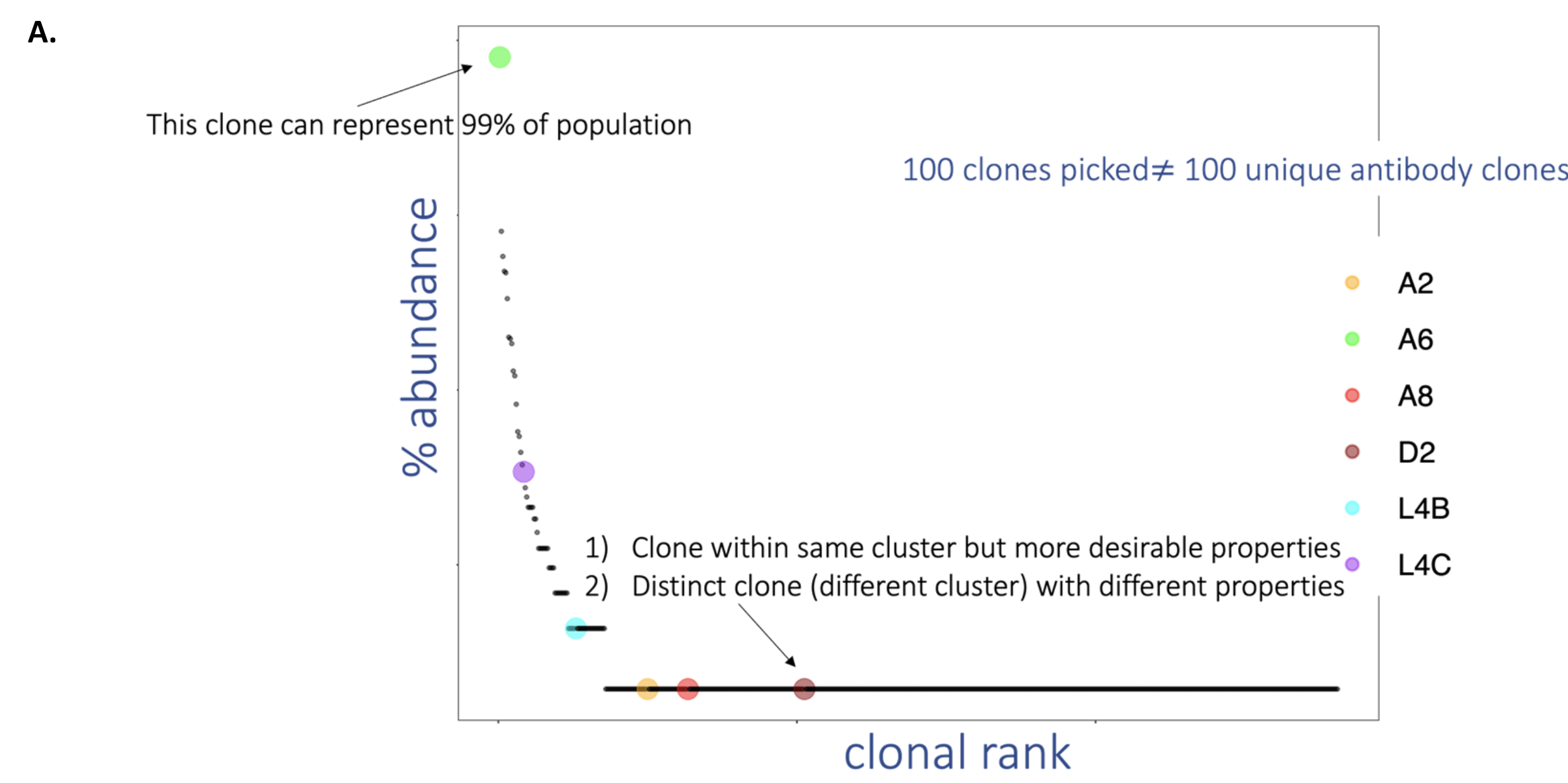
Current industry practice for antibody (Ab) generation and validation can take between 6-12 months, involving extensive wet lab labor and resource usage. Even after an elaborate Ab campaign, the candidates often still have developability issues that can result in late-stage failure. This inefficient process is laborious and costly, thus there is a need for new ways to discover Ab lead candidates with precision and efficiency.

Azenta's *in silico* antibody discovery module (ADM), developed by Specifica and powered by OpenEye, uses important heuristics and machine learning for Ab sequence analysis to generate a diverse list of Ab candidates for recombinant production. Ab sequences are clustered together to easily query a dataset of highly functional binders with distinct epitopes which exhibit favorable developability properties. By setting parameters to define liabilities early in the antibody discovery process this results in a more comprehensive and diverse of Ab leads that have better potential for developability.

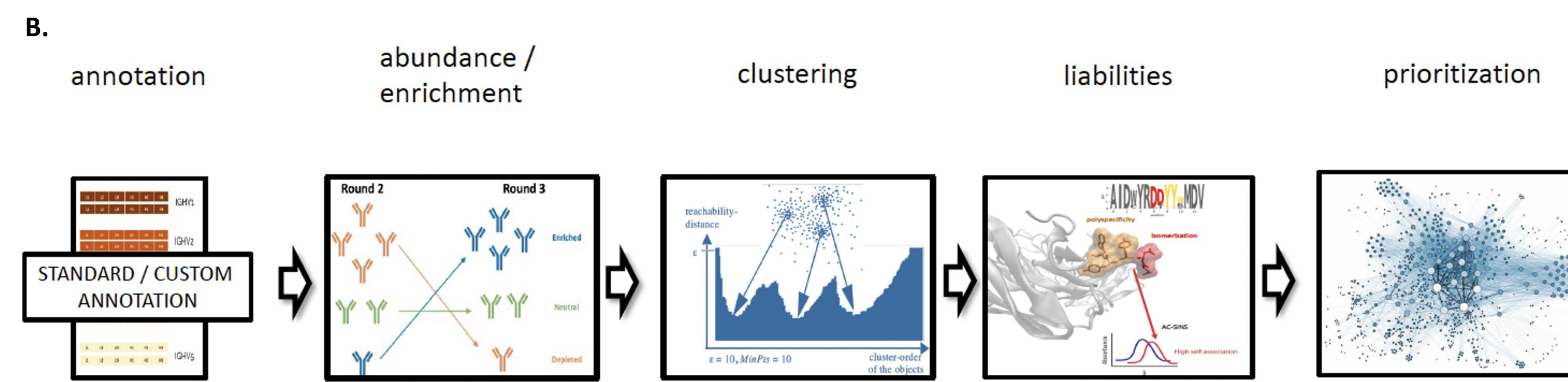
Here we present an innovative end-to-end Ab discovery solution combining the strengths of *in vitro* and *in silico* technology to provide a high-throughput workflow that increase antibodies' pool diversity, making the discovery and development of mAb therapies quicker and more efficient.

## Methods

The Azenta ADM allows for identification of diverse of antibody (Ab) leads/candidates with broad epitope coverage and exhibit or have favorable developability properties (Figure 1).



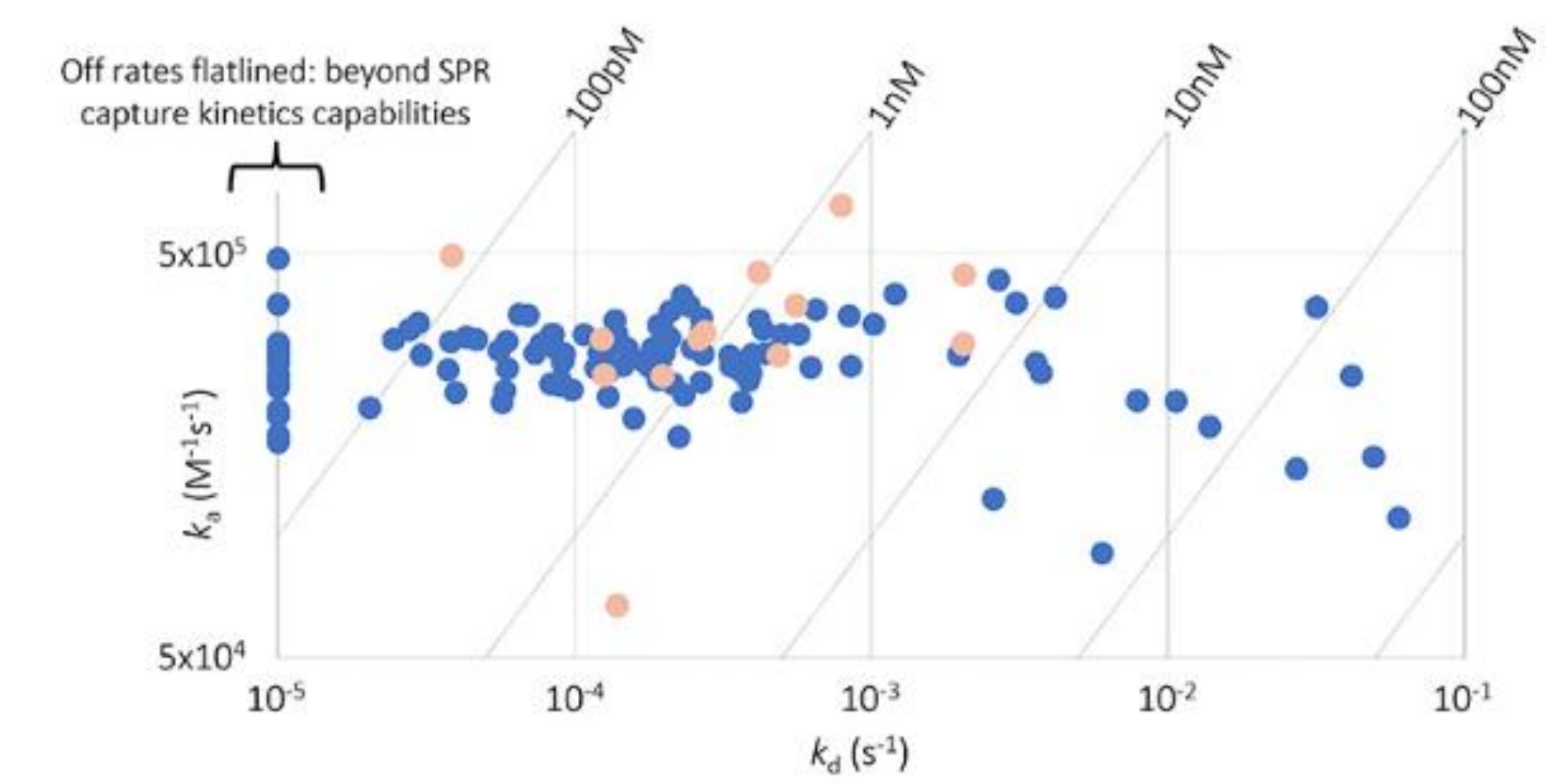
**Figure 1. A. Antibody clones identified by ADM.** Antibody discovery approaches that only rely upon random colony picking are often insufficient in their exploration of the underlying diversity. NGS & computational processing can guide lead cluster & candidate prioritization to 1) overcome situations where diversity is dominated by a few clones, 2) to use NGS statistics to rank order leads within and across clusters.



**Figure 1. B. ADM Computation Analysis-** The bioinformatics pipeline to allow for prioritization of optimal leads starts with quality filtering of the input NGS data followed by annotating the sequences to identify regions of interest (ROI) and extract features. Relative Abundance and enrichment based on ROI can be calculated, the module then identifies abundant and rare clusters with unsupervised ML based on density-based clustering and quantifies sequence-based biophysical liabilities. The platform prioritizes the leads based on favorable NGS metrics to provide a gene synthesis ready output.

## Results

ADM identified  $\geq 1000$  antibodies (Ab) candidates selected against SARS-CoV-2 Spike trimer protein, its monomer S1 and the receptor binding domain (RBD). Utilizing PacBio NGS followed by *in silico* ADM analysis and recombinant Ab production, 200 Ab were produced as IgG and recognized receptor binding domain (RBD). The RBD binding affinities of 143 Abs ranged from 34 pM to 1  $\mu$ M, with 30 Ab better than 100 pM, as measured by surface plasmon resonance (Figure 2). The Ab selected with the traditional colony screening method (pink dots) had overall worse affinity when compared to clones identified by ADM (blue dots).



**Figure 2. Clones and their affinities by traditional screening method versus NGS Isoaffinity plot** of 13 picked clones (Pink Dots), or 143 clones identified by ADM, synthesized, expressed, and purified (Blue Dots). Affinities are indicated by the diagonal lines.

## Highlights

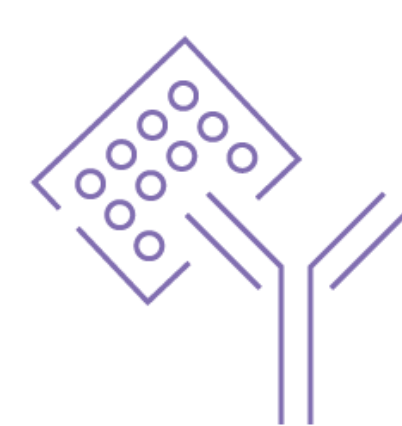
### KEY FEATURES OF AZENTA WORKFLOW

Next generation sequencing (NGS) screening complements *in silico* lead selection, reducing costs by up to 60% over traditional workflows

Candidate identification up to 2x faster than traditional methods

Discover leads with greater functional diversity, broader affinity range and fewer biophysical liabilities than *in vitro* only approaches

Entire project managed by one research partner to protect valuable intellectual property and products



**In Vitro Display**



**Animal Immunization**

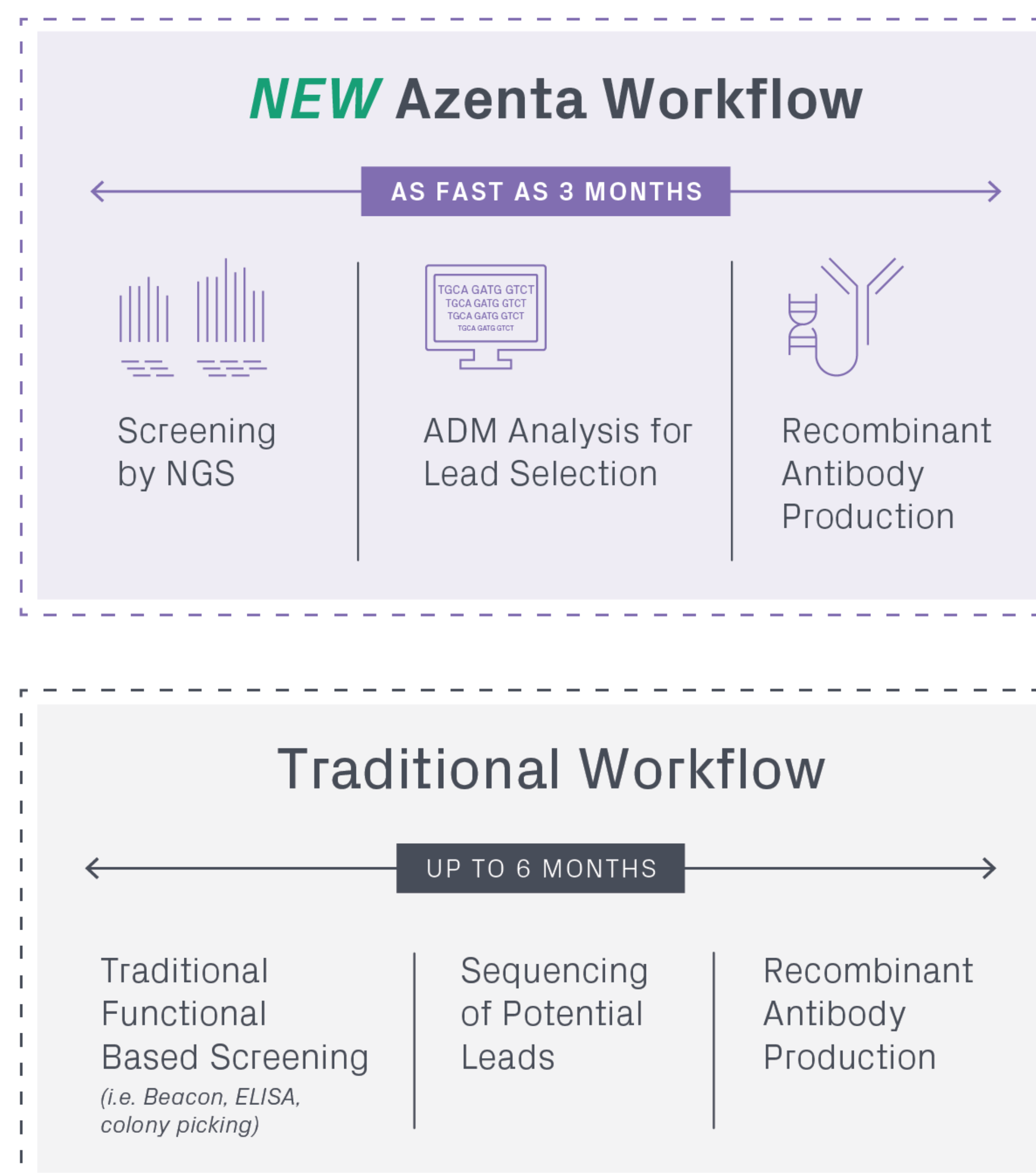


Figure 3. Schematic of Antibody Discovery Workflow at Azenta

## Advantages

In conclusion, Azenta Life Sciences offers one a kind end-to-end workflow from next-generation screening to gene synthesis and antibody production.

The workflow we presented compared with traditional colony screening methods:

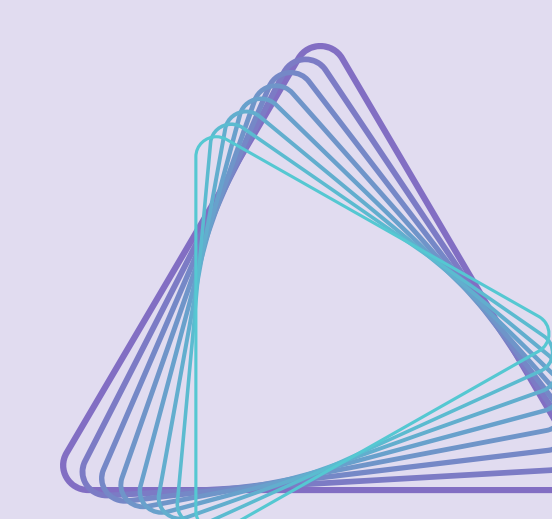
- Uncover more leads with greater functional diversity, broader affinity range and fewer biophysical liabilities
- Prioritization of promising leads ready to be used for phenotyping assay while minimizing costs and turnaround time (3X time faster than traditional methods)
- Allows your antibody discovery engineers and scientists to focus on research and development of subsequent pipeline for antibodies therapies.

## References

1. Erasmus, MF et al. Insights into Next Generation Sequencing Guided Antibody Selection Strategies. To Be Submitted.
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3. Teixeira, A., Erasmus, M.F et al. Drug-like antibodies with high affinity, diversity and developability straight from next-generation antibody libraries. MAbs vol 13, 1 (2021).

## Key Technical Contacts

For NGS, Antibody Discovery analysis, gene synthesis, and antibody production services please contact our expert project management team at [gs@azenta.com](mailto:gs@azenta.com). For technical questions please contact our subject matter expert, Dr. Crystal Richardson, Ph.D. at [crystal.richardson@azenta.com](mailto:crystal.richardson@azenta.com).



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