ReCognitION, a milestone in an alternate pathway towards a personalized medicine

Most of the ongoing research about Myotonic Dystrophies is based on sophisticated approaches dedicated to fix the genetic abnormality at the origin of the disease.

These scientific investigations can be promising but the roadway is long before achieving a systemic drug formulation, its testing, and approval for delivery to the patient.

In contrast, ReCognitION is a follow-up program of the European OPTIMISTIC clinical trial, which explored an alternative, approach aimed to improve patient quality of life in combination with drug repurposing.

OPTIMISTIC, the largest European trial up to date in Myotonic Dystrophy type 1 (DM1) took place between 2014 and 2017 in 4 countries: The Netherlands, France, U.K., and Germany.

A cohort of 255 patients was recruited to evaluate the effect on the patient quality of life of a combination of Cognitive Behavioral Technique (CBT) and physical training. Additionally, a thorough clinical characterization of the enrolled patients was performed, and human samples were collected during the clinical interventions.

CBT is a form of healthcare based on the concept that patient thoughts, feelings, physical sensations and actions are interconnected. Negative thoughts, feelings and behavior can trap them in a vicious cycle.

In an adaptive way, the therapist proposes practical solutions to improve state of mind and promote healthy behavior. Unlike some other therapies, CBT deals with current condition rather than focusing on issues from the past.

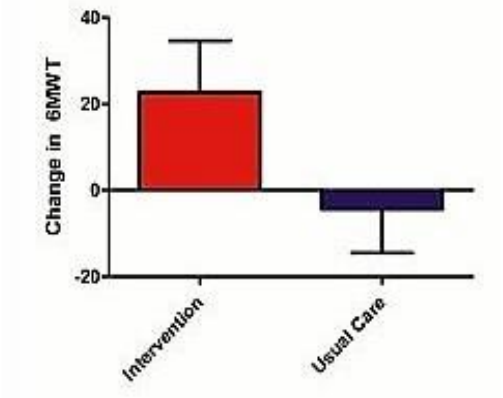
In OPTIMISTIC, the cohort was divided in 2 groups, the first one received CBT, the second one continued usual care.

- CBT consisted of up to 14 sessions with a psychologist for 10 months focused on problems and symptoms of DM1 patients visible in their behavior on a daily basis, such as reduced activity, stress, anxiety, fatigue, reduced initiative, social interaction, sleep quality, pain….

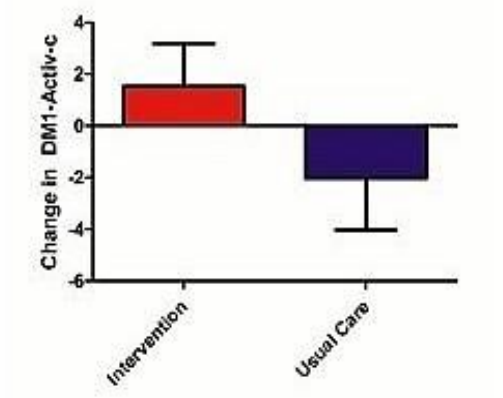
- Additional Physical training consisted of aerobic exercise, under control of a physiotherapist, with measurements of activity performance in all patients (walking distance, muscle condition).

Summary: For most of the patients, OPTIMISTIC demonstrated a visible and measurable beneficial effect in evaluated domains: social participation, exercise capacity (walk test), fatigue, objective physical activity, and muscle condition, all positive effects being maintained at follow up of the trial.

Walking tracker (6mn walk)



Activity tracker (DM1-Activ-c)



A subgroup of non-responder patients was also identified enabling us to study the question why certain patients improved and others did not. This is where ReCognitION comes in.

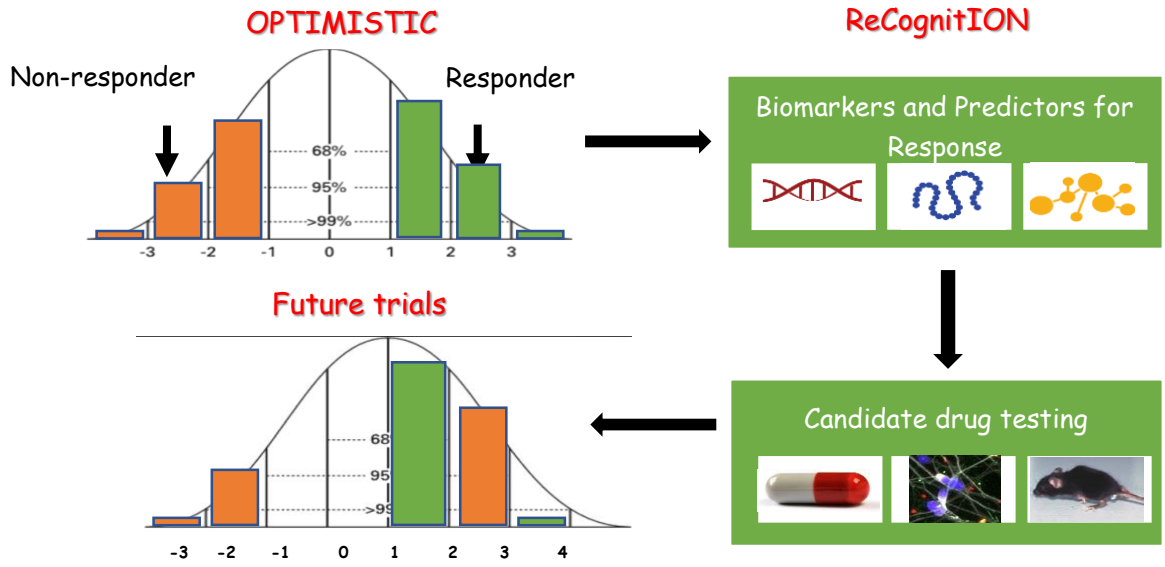
Optimistic trial → **ReCognitION** → Personalized medicine

The central hypothesis of ReCognitION is that pathways associated with the positive response to CBT can be consolidated or reinforced by conventional drug therapies targeting the same pathways.

The trial is a pre-clinical study, taking advantage of all information and material collected from OPTIMISTIC. No additional clinical investigation is required.

It will cover the following activities:

- Provide a detailed analysis of positive responses to a CBT behavioural intervention in the Optimistic responding group.
- Identify the molecular signature of the response by means of bioinformatics approach and characterize the molecular processes and pathways associated to CBT as observed and quantified in OPTIMISTIC.
- Identify drugs which target the same pathways, prioritizing drugs which are already approved for clinical use (drug repurposing).
- Measure the effect of these drugs on the molecular profiles of DM1 patient cells and the behavioural phenotypes of DM1 mouse models.



Summary: At the end of the project, the selected drug-candidates will be tested in animal models and human cells. Scientists will have a better knowledge about the reasons why patient respond or not to the CBT interventions, but further investigations involving patients will be necessary before approval of the drug for use in Myotonic Dystrophy type 1. The safety and tolerability studies could be accelerated if the expected dose for DM1 stays in the limits of the drug certification for its original pathology, but a "randomly versus placebo" phase 3 study will be required to confirm the positive effect of the drug on patients.

Optimistic trial → ReCognitION trial → Personalized medicine

ReCognitION program is a precursor of innovative care techniques in many points.

At first, the cure is not based on a pre-established protocol validated for the disease in all patients at the same time, but built individually after a detailed analysis of the patient needs to improve his quality of life. This approach is promising for Myotonic Dystrophy whose variability of symptoms is well known, but could be adapted to other neurological diseases.

Also, the drug repurposing strategy based on the reverse engineering of a positive response to a behavioural intervention, may set the scene for future drug development trajectories in rare diseases.

Finally, the combination of care techniques given by different communities in order to maximize the effects is very innovative. For Myotonic Dystrophy type 1, the psychologist together with the patient identifies in shared decision making the patient needs and realizes the CBT intervention; additional physical training is performed by a physiotherapist or even a sport coach, and the drug delivery is controlled by a clinician.

This diversity of actors converging towards the quality-of-life improvement of the patient is also an attractive way to obtain and maintain the commitment of patients sometimes affected by apathy and misestimation of themselves.

Somewhere, a new highly personalized medicine is emerging...