Challenges in the Development and Quality Control of Individualized mRNA Products

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Disclosure

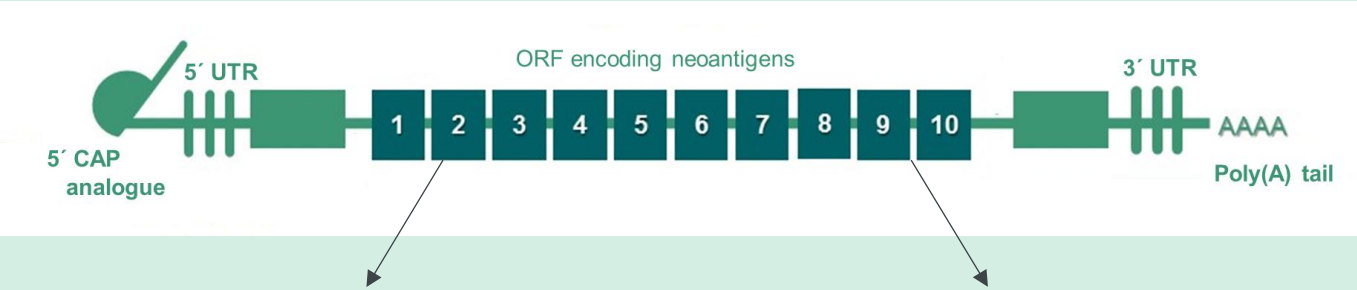
I am an employee of BioNTech SE, and I hold shares in the company.
The views expressed here are those of the presenter and may not represent those of BioNTech SE or its subsidiaries.

Targeting tumor specific neoantigens with an investigational individualized RNA immunotherapy, Autogene cevumeran[1] (RO7198457/BNT122)



Collecting individual patient samples (blood and tissue) › Mapping of mutations › Neoantigen prediction › On-demand tailored RNA manufacturing › Individualized immunotherapy › Intravenous administration

Individualized neoantigen mRNA [1,2,3]



Innate immune stimulation
Intrinsic TLR7/8 agonist

Antigen expression
Up to 20 neoantigens (2 decatopes)

RNA lipoplex delivery formulation[4]

- mRNA embedded between a lipid layer
- Allows systemic dendritic cell targeting

1 Türeci *et al* Clin Canc Res 2016
2 Vormehr Ann Rev Med 2019
3 Sahin *et al* Science 2018
4 Kranz *et al* Nature 2016

 1: Autogene cevumeran (RO7198457/BNT122) is an investigational product and is partnered with Genentech, a member of the Roche Group.

The downstream manufacturing process for Autogene cevumeran[1] (RO7198457/BNT122)

DNA template manufacturing



Manufacture of the medicinal product



Label & packaging



Quality control & release



Transportation to hospital



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Confidential

Key Challenges for Individualized mRNA Products

Ensuring consistent product quality when every batch contains a unique sequence



Rapid Product Release Requirements

Individualized products are often used in combination therapies where strict timelines must be met

→ Automate and digitize manufacturing and quality processes

→ Develop rapid, high-throughput analytical methods

Time is critical



Shift from Product Control to Process Control

Traditional quality control approaches focusing on product attributes are less feasible

Robust process control strategies are needed

→ Regular manufacturing of representative sequences to demonstrate process robustness

→ Implement lean panels focusing on process over product control

Consistency is key



Building a Representative Dataset

Each batch contains a unique mRNA sequence so manufacturing data cannot easily be pooled due to sequence-dependent variability

→ Distinguish sequence-driven from process-driven variability

→ Define representative sequences

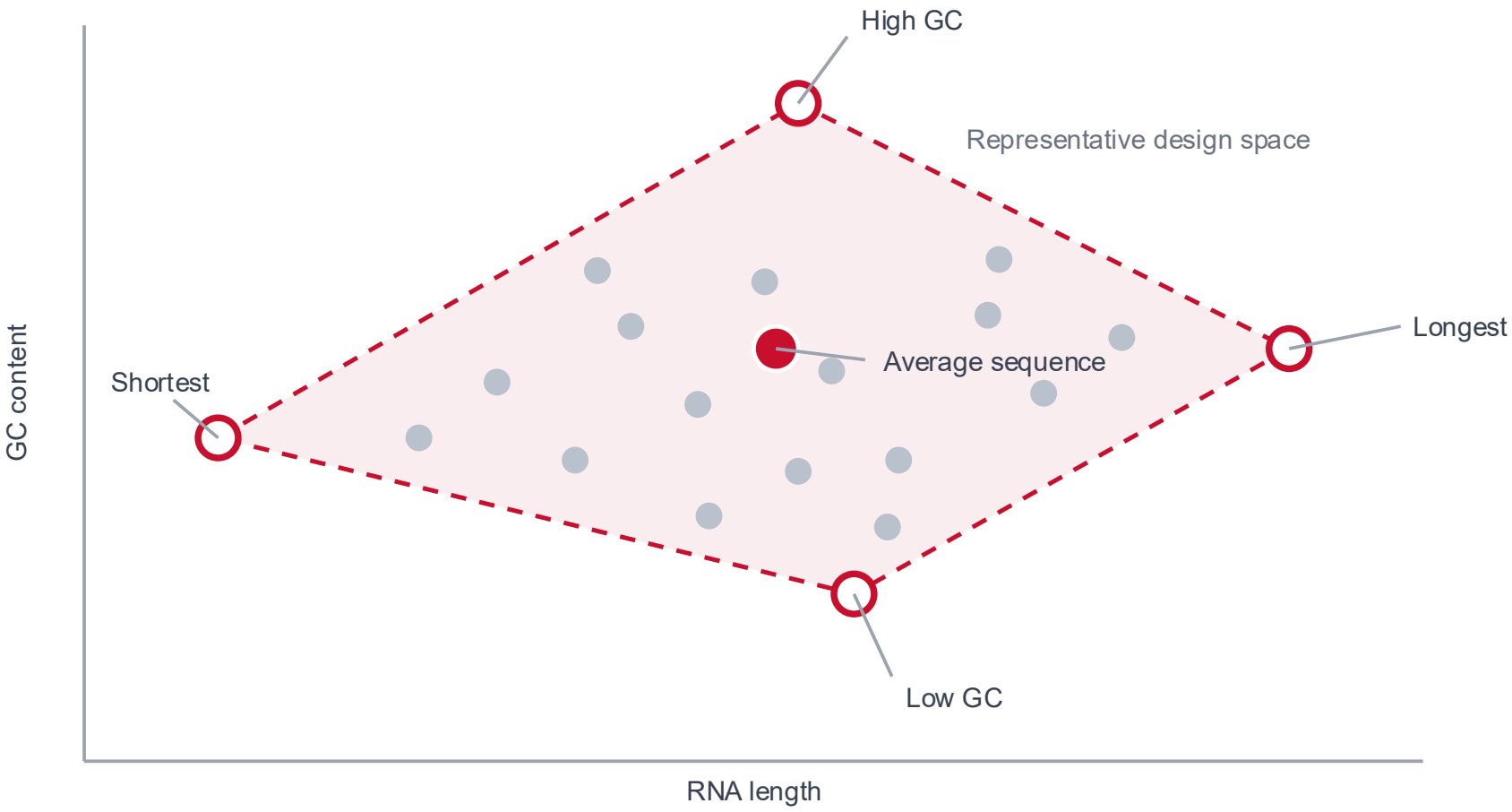
Not all data are transferable

Patient-representative sequences define the design space

RNA representativeness *– ensuring that sequences used for development are representative of the product variability*

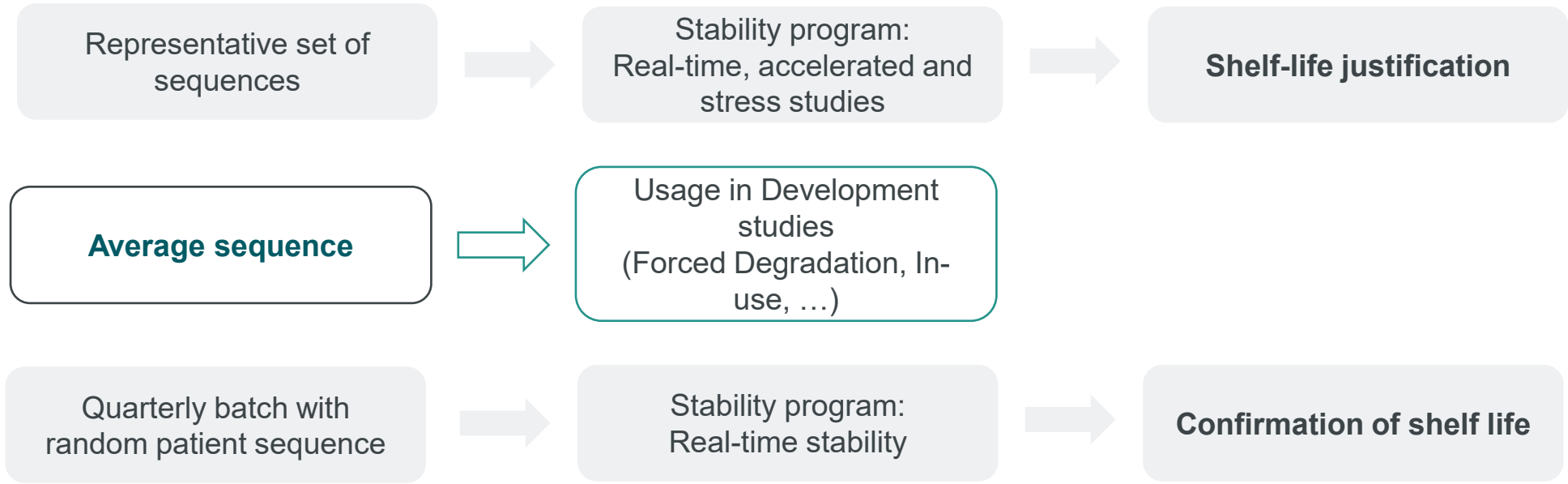
Patient sequence space

Illustrative representation of representative sequence design space



Representative Sequences Enable Stability Assessment

A representative set of sequences provides a practical framework for establishing and maintaining shelf life across individualized mRNA products.

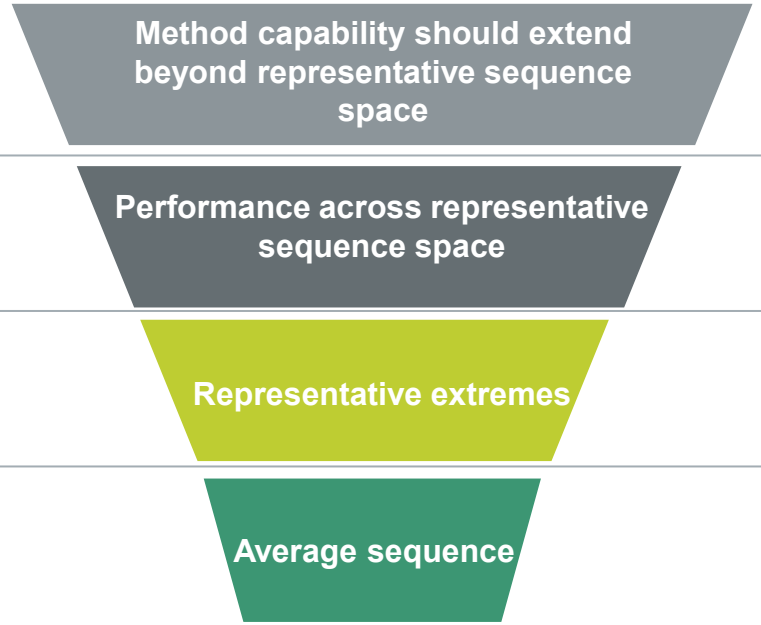


Representative ≠ worst case: average sequence may not represent the most stability-sensitive construct
Limited statistical power: representative sequences typically studies with limited replication, quarterly patient batches introduce sequence-dependent variability

Representative stability dataset provides a framework for shelf-life justification despite sequence diversity

Method Validation focuses on method capability across sequence diversity

How can analytical methods be validated when each batch has a unique RNA sequence?



Generic methods should be considered early during method development

RNA length, GC content, or secondary structure may influence assay performance

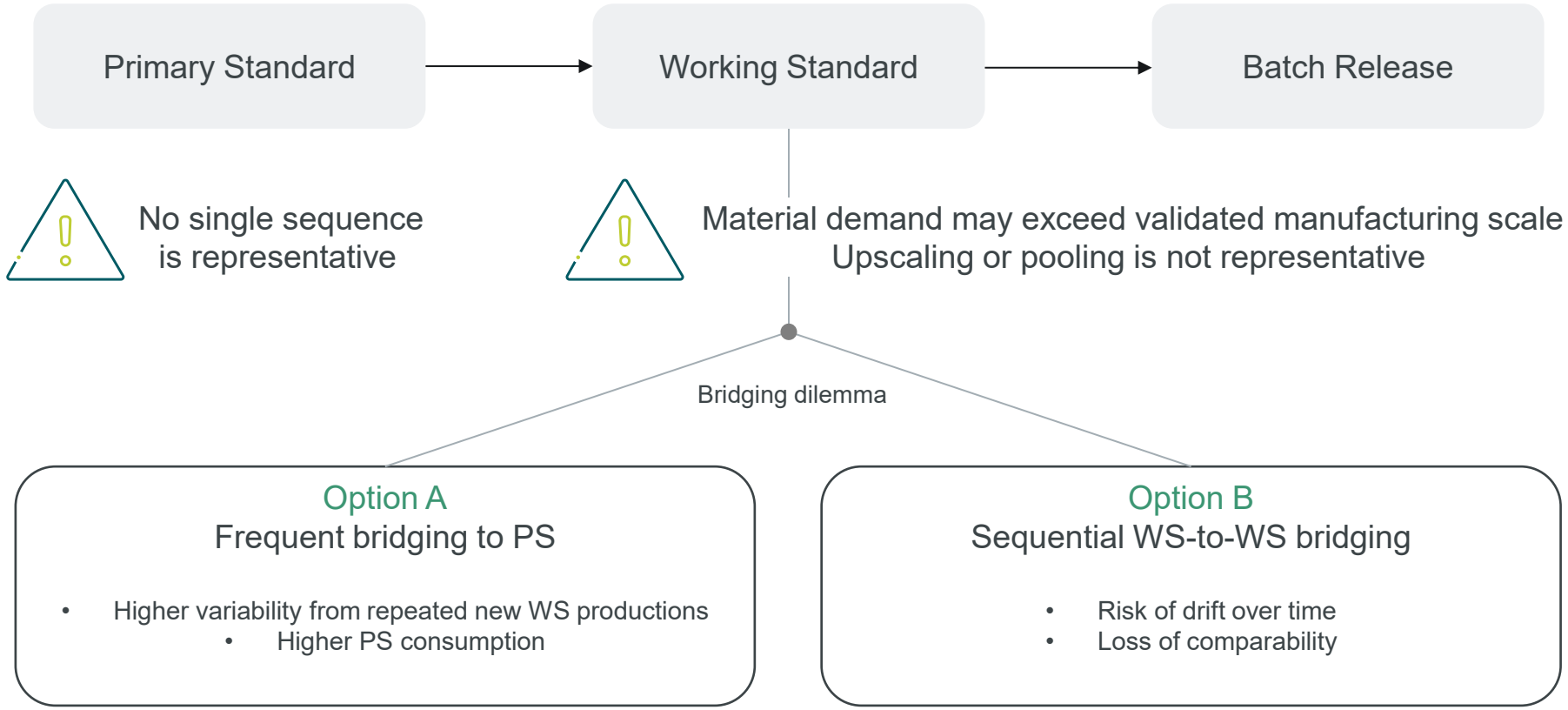
Method robustness studies demonstrating performance across the defined sequence space

Specificity assessment e.g. using long and short sequence to confirm proper migration order through gel

Validation based on representative sequence coverage, not individual sequence validation

Classical reference standard concepts are difficult to apply to individualized mRNA

Regulatory Expectation: Reference standard required in late-stage development



Bridging strategies have different risk profiles

Representative Sequences Enable Comparability Assessment

Representative sequences provide a practical framework for assessing manufacturing changes in individualized mRNA products

Comparability Assessment

Scenario 1

Approach

- Same representative sequences manufactured pre- and post-change
- Side-by-side analytical comparison
- Acceptance criteria based on process knowledge

Strength

- Direct assessment of change impact
- High degree of confidence

Limitations

- Dedicated manufacturing required
- Multiple representative sequences may be needed

Scenario 2

Approach

- Historical representative-sequence dataset defines quality ranges
- Post-transfer batches compared against predefined ranges

Strength

- No dedicated pre-transfer manufacturing required
- ➢ Operationally efficient approach for technology transfer

Limitations

- Greater reliance on historical data
- Statistical justification of ranges with limited dataset
- Side-by-side analytical comparison not possible
- ➢ Difficult to isolate differences between process changes and analytical variability

Observed differences may result from both process changes and sequence diversity.
Representative sequences provide a common comparator to isolate process-related effects.



How does this differ from traditional Q5E comparability?

How does this differ from traditional Q5E comparability?

Q5E principles remain applicable, but sequence diversity requires alternative approaches to generate comparability evidence.

Traditional approach	Individualized approach
Direct comparison of pre- and post-change material is feasible	Representative sequences required as common comparators
Variability predominantly process-driven	Variability driven by both process and sequence effects
Comparability assesses impact of the manufacturing change	Comparability must distinguish process effects from sequence effects
Acceptance criteria supported by extensive prior knowledge and datasets	Acceptance criteria established only from limited representative-sequence datasets
Historical manufacturing data directly support future comparability assessments	Representative datasets become a critical source of process understanding early in development

Representative sequences serve as a surrogate product to generate comparability evidence across individualized products.

Conclusion and Outlook



Representative datasets enable development

→ Representative sequences define a practical design space for individualized mRNA products

→ The same representative dataset can support stability, validation, comparability and reference standard strategies



Process understanding becomes the primary control strategy

→ Representative datasets help distinguish sequence-driven from process-driven variability

→ Robust process understanding increasingly complements traditional product control



Rapid and scalable analytics are essential

→ Generic methods, automation and digitization are critical to support individualized manufacturing timelines

→ Future development should focus on high-throughput and platform-compatible analytical approaches

Individualized mRNA products require a shift toward representative datasets, process understanding, and scalable analytical frameworks.

Thank you

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