

Full Genomic Analysis of ANAVEX®2-73 Phase 2a Alzheimer's Disease Study Identifies Biomarkers Enabling Targeted Therapy and a Precision Medicine Approach

Harald Hampel, Prof., MD, PhD¹; Mohammad Afshar, MD, PhD²; Frédéric Parmentier, PhD²; Coralie Williams, MSc²; Adrien Etcheto, MSc²; Federico Goodsaid, PhD³; Emmanuel O Fadiran, PhD⁴; Christopher U Missling, PhD⁴;
1. Sorbonne University, Paris, France, 2. Ariana Pharma, Paris, France, 3. Regulatory Pathfinders LLC, Pescadero, CA, USA, 4. Anavex Life Sciences Corp., New York, NY, USA



Overview

- ANAVEX®2-73 focuses on a new target relevant to Alzheimer's disease and other neurological diseases
- Sigma-1 receptor (SIGMAR1) serves as an intracellular chaperone and functional modulator of calcium homeostasis and synaptic plasticity. It is involved in several pathways related to Alzheimer's disease, i.e. reduction of beta amyloid, hyperphosphorylated tau, oxidative stress, and neuroinflammation
- The direct occupancy of ANAVEX®2-73 at the SIGMAR1 has been established using quantitative PET scan (AAIC 2018)
- Anavex Life Sciences identified genomic biomarkers for increasing success rate in Alzheimer's disease clinical studies
- Full genomic analysis of ANAVEX®2-73 Phase 2a Alzheimer's disease study identifies biomarkers enabling targeted therapy and a Precision Medicine approach
- Targeted therapy benefit is expected for about 80% of patient population

What is a Patient Selection Marker for Precision Medicine in Alzheimer's?

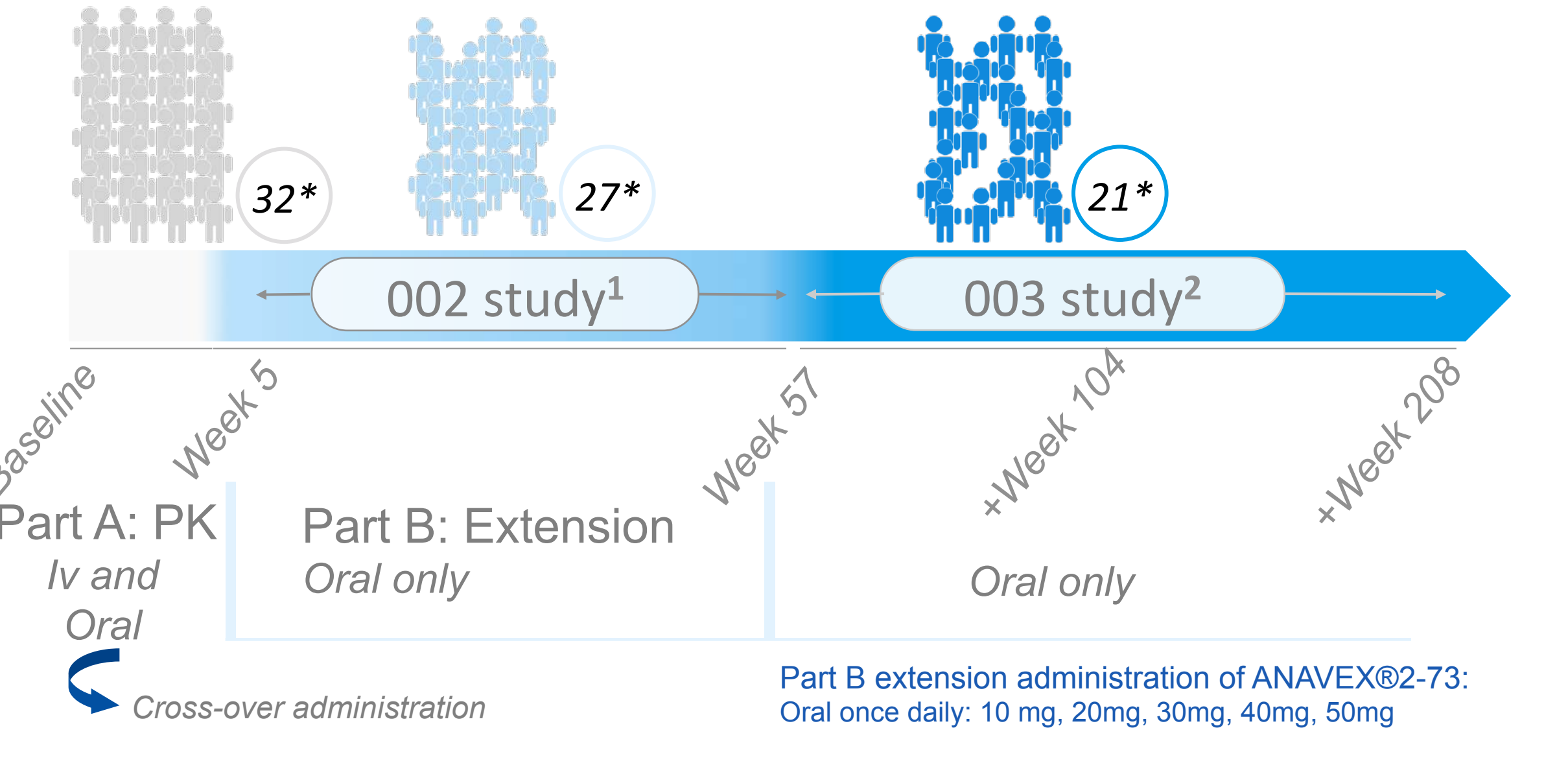
Objective criteria for selecting patients into a clinical study who are likely to benefit from the therapy

- Minimum baseline thresholds for cognitive or functional evaluations
- Genomic biomarkers: variants in DNA which identify who will – or will not – benefit from the therapy

Anavex did a preliminary Phase 2a study with ANAVEX®2-73 to identify patient selection markers

- Study results were analyzed by Ariana Pharma using their proprietary AI KEM® platform
- The results of this analysis showed strong patient identification markers for clinical studies

ANAVEX®2-73 AD Phase 2a: Timeline and Description of the Cohort

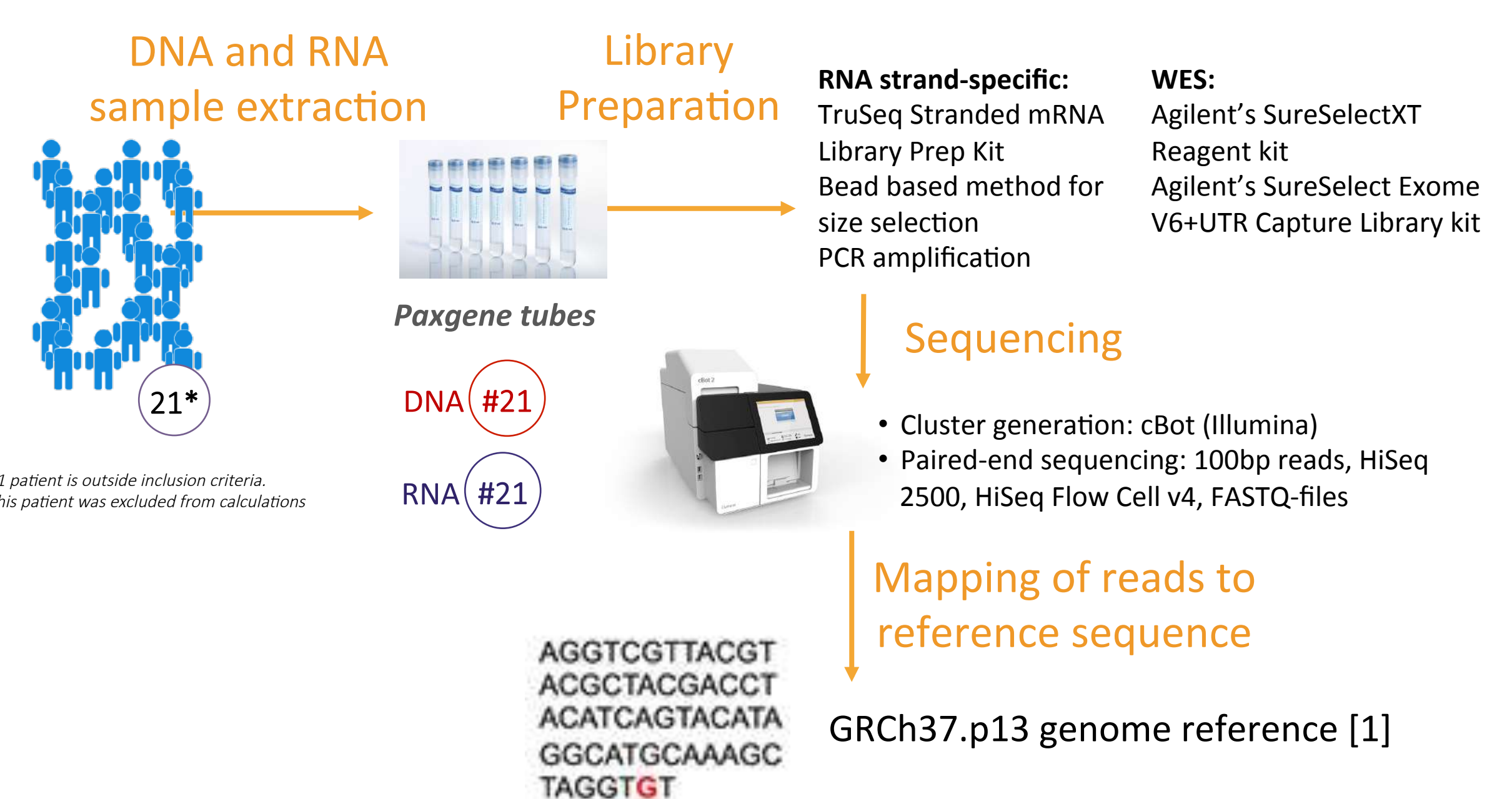


Cohort characteristics:
Alzheimer's disease patients
Age range: 55 to 85
Diagnosed with MRI and/or PET scans

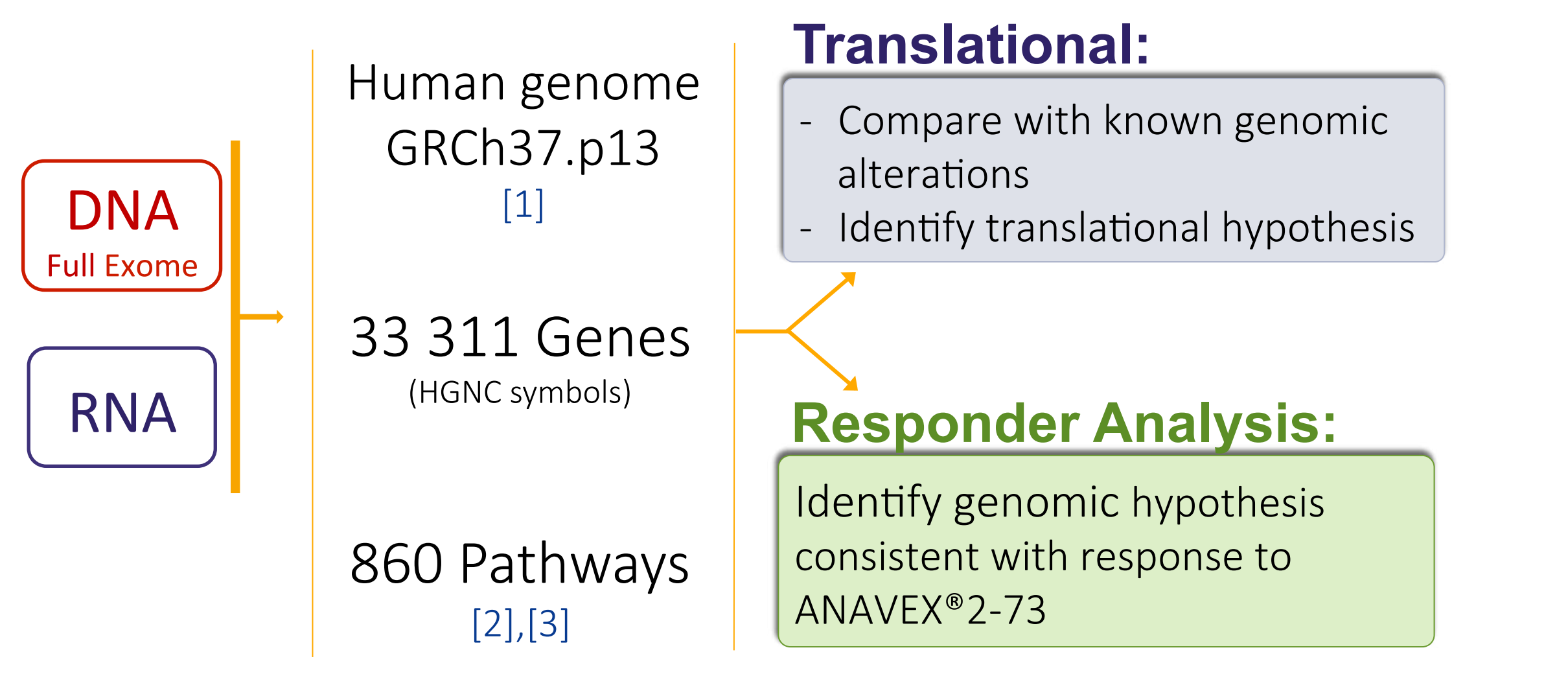
*1 patient is outside inclusion criteria. This patient was excluded from calculations.
*2: ClinicalTrials.gov Identifier: NCT02244541; *NCT02756858

References
[1] Genome Reference Consortium Human Build 38 patch release 10 [GRCh38.p10]. https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.25/#/st
[2] Kanehisa M, Goto S. (2000) KEGG: Kyoto encyclopedia of genes and genomes. Nucleic Acids Res. 2000;28(1):27-30. doi: 10.1093/nar/28.1.27.
[3] Fabregat A, et al. The Reactome pathway knowledgebase. (2016) Nucleic Acids Res. 2016;44:D481–D487. doi: 10.1093/nar/gkv1351.
[4] Afshar M, Lanoue A, and Sallantin J. (2007) Multiobjective/Multicriteria Optimization and Decision Support in Drug Discovery. Comprehensive Medicinal Chemistry II. Volume 4, edn. 2007: 767-774.

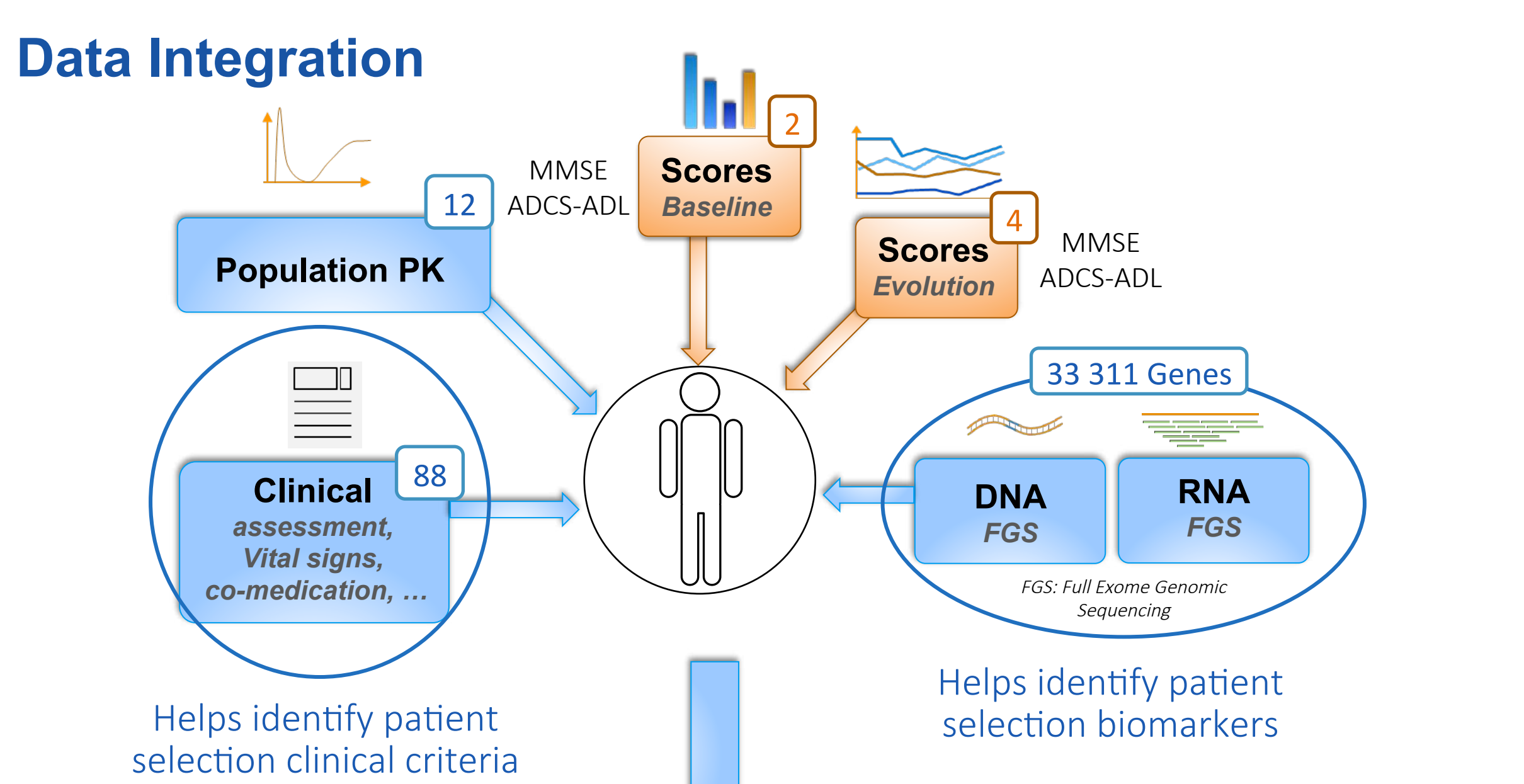
Material and Methods: DNA and RNA Sequencing



ANAVEX®2-73 Genomic Knowledge Base :



Material and Methods: Data Integration and Analysis



Data Analysis

Using AI platform KEM® version 3.6.2

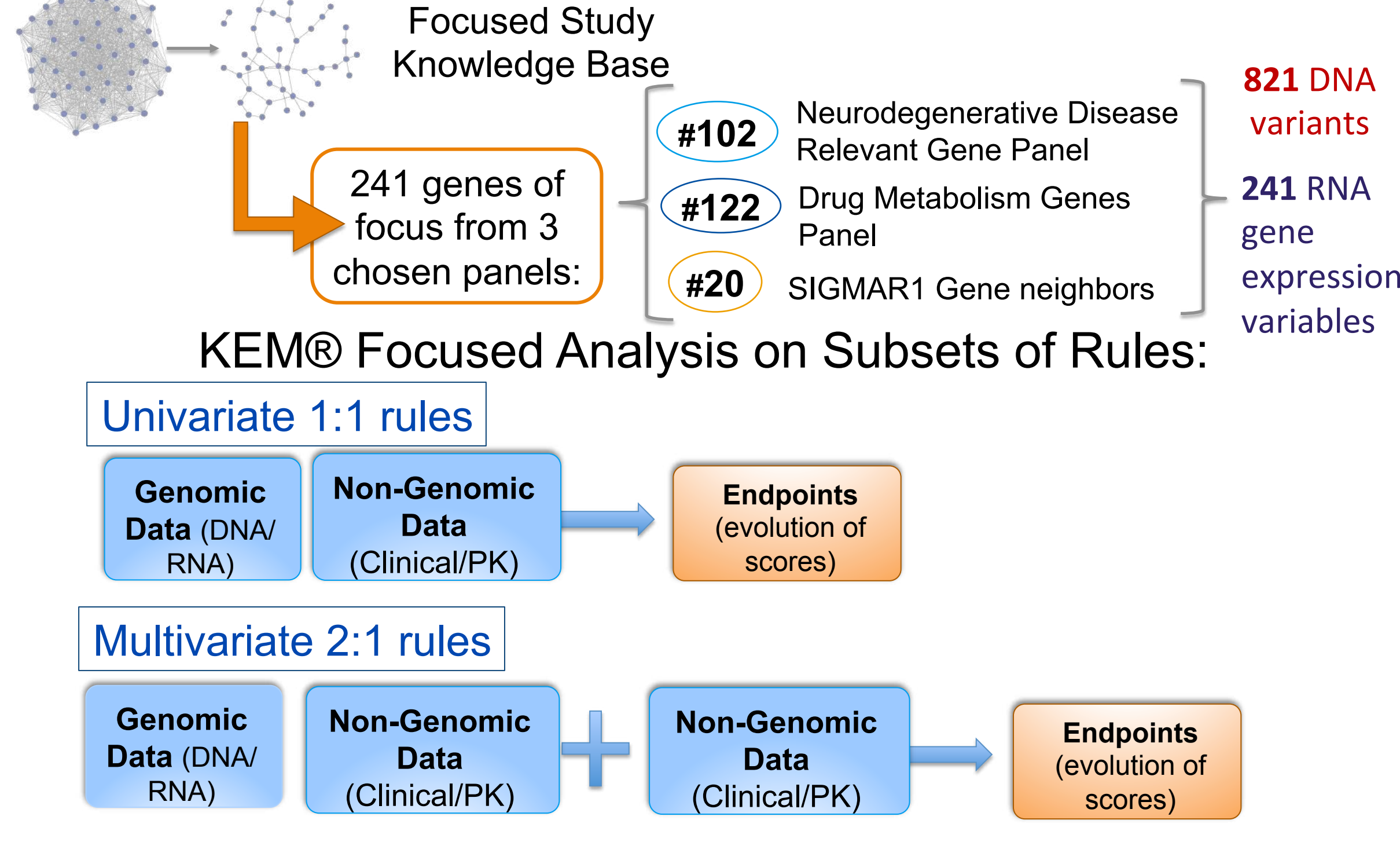
Systematic Generation of all Association Rules
>20 Million relations extracted and characterized from study data

- Association rules provide unique, unbiased results and generate new hypotheses
- KEM® (Knowledge Extraction Management) helps overcome the challenges of analysis of biomarker data in small clinical studies [4]

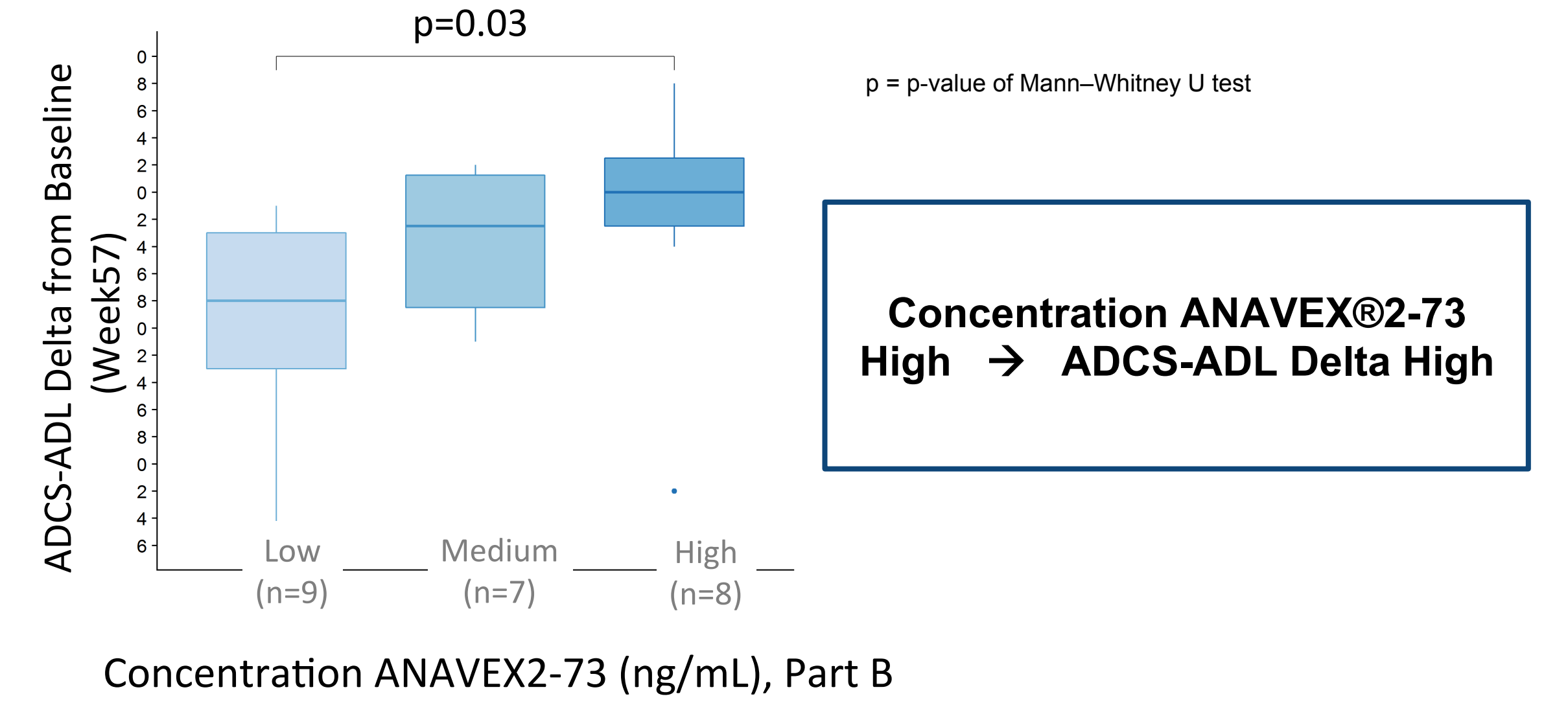
Rule example
Var 1 = High → Ept 3 = High

Metrics
Support: number of times that the rule is checked in the dataset
Confidence: proportion of cases verifying Var 1 = low and Var 3 = True
Lift: ratio of the observed support to that expected if Var 1 = low and Var 3 = True were independent
P-value: Fisher's exact test

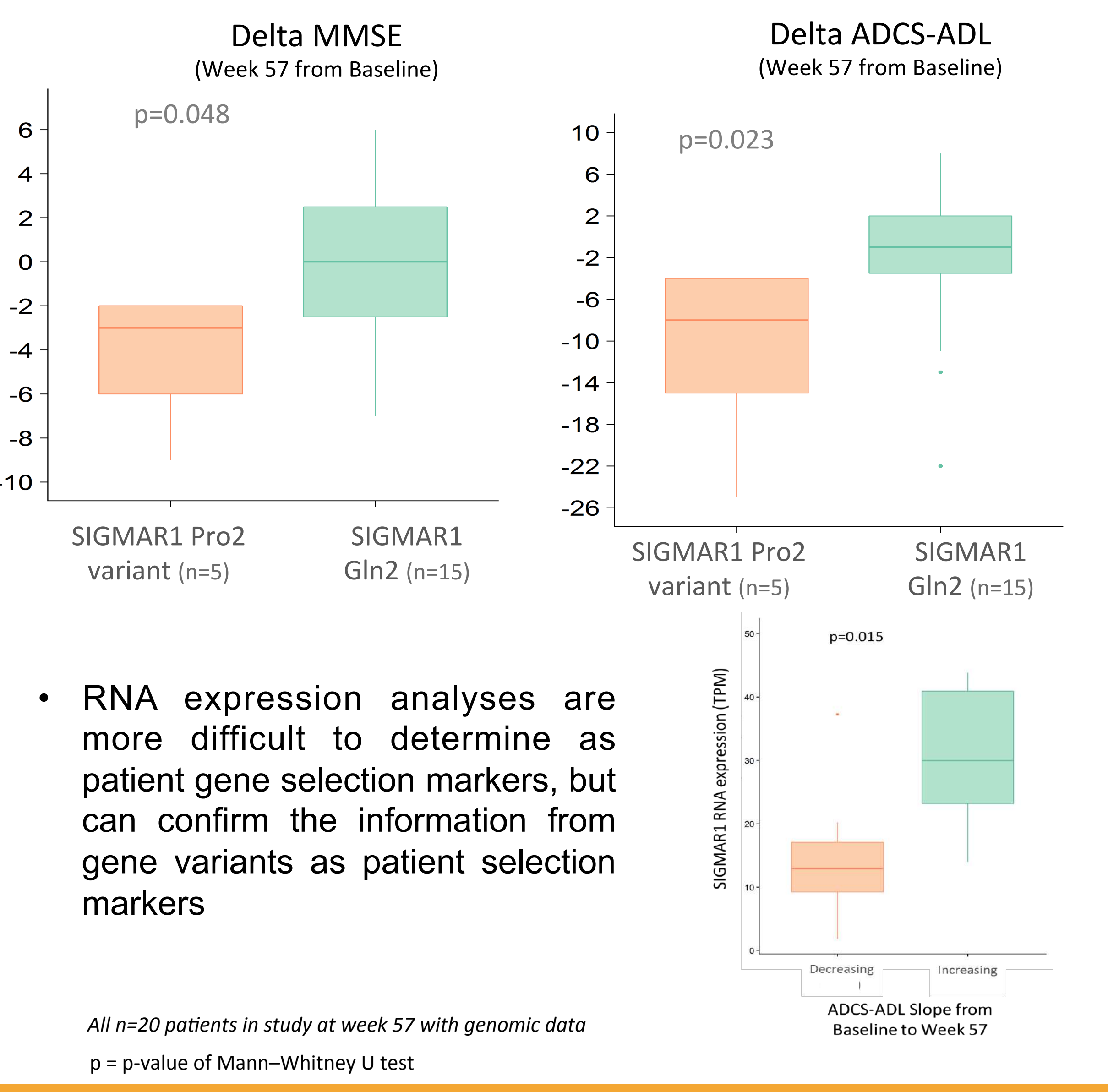
Material and Methods: Focused Data Analysis



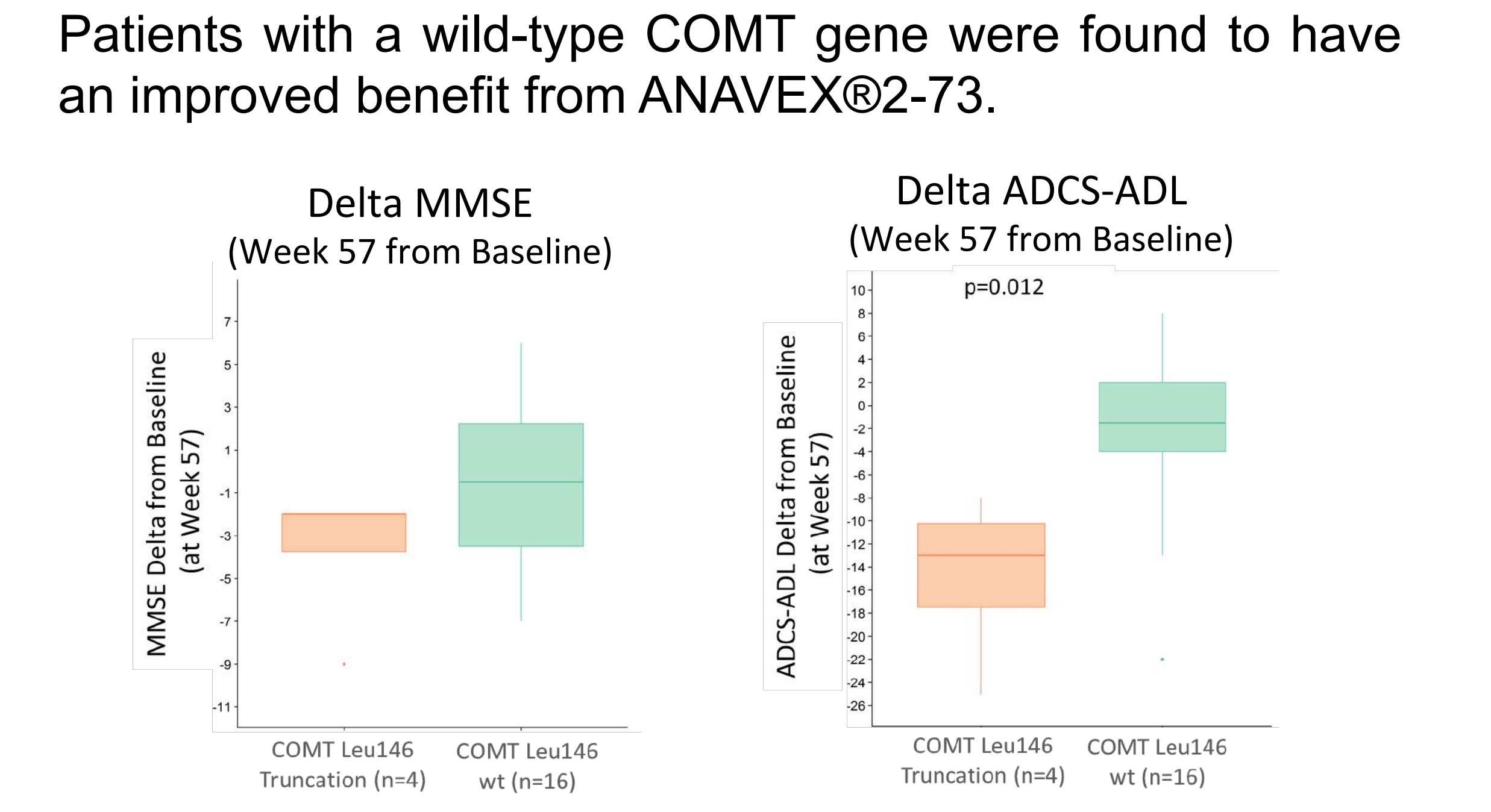
Results: Significant Relation between ANAVEX®2-73 Concentration and Response (ADCS-ADL)



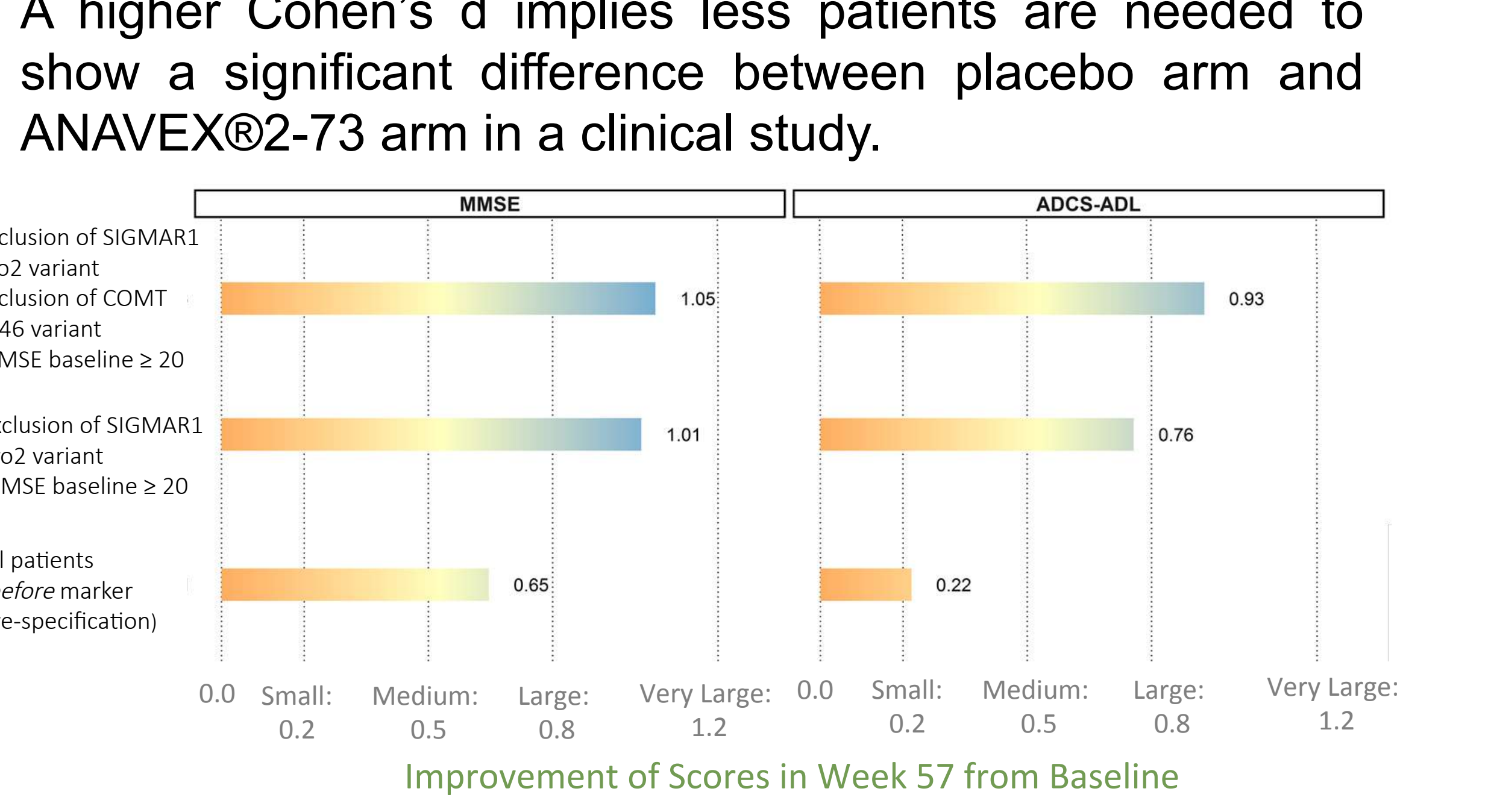
Results: SIGMAR1 Gene Variant Associated with Differentiated Response



Results: COMT Gene Variant Associated with Differentiated Response



Gene Variant Markers Improve Effect Size (Cohen's d) with ANAVEX®2-73



Summary

- Systematic analysis using KEM® identifies actionable parameters enabling a precision medicine approach to include best responders in follow-up Phase 2b/3 study
- Patients with a wild-type SIGMAR1 gene were found to have an improved benefit from ANAVEX®2-73. Patients with a variant of the SIGMAR1 gene (rs1800866) were found to have a limited benefit from ANAVEX®2-73. Same for COMT variant (rs113895332/rs61143203)
- Including patients with milder disease stage (baseline MMSE ≥20) and the exclusion of AD patients carrying SIGMAR1 variants results in a score improvement of +1.7 MMSE and +3.9 ADCS-ADL, respectively at week 57. The additional exclusion of the COMT variant results in a score improvement of +2 MMSE and +4.9 ADCS-ADL, respectively for the same period. Both effects would be clinically meaningful
- The minority of the population (about 20%) has the variant SIGMAR1 gene, hence the majority of patients (about 80%) is expected to benefit from ANAVEX®2-73
- Gut microbiota has been collected and will be incorporated in future analysis
- The data provides support to further clinical development of ANAVEX®2-73 and further clinical studies in other indications are planned or underway
- Anavex is pioneering the use of precision medicine in CNS disorders, including Alzheimer's disease