More efficient DMOAD trials via innovative screening strategies

Thibault Helleputte, PhD[1] Yves Henrotin, PhD[2]

1: DNAlytics SA, Chemin du Cyclotron 6, 1348 Louvain-la-Neuve, Belgium info@dnalytics.com; 2: Bone and Cartilage Research Unit, University of Liège, B-4000 Liège, Belgium

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Background

The number of patients to recruit for assessing effectiveness of DMOAD in RCTs depends on the proportion of progressors in the population. Progressors in general OA population: 10-30%[1] ⇒ large cohorts, long / expensive RCTs.

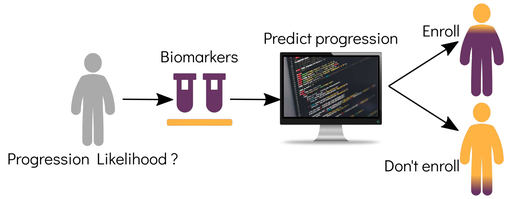
Low Progressor Proportion: Larger Sample Size

High Progressor Proportion: Smaller Sample Size

Objectives

Use predictive modeling and cartilage degradation markers to:

1. Screen patients,
2. Make individual predictions about future progression,
3. Recruit a progressor-enriched cohort
4. Achieve same / better success rate with smaller cohorts / lower budgets



Data

Markers of cartillage degradation (Coll2-1 & Coll2-1-NO2, Artialis, BE) measured at baseline on 182 OA patients from the placebo arm of a previous RCT [2]. Only women of 55±5.8 y.O. with BMI 36.5±6 mostly with K&L grade II-III (0-I for contralateral knee). Progression at 30M is defined as in [3].

Method – Progression Modeling

First challenge: Build predictive models (regularized logistic regressions) of progression over 30M based on biomarkers:

- based on **Coll2-1** (see graphs below)
- based on both **Coll2-1 and Coll2-1-NO2**

Moderate AUC of 60 to 65% is obtained through cross-validation.

Method – Trial Optimization

Second challenge: Use the model and study design parameters to optimize trial.

Hypotheses to play with:

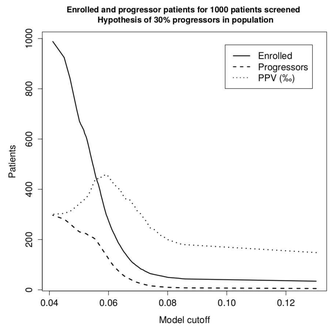
- Natural progressor rate in general OA population: 10 to 20%
- Expected drug effect: 30 to 50%.
- Costs of the trial (cost of a screening visit, cost of other visits, cost of IMP, cost of Imaging, etc.).
- Extra cost of the biomarker testing.

⇒ Optimize overall cost by playing with progression model cutoff, i.e. find optimal balance

- between sensitivity and specificity,
- between number of patients screened and number of patients actually enrolled.

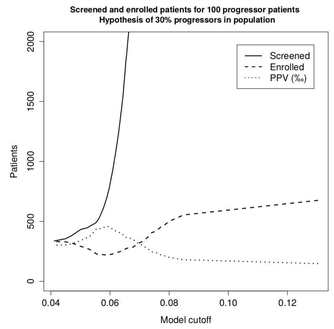
Increase model threshold

⇒More progressor-enriched cohort, but lots of patients screened and not enrolled.



Decrease model threshold

⇒Less progressor-enriched, but fewer patients screened and not enrolled.

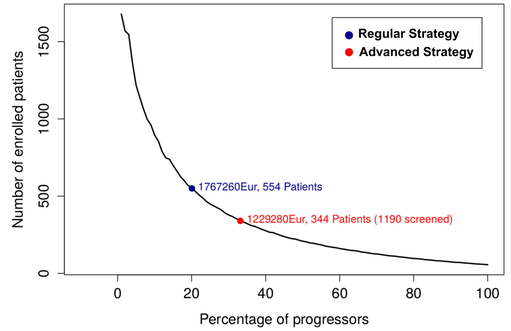


Results

Gain up to 30% cost reduction and 40% sample size reduction. Example:

- Natural progressor rate: 20%;
- Actual effect of DMOAD to be tested: 50%;
- Study design: 6 visits (screening, follow-up, final), 2 x-rays, 2 MRIs.

Hypotheses have been made about item costs according to Belgian practice.



Conclusions

- Shows interest for biomarker-based OA-progressors cohort enrichment.
- Simulates potential gains for the conduct of RCTs.
- Results should be replicated on other, more representative cohorts
- Additional markers / clinical factors could be considered for the models.

References

[1] Deberg *et al.*, Ann Rheum Dis. 2008 Feb;67(2):168-74.
[2] Brandt *et al.*, Arthritis and rheumatism. 2005;52(7):2015-25.
[3] Ornetti *et al.*, 2009; OARSI-OMERACT

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