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Automatic Defining ADaM for new Clinical Studies Using Machine Learning

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Meet the Speakers

Thomas Rye Olsen

Title: Student

Organization: Department of Computer Science, University of Copenhagen

- Studying Machine Learning and Data Science on his third year
- Have been working with Biostatistics, Novo Nordisk applying ML
- Recently become a student assistant at Novo Nordisk

Henning Pontoppidan Föh

Title: Statistical Programming Director

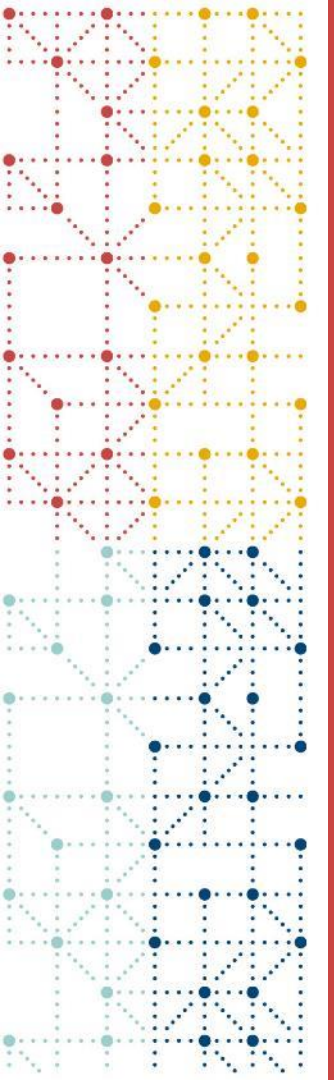
Organization: Biostatistics, Novo Nordisk A/S

- 15+ years of pharmaceutical industry experience, within various arears
- MSc in Physics and worked as researcher as well as SAS consultant
- Currently main interest is the strategic clinical development for new drugs and indications

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC nor of Novo Nordisk*

- *The author(s) have no real or apparent conflicts of interest to report.*



Agenda

1. Background
2. The idea of using ML for ADaM definition
3. Details of the ML algorithm
4. Results and usability

Background

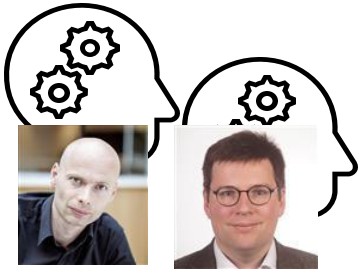
Data is gold

Data = clinical data + clinical metadata

- Data collected from patients
  - Demographics, AEs, endpoints
- Highly regulated by authorities + CDISC
- Available for all studies in standardised format
- All pharma companies have it from their studies

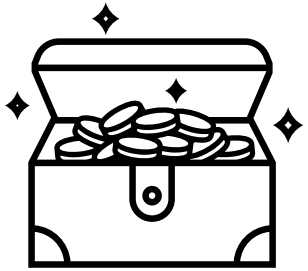
- Descriptions of studies, created by Novo staff
  - Protocol Metadata document (PMD) containing items such as flowchart, study descriptive keywords, etc
  - Analysis data/ADaM description (within the CST)
- Generally, not regulated by authorities
- Available for all studies running in the last decade
- A unique feature of Novo Nordisk !?

A quest for gold requires 3 items…



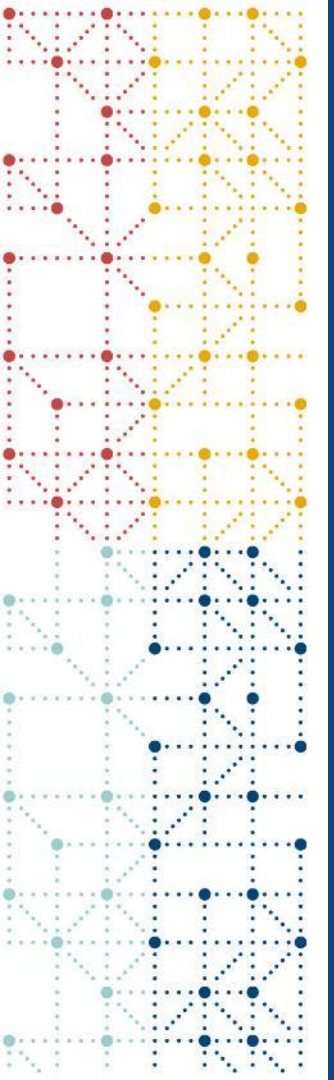
Bright minds

Hard labour



Someone who what to **spend** the gold

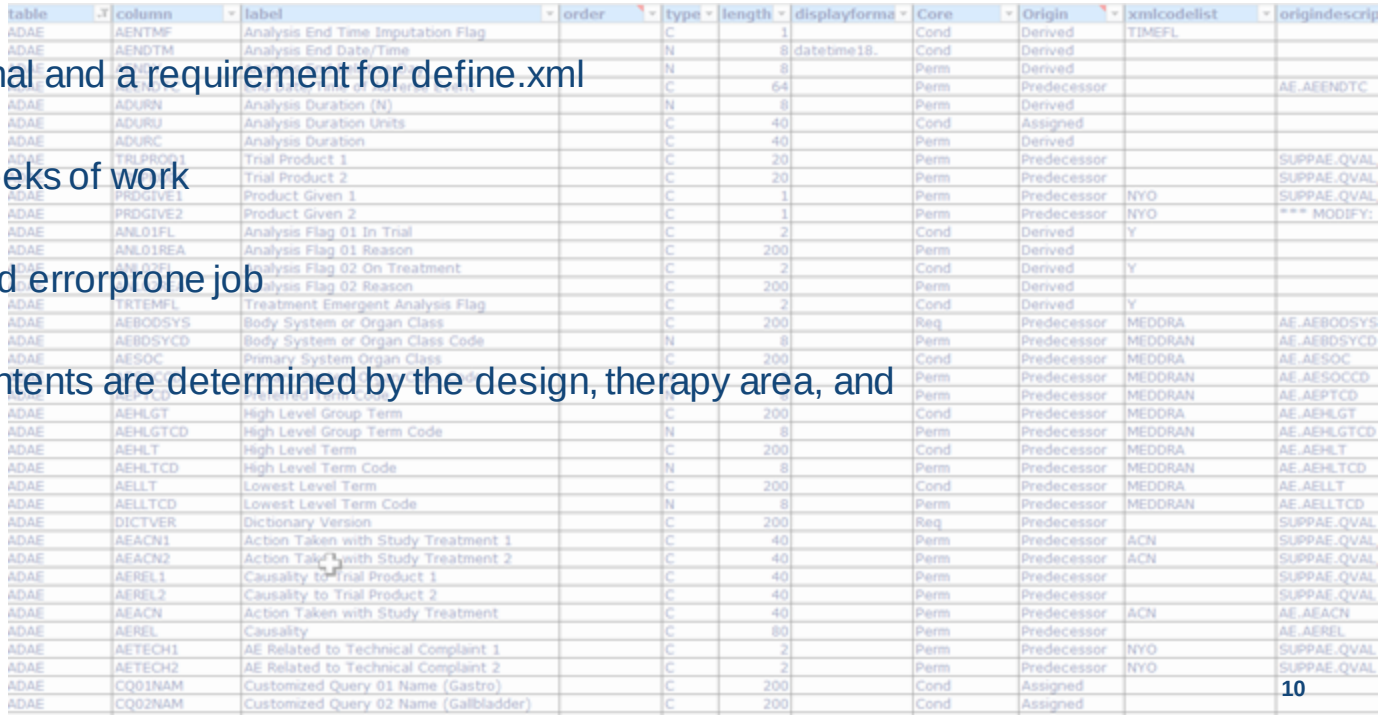
Let’s mine the metadata gold



The idea of using ML for ADaM definition

Creating analysis metadata today

- For every study, the trial programmer has to create a structured description of all analysis (ADaM) datasets in an Excel sheet (CST)
  - Both a functional and a requirement for define.xml
  - Takes days/weeks of work
  - Is a tedious and errorprone job
  - Most of the contents are determined by the design, therapy area, and clinical project



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ADAE	ADURN	Analysis Duration (N)		N	8		Perm	Derived		
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ADAE	ADURC	Analysis Duration		C	40		Perm	Derived		
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ADAE	PRDGIVE1	Product Given 1		C	1		Perm	Predecessor	NYO	SUPPAE.QVAL
ADAE	PRDGIVE2	Product Given 2		C	1		Perm	Predecessor	NYO	*** MODIFY:
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ADAE	ANL01REA	Analysis Flag 01 Reason		C	200		Perm	Derived		
ADAE	ANL02FL	Analysis Flag 02 On Treatment		C	2		Cond	Derived	Y	
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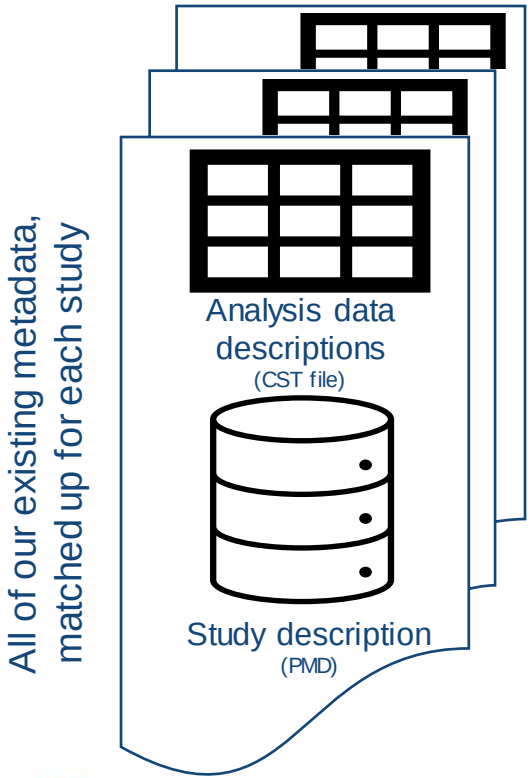
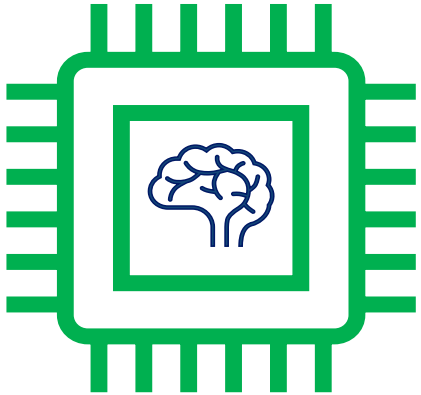
Creating analysis metadata using ML

Step 1: Train a machine learning model

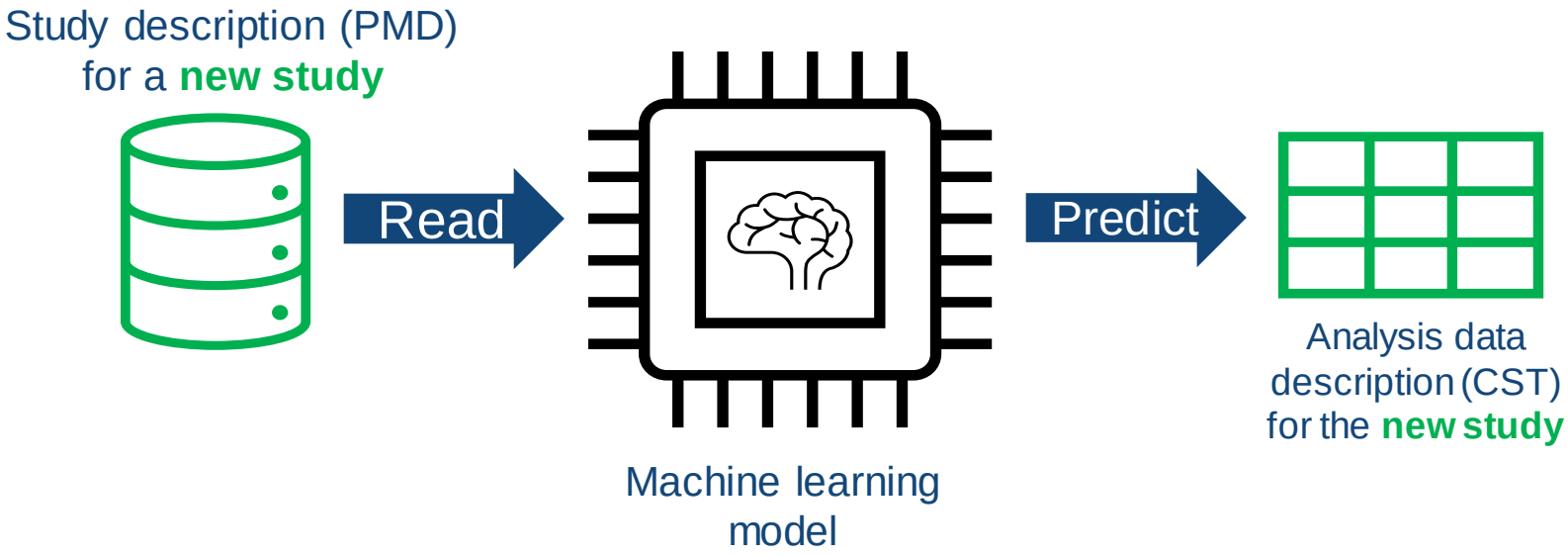


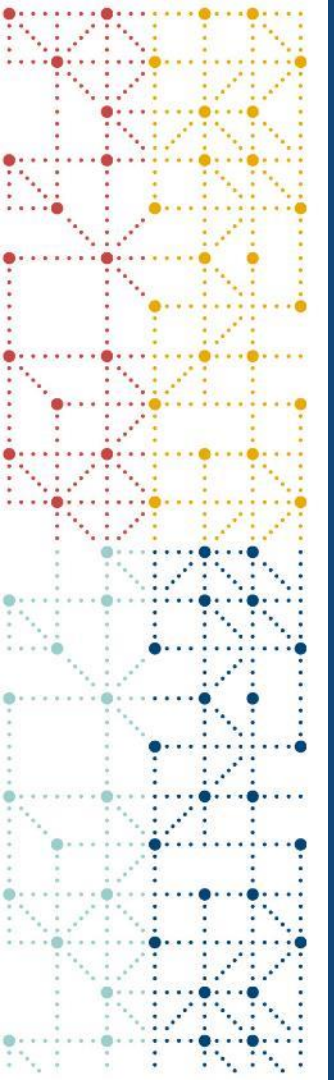


Machine learning model under construction

Creating analysis metadata using ML

Step 2: Use the machine learning model

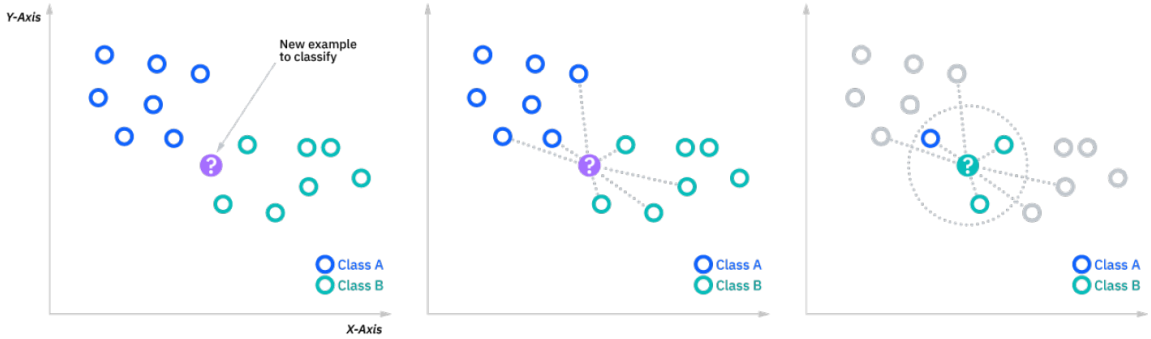




Details of the ML algorithm

Inside the belly of
Supervised learning with RKNN-FS

- Supervised learning: We know what we are looking for
- Random K Nearest Neighbors (RKNN)
  - KNN: Distance by similarity in features
  - Random choice of features
  - Ensemble model



- Feature Selection (FS):
  - Check what features gives best forecasts
  - Iteratively discard features that seem redundant
  - Better generalization in theory and better results in practice
  - Better insights

Evaluating performance

- Confidence is key!
- Tested against complete studies
  - Confidence of correct classifications
- Cross validation:
  - Train on 80% data, test on 20%
  - 5 Rounds
  - Unbiased estimate
- Threshold: 80% confidence

include	tables
1	ADSL
0,96133333	ADAE
0,95966667	ADEC
0,50333333	ADECEN
0,94266667	ADEG
0,485	ADHYPOEN
0,99966667	ADLB
0,94333333	ADPC
0,60866667	ADPDC
0,60866667	ADPDP
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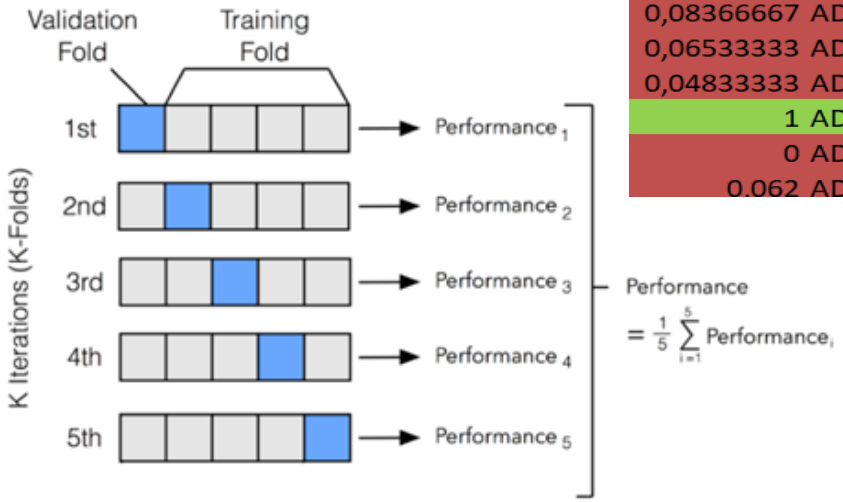


Workload spared

- Classifications with high confidence (above 80%):
  - ~25 ADaM datasets out of 38
  - ~3128 variables/columns out of 3479
  - Much better than expected!

- Errors? 
  - 98% of datasets with high confidence are correct
  - 0.6 datasets per study are incorrect
  - 97% of variables with high confidence are correct
  - 123 variables per study are incorrect
  - Handled by project-responsible programmer

Results and usability

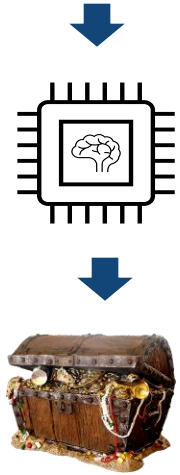
How much gold did we extract so far?

~80% of analysis data description can be correctly predicted

Much less manual work on this task

Going forward – spending the gold

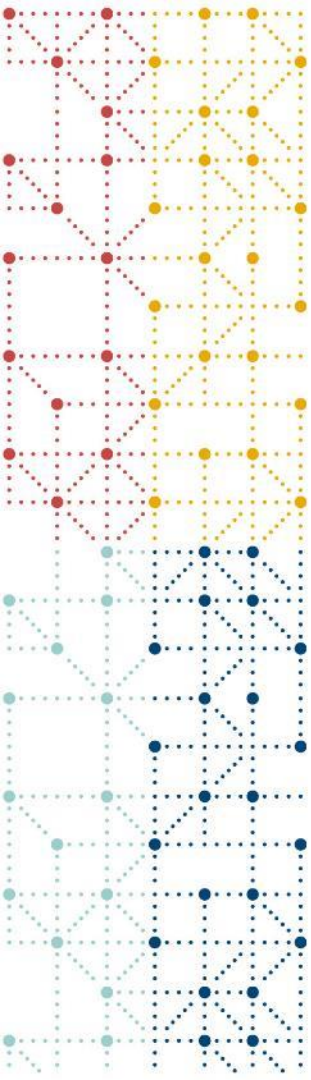
- Build and deploy a user **application**
- Interactive tool to build the ADaM-definition
- Upload study description (PMD)



- High confidence predictions automatically defined
- ADaM datasets and variables with low confidence are presented
- Programmer decides when the confidence is low

Going forward – purifying the gold

- Examine an **adaptive recommender system**
  - Recommend tables and columns that have not been defined in ADaM
  - Learns iteratively from the choices the programmers make
  - Potentially even more automation



Conclusion

Learnings & conclusions

- We can use ML for predicting new ADaM trials definitions using supervised learning trained on previous clinical metadata
- RKNN-FS seems to be a good performing algorithm for when we have few data to train on
  - RKNN-FS can predict approximately 80% of ADaM datasets including variables correctly and with high confidence
- Tedious and repetitive ADaM definitions that can be automated → Trial programmer can focus on non-standardized items
- In the future we are looking into building an app using the ML algorithm to forecast ADaM definitions for new trials
  - Examining the possibility to build an adaptive recommender system

Thank You!

Questions and comments are welcome!

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