Rare Disease Research UK.

UK Platform for Nucleic Acid Therapies - UPNAT

The UK Platform for Nucleic Acid Therapies - Developing Target Selection Guidelines

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Background

Nucleic acid therapeutics (NATs) are a major drug class which utilise nucleic acid-based approaches to target gene expression level and induce therapeutic effects. NATs are designed to selectively bind and modulate target RNA via either promoting degradation, altering splicing, or preventing RNA-protein interactions.

Antisense oligonucleotide (ASO) therapies currently represent the most successful class of NATs, with advancements in technologies leading to a number of both FDA and EMA approvals (Fig 1).

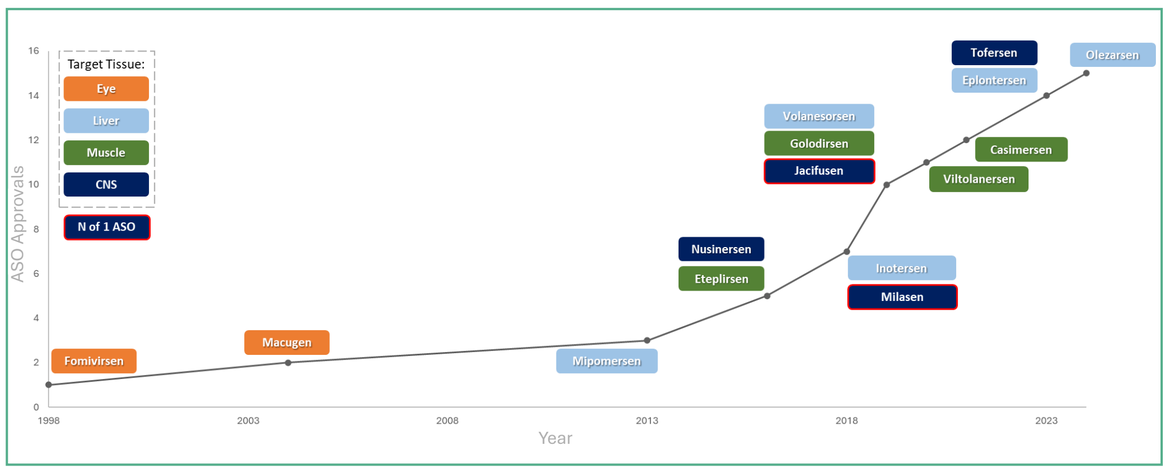

Figure 1: Approved ASO therapies. Date of approval indicates FDA approval (or EMA approval, if the ASO has not yet been approved by the FDA).

Increased interest and investment in the field has led to a number of guidance publications addressing patient selection, preclinical development and regulatory considerations (Fig 2).

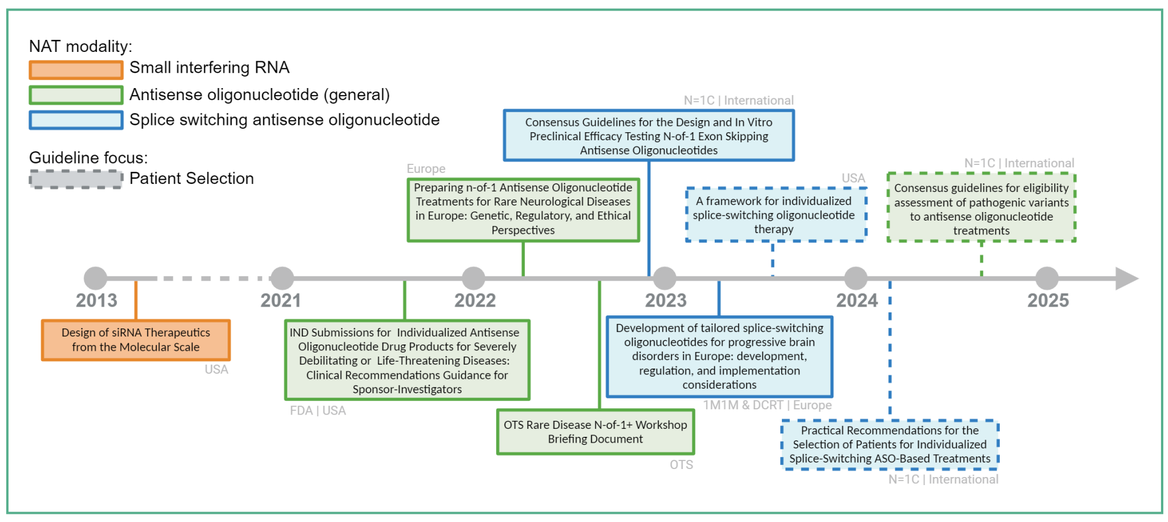

Figure 2: Guidance publications for the development of NATs.

Challenges Faced within the UK

There is currently a **lack of UK specific guidance** and **infrastructure** to enable patient selection for NATs.

The UK holds expertise in rare disease management and is a world leader in genetic health care; combined with an established national-level genomic infrastructure, this presents the UK **an opportunity to deliver NAT therapies to rare disease patients in need.**

Aims

To enable UK therapy providers to rapidly prioritise patients for NATs & identify modifiable barriers to treatment, we aim to:

1. Develop a NAT target selection guideline, piloting with ASO target selection
2. Facilitate implementation of this framework into the NHS

UPNAT Target Selection Guidelines

The UPNAT pilot ASO target selection guidelines were drafted by a UK-based multidisciplinary group of experts (Fig 3), which were subsequently calibrated against publicly available data (Fig 4).

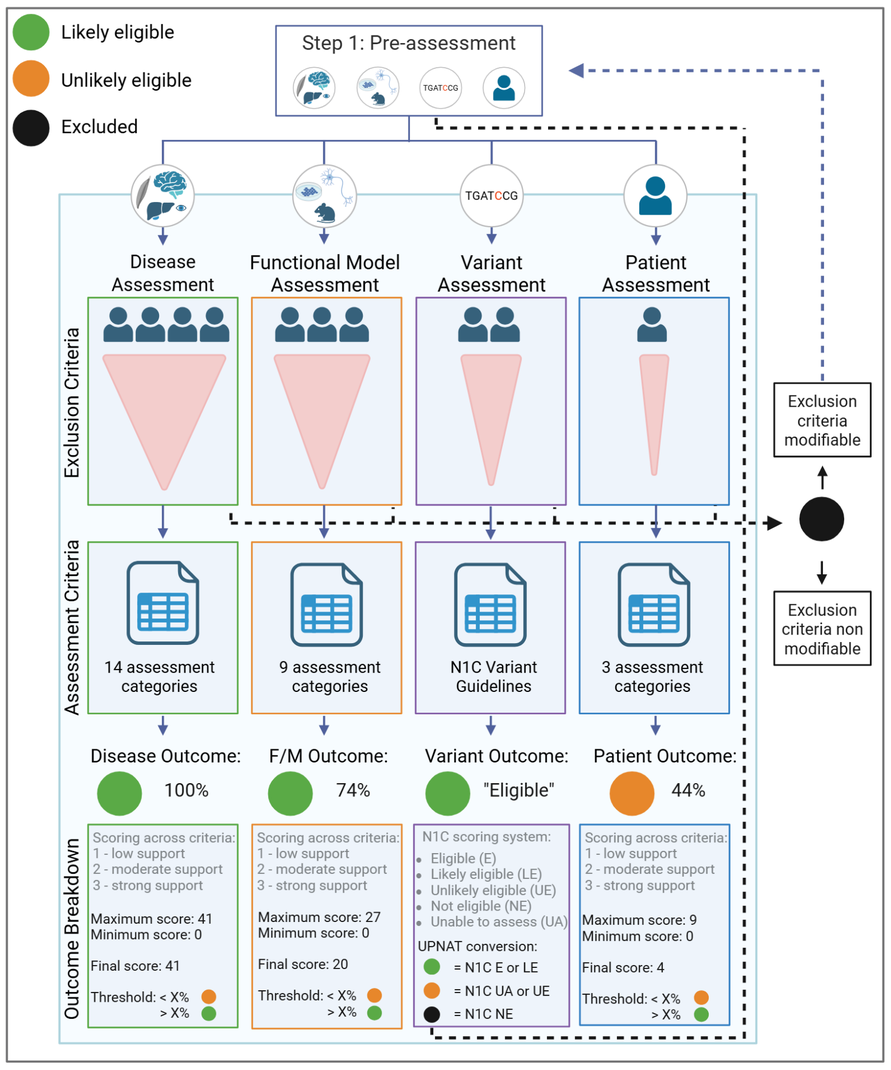

Figure 3: Pilot ASO target selection guidelines exemplifying an 'unlikely eligible' patient assessment. Although no exclusion criteria were met and the disease, functional model and variant present 'likely eligible' targets, the patient does not meet the hypothetical scoring threshold and so ASO development is not recommended. Guideline calibration is ongoing to define scoring thresholds.

Guideline Characteristics

- Four complementary subcategories: disease, functional model, variant and patient
- Multiuse design
  - Sub-guidelines can be used in isolation or together
  - Flexibility in order of sub-guideline use
- Preassessment for quick 'go' or 'no go' decision
- Streamlined assessment starting with strong exclusion criteria
- Simple initial scoring system to build upon
- Modifiable exclusion criteria to allow future re-assessment of targets
- Designed for automation and dependence upon open-source data

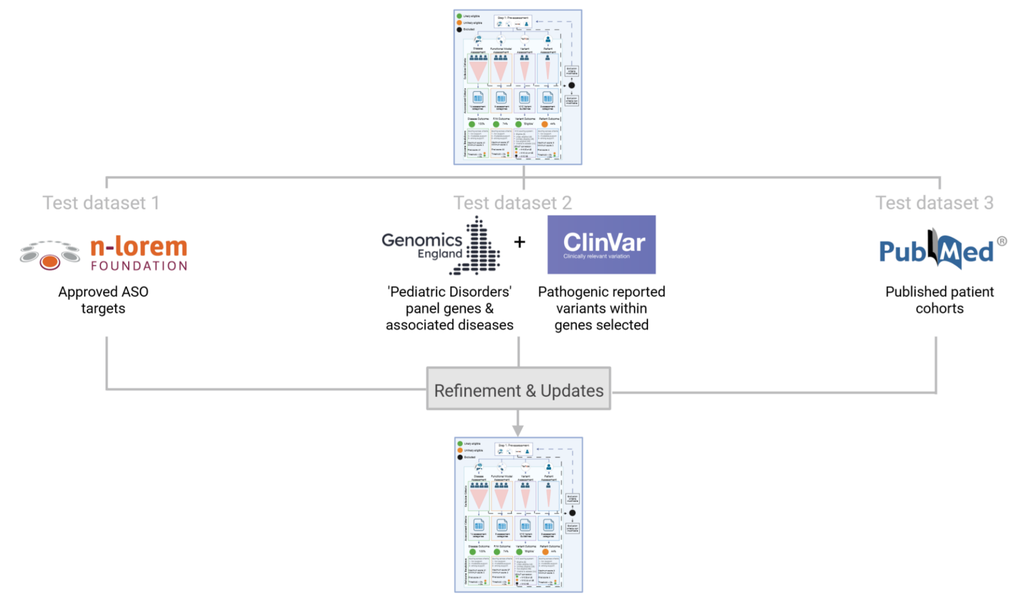

Figure 4: Guideline testing and calibration methodology.

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