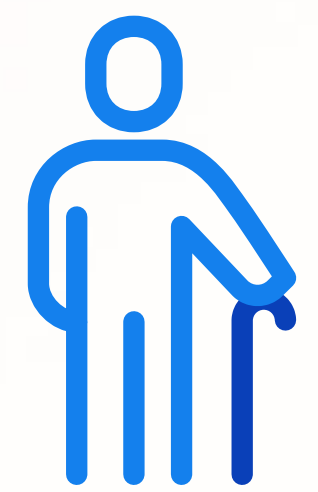
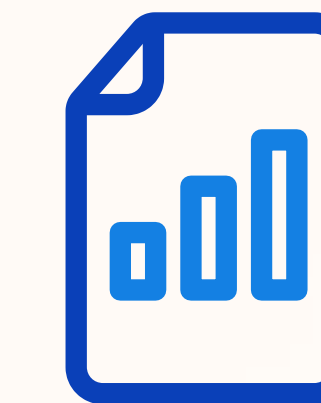
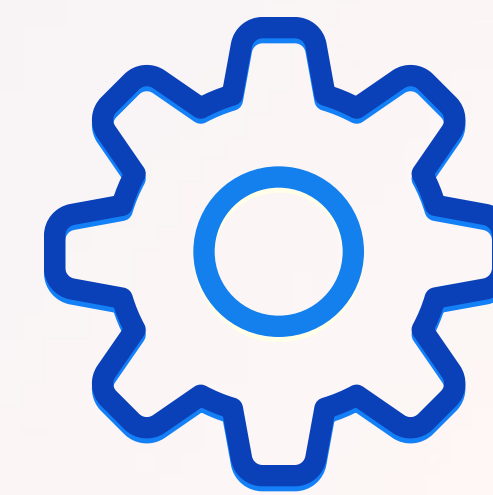
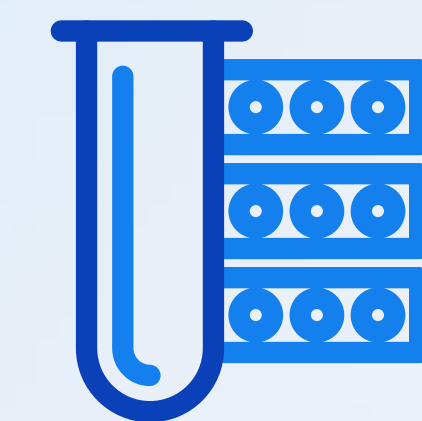
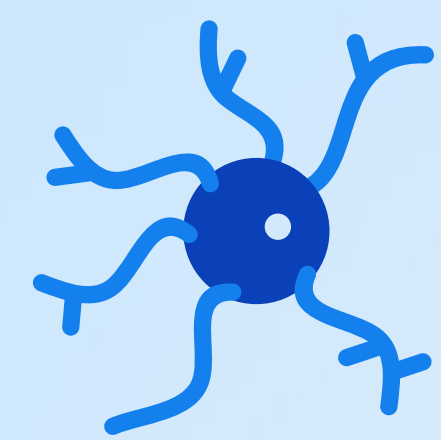


NeuroToolKit (NTK)

The bridge between the biomarker and the patient



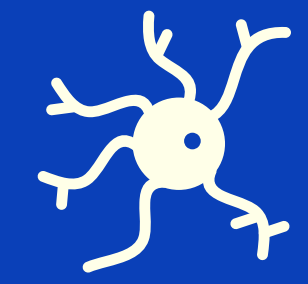
The search for
reliable biomarkers

Assay advancement

The power of NTK

Accelerating
evidence generation

The promise to patients



The search for reliable biomarkers

Today, there is a rising sense of urgency to advance science for the fastest growing societal burden—neurodegenerative disorders.

As new therapies for neurodegenerative disorders are introduced, it is increasingly important to have diagnostic solutions along the patient care continuum.

Once the need for a diagnostic solution is identified, the proper immunoassay needs to be developed. The first step in immunoassay development is the identification and thorough assessment of antibodies, which can be either generated in-house at Roche or supplied by external partners. Antibodies are then characterised and tested for suitability on the Elecsys® platform with a special focus on kinetic properties and specificity for the biomarker of interest.

Once suitable antibodies are identified, the biomarker can proceed to the robust prototype assay (RPA) development phase.

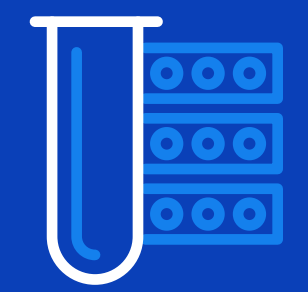


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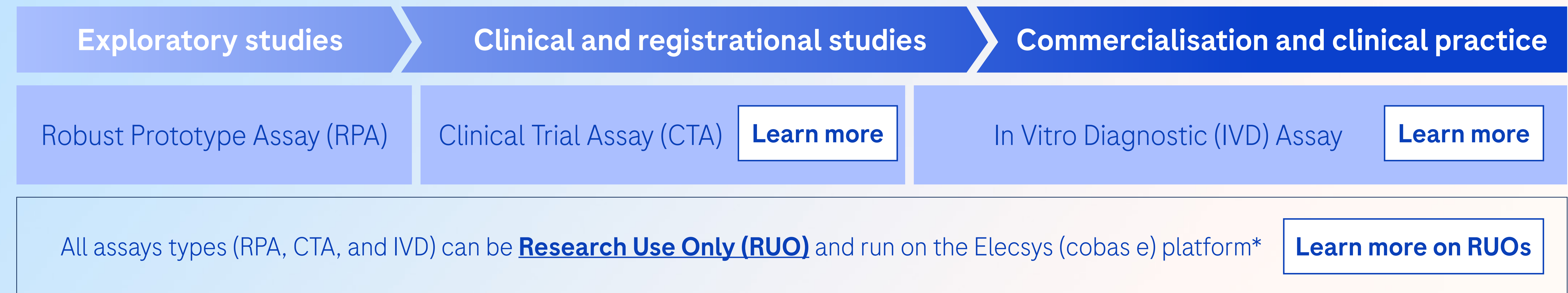
Assay advancement

During Robust Prototype Assay (RPA) development phase, it is ensured that assays are designed with a special focus on performance, quality, and robustness. This includes a rigorous assay validation, for example, including precision, interference, stability and different sample type testing. As a result, only assays that meet the high quality standards are implemented in the NTK.

Not only biotech and pharmaceutical research development teams, but also academic partners rely on RPAs when conducting early clinical or research studies to explore the potential value of specific biomarkers.

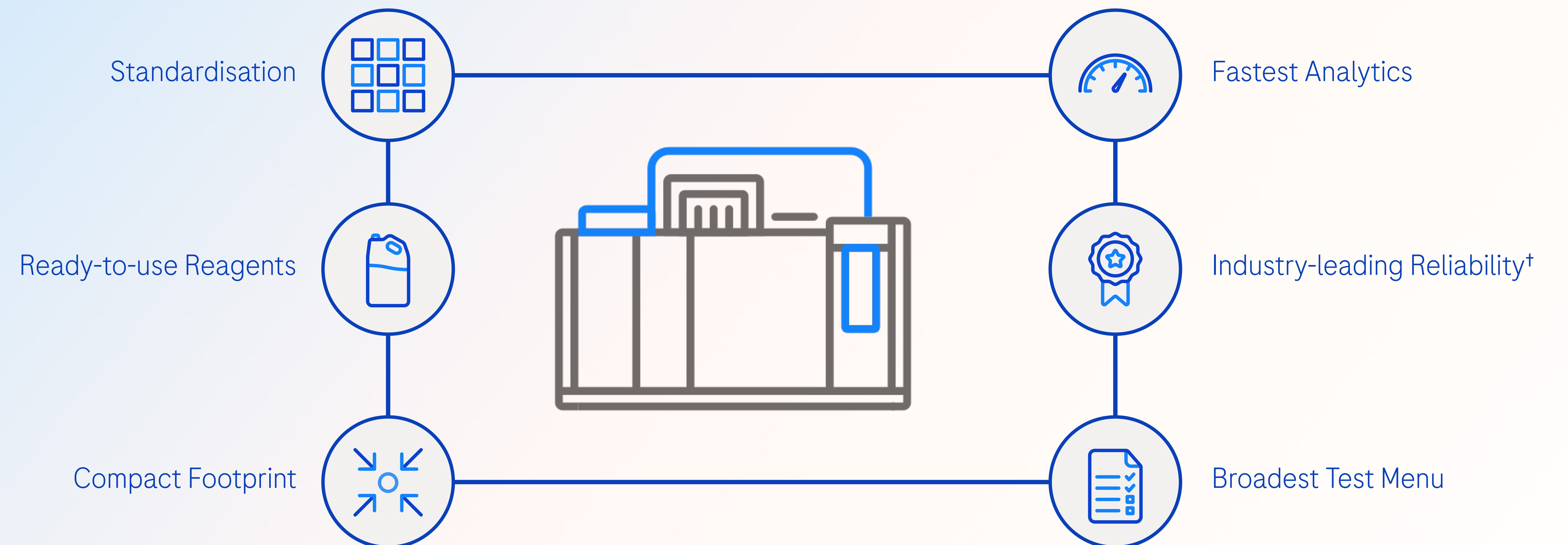
RPAs are implemented to analyse samples from early clinical and research studies collected by industry and academic partners.

Assay evolution beyond RPAs



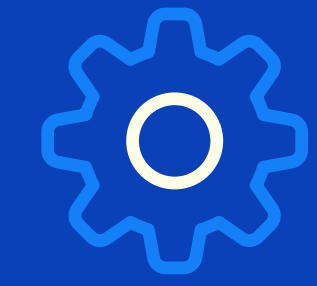
Reliable results powered by the Elecsys® (cobas® e) platform

The simplicity of a fully-automated IVD analyser, built on the same core values, delivers standardisation for quality and reliability, and also streamlines workflow.



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*cobas® e modules include e 411, e 402, e 601/602, and e 801
[†]Competitive mean time between failure rate published by CAP Today: Chemistry and Immunoassay Analyzers for Mid- and High-Volume Laboratories, July 2022. Internal Roche MTBF data on file.



The power of NTK

The NeuroToolKit (NTK) represents a transformative change, providing an innovative bridge between biomarker research today and the clinical utility of tomorrow.

The NTK offers a step forward in biomarker statistical analysis using analytical apps for a collaborative approach through results-sharing that creates an ideal ecosystem for scientific discussion—resulting in groundbreaking connections for a greater understanding of the biomarker potential clinical utility. NTK is a cutting-edge proof statement that working together gets us further.

The NeuroToolKit facilitates and accelerates the journey from biomarker research to the biomarker clinical application, with the vision of bringing High Medical Value assays to the clinical community when and where they are needed most.

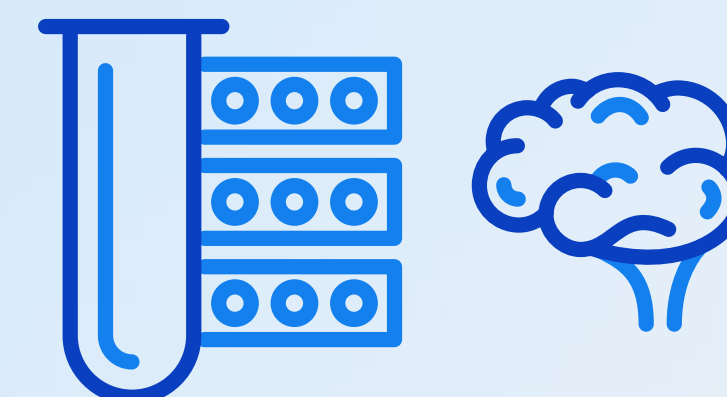
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The power of partnership

[Learn more](#)

Through a combined effort between academia, industry, and philanthropy, NTK sets the foundation upon which new diagnostic solutions will be built. As part of NTK, we are proud of this groundbreaking path to the future, and even more proud of the partnerships that have made it possible.

The power of results-sharing



NTK Portfolio

The NTK assays are run on the fully-automated Elecsys® platform, assuring the highest performance and quality in four validated labs.

Regularly the portfolio is updated with the most promising biomarkers as agreed upon by the key opinion leaders. These biomarkers are thought to be clinically useful in neurological disorders.

[Learn more](#)

Workbench

Digital research environment (DRE) is a collaborative, cloud-based platform with data analytics functionalities (apps). It provides access to data, tools and resources under one ecosystem.

[Learn more](#)

The Apps

From the Workbench, access to 3 interlinked Apps allows users to curate, analyse and compare results from different cohorts around the world.

[Learn more](#)



Accelerating evidence generation

The published NTK data is a step closer to understanding the role of neurodegenerative biomarkers and their clinical utility. This helps ensure that the right product is mapped to the right indication and is brought to market, further enabling novel physician decision-making along the continuum of a patient's journey.

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Johnston et al. *Alzheimer's Research & Therapy* (2023) 15:25

Open Access

Identifying clinically useful biomarkers in neurodegenerative disease through a collaborative approach: the NeuroToolKit

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Abstract Alzheimer's disease (AD) is a complex and heterogeneous disease, which requires reliable biomarkers for diagnosis and monitoring disease activity. Preanalytical protocol and technical variability associated with biomarker immunosassays makes comparability of biomarker data across multiple cohorts difficult. This study aimed to compare cerebrospinal fluid (CSF) biomarker results across independent cohorts, including participants spanning the AD continuum.

Methods Measured on the NeuroToolKit (NTK) prototype panel of immunosassays, 12 CSF biomarkers were evaluated from three cohorts (ALFA+ Wisconsin and Abby/Blaze). A correction factor was applied to biomarkers found to be affected by preanalytical procedures (amyloid-β₁₋₄₂, amyloid-β₁₋₄₀ and alpha-synuclein), and results between cohorts for each disease stage were compared. The relationship between CSF biomarker concentration and cognitive scores was evaluated.

Results Biomarker distributions were comparable across cohorts following correction. Correlations of biomarker values were consistent across cohorts, regardless of disease stage. Disease stage differentiation was highest for neurofilament light (NFL), phosphorylated tau, and total tau, regardless of the cohort. Correlation between biomarker concentration and cognitive scores was comparable across cohorts, and strongest for NFL, chitinase-3-like protein-1 (YKL40), and glial fibrillary acidic protein.

Discussion The precision of the NTK enables merging of biomarker datasets after correction for preanalytical factors. Assessment of multiple cohorts is crucial to increase power in future studies into AD pathogenesis.

Keywords Alzheimer's disease, Amyloid-β, Cerebrospinal fluid biomarkers, Glial activation, Inflammation, Neurodegeneration

Introduction High-quality, reliable, well-validated biomarkers, reflective of biological neurodegenerative diseases, such as Alzheimer's disease (AD) [1]. In AD, using biomarkers allow for increasing diagnostic accuracy, guiding patient stratification, monitoring the effects of treatment on underlying pathologies, and providing surrogate measures of disease activity to monitor and evaluate outcomes [2]. Comparability of cerebrospinal fluid (CSF) biomarkers between studies has been limited. This issue due to methodology differences across cohorts. This issue has been somewhat circumvented by fully automated assays used in research and standardized, partially manual procedures [3, 4]. Importantly, some CSF biomarker assays (amyloid-β₁₋₄₂ [Aβ₄₂], phosphorylated tau [pTau], and total tau [TTau]) are well validated for future wide-spread use in the clinical setting [5–7]. However, the challenge remains to have standardized clinical endpoints, statistical approaches, and immunosassay platforms that would enable unified biomarker multi-center studies.

The NeuroToolKit (NTK; Roche Diagnostics International Ltd) is a panel of 12 automated CSF immunosassays for biomarkers linked to neurodegeneration [8, 9]. This panel is designed to accelerate biomarker development in AD and other neurological disorders by generating robust, comparable, high-quality biomarker data across multiple research and clinical cohorts.

Using CSF biomarker data collected from participating sites, we aimed to address three correction factor questions: (i) Comparative: Can a correction factor for biomarkers affected by different preanalytical procedures be applied that allows for comparison across multiple cohorts? (ii) Diagnostic: How much do the biomarker concentrations vary between cognitively unimpaired (CU) individuals and patients with mild cognitive impairment (MCI) or AD-dementia? (iii) Clinical: How well do biomarker concentrations correlate with clinical measures of cognition?

Methods This analysis utilizes data from three cohorts participating in the NTK project, which were selected to provide data spanning the entire AD continuum. The ALFA+ study (NCT02485730) aimed to characterize preclinical AD in CU individuals, most with a family history of AD (n=298) [8]. The Wisconsin cohort (n=651) comprised

several longitudinal studies that utilized the same pre-analytical protocol and included CU individuals, participants with MCI, or AD-dementia, enriched for parental history of AD [10]. The Abby/Blaze cohort (n=164) comprised participants in the ABBY (NCT01343966) and the BLAZE (NCT01397578) studies for patients with mild to moderate AD-dementia [11, 12]. Full eligibility criteria for each of the respective cohorts are described in the **Supplementary Methods**. All cohorts had comorbidities that were excluded. Some medications that affected cognition, such as sleep aids, were permitted in the Wisconsin cohort.

For the purposes of this analysis, the correction reference group for each cohort was defined as participants who were CU, APOE-ε4 allele non-carriers, and aged <65 years. As the Abby/Blaze cohort only included participants with AD-dementia, a correction reference group could not be defined.

Biomarkers CSF biomarkers included chitinase-3-like protein-1 (YKL40), soluble triggering receptor expressed on myeloid cells 2 (sTREM2), glial fibrillary acidic protein (GFAP), interleukin (IL)-6, neurofilament light (NFL), neurogranin, S100, alpha-synuclein (α-Syn), amyloid-β₁₋₄₀ (Aβ₄₀), Aβ₄₂, pTau, and tTau. CSF biomarker samples obtained at baseline/enrollment were included. All biomarkers were measured using the panel of immunosassays, which currently includes the commercially available Elecsys β-amyloid (1–42) CSF, Elecsys total Tau CSF, and Elecsys p-tau (181P) CSF immunosassays, and robust prototype assays for the remaining biomarkers. Biomarkers Aβ₄₂, Aβ₄₀, pTau, tTau, s100, and IL-6 were measured using the cobas e601 analyzer, and the remaining biomarkers were measured using the cobas e411 analyzer (both Roche Diagnostics International Ltd).

Preanalytical factor correction The preanalytical procedures employed by each cohort are detailed in the **Supplementary Materials**. Sample collection within the Wisconsin protocol dissemination of standardized correction factors are calculated [9]; therefore, the correction reference groups (participants of the respective correction reference groups and aged <65 years) of the Wisconsin and ALFA+ cohorts assuming who were CU, APOE-ε4 allele non-carriers, and aged <65 years) of the ALFA+ cohort being the "standard cohort". The correction factor was calculated using the formula:

$$\text{Correction factor} = \frac{\text{median(ALFA+ cohort)}}{\text{median(Wisconsin cohort)}}$$



The promise to patients

The final purpose of the biomarker journey is to bring solutions to patients. Through the NeuroToolKit collaboration, the field joins forces to understand the utility of biomarkers in neurological disorders. This is a big step towards accelerating future IVD solutions and bringing reliable products to clinical practice. This is a promise to further support the patient journey.

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Partnering

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Diagnostic

Roche Diagnostics provides access to the NTK portfolio for measurement of reliable and high-quality biomarker data.

Philanthropic

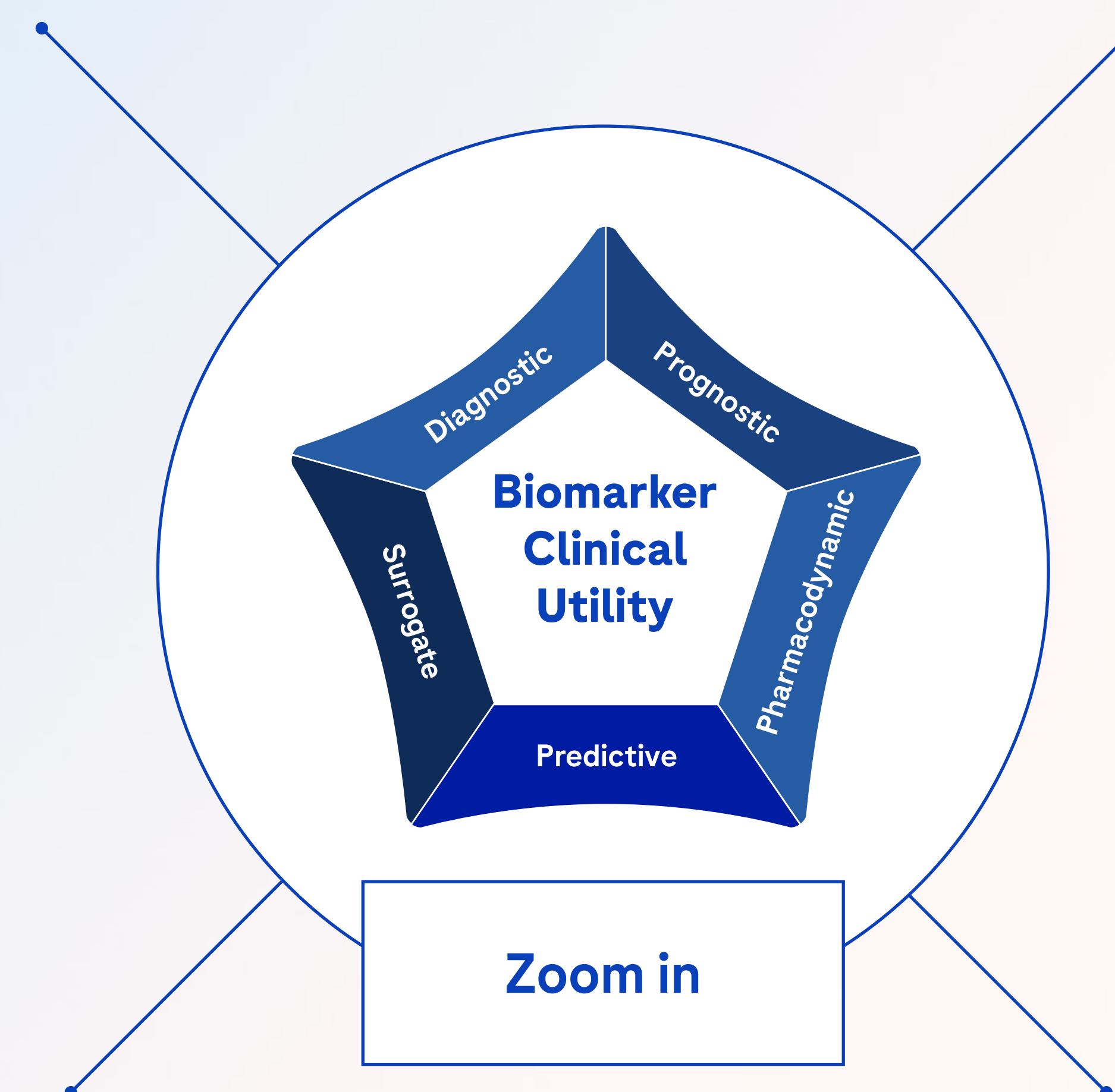
Supports patients and science through ongoing commitment and advancement of digital innovation. An innovative and secured IT infrastructure enables data- and results-sharing, while preserving data ownership.

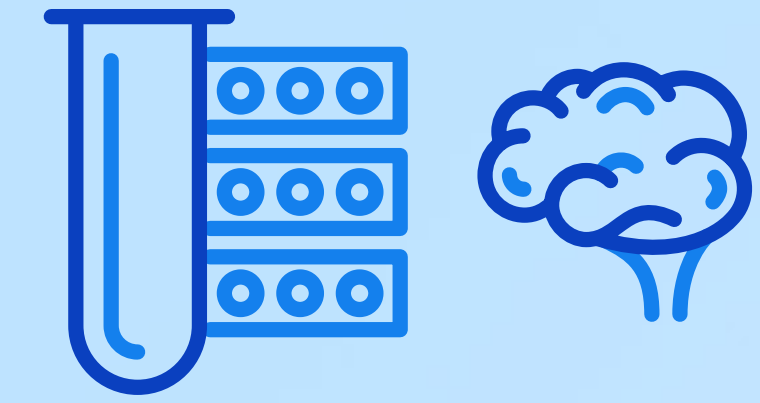
Academic

Academia collects patient cohorts and conducts research with the NTK biomarker portfolio to better understand the utility of the assays in the various patient populations. Using the NTK app, statistical analysis modules are developed and used to assess the clinical utilities around each biomarker.

Pharmaceutical

Pharma partners investigate biomarker utility in clinical trials.





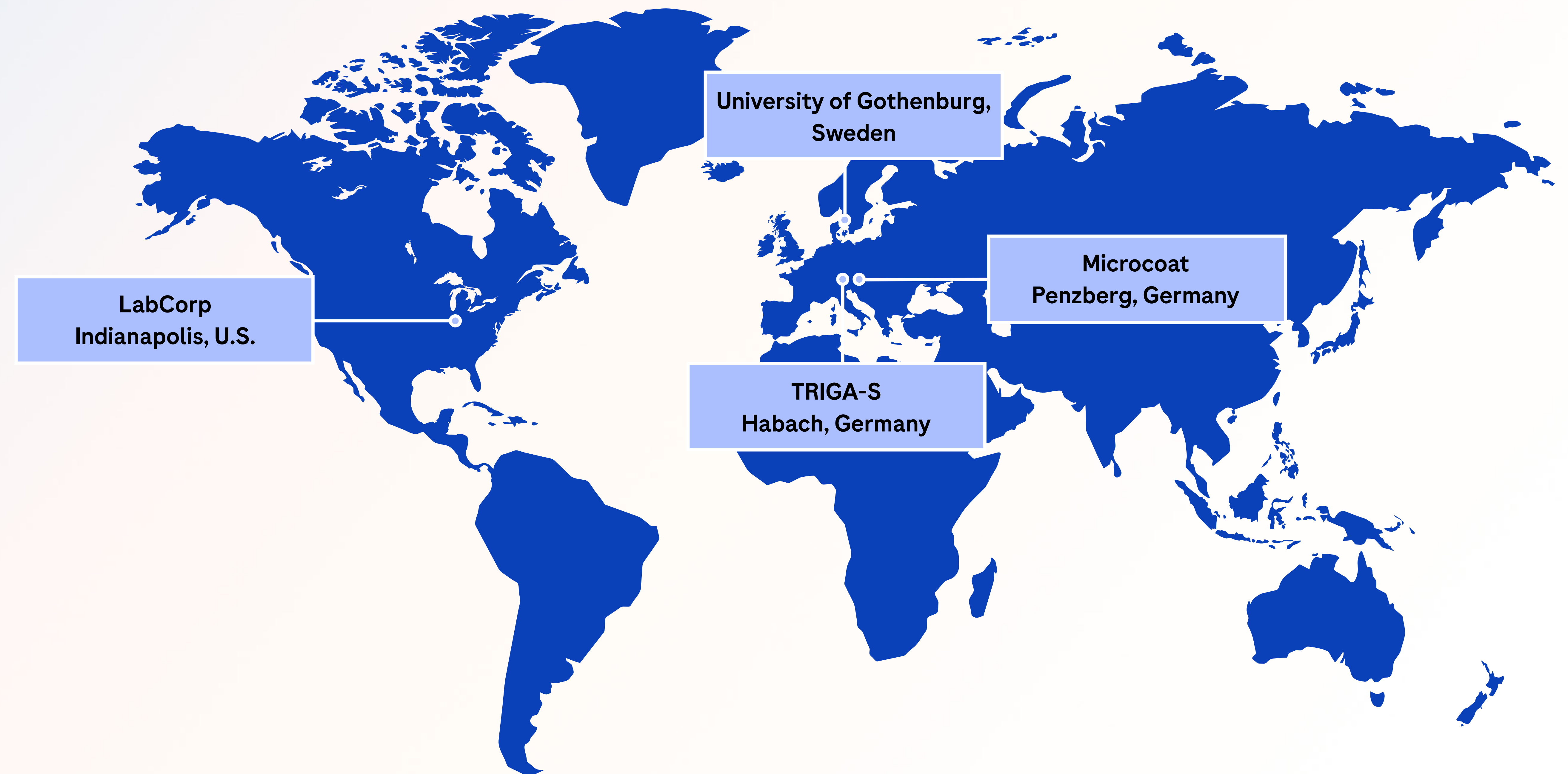
NTK Portfolio

NTK currently offers an intended-use agnostic portfolio of 14 CSF and 16 serum/plasma assays, with more in development.



	CSF Assays	Plasma/Serum Assays
Assay Maturity		
RPA	AB40 NfL STREM2 YKL40 GFAP Alphasynuclein Neurogranin IL-6 S100b SNAP25 NPTX2	AB42 AB40 tTau STREM2 YKL-40 GFAP IGFBP7 NSE pTau181 APOE4 SNAP25 NPTX2
CTA		NfL
IVD	AB42 tTau pTau181	IL-6 S100b GDF-15

The NTK Portfolio is measured in four measurement sites.

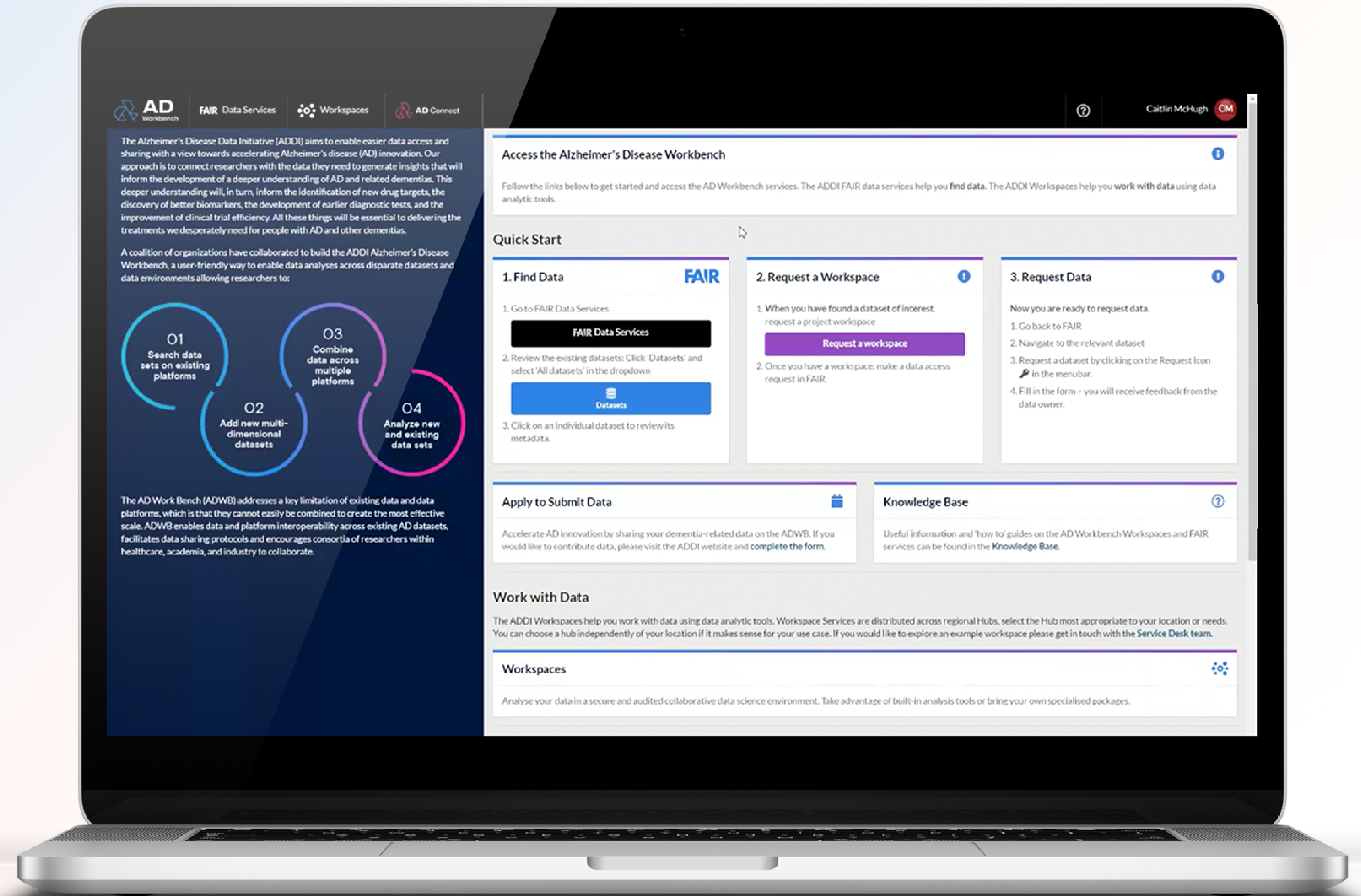




Workbench

The AD Workbench is a collaborative, cloud-based platform that offers access to data analytics and a suite of apps that fosters cross-domain research collaboration with:

- Secure workspaces
- Statistical analysis tools
- Trusted data governance
- FAIR data services

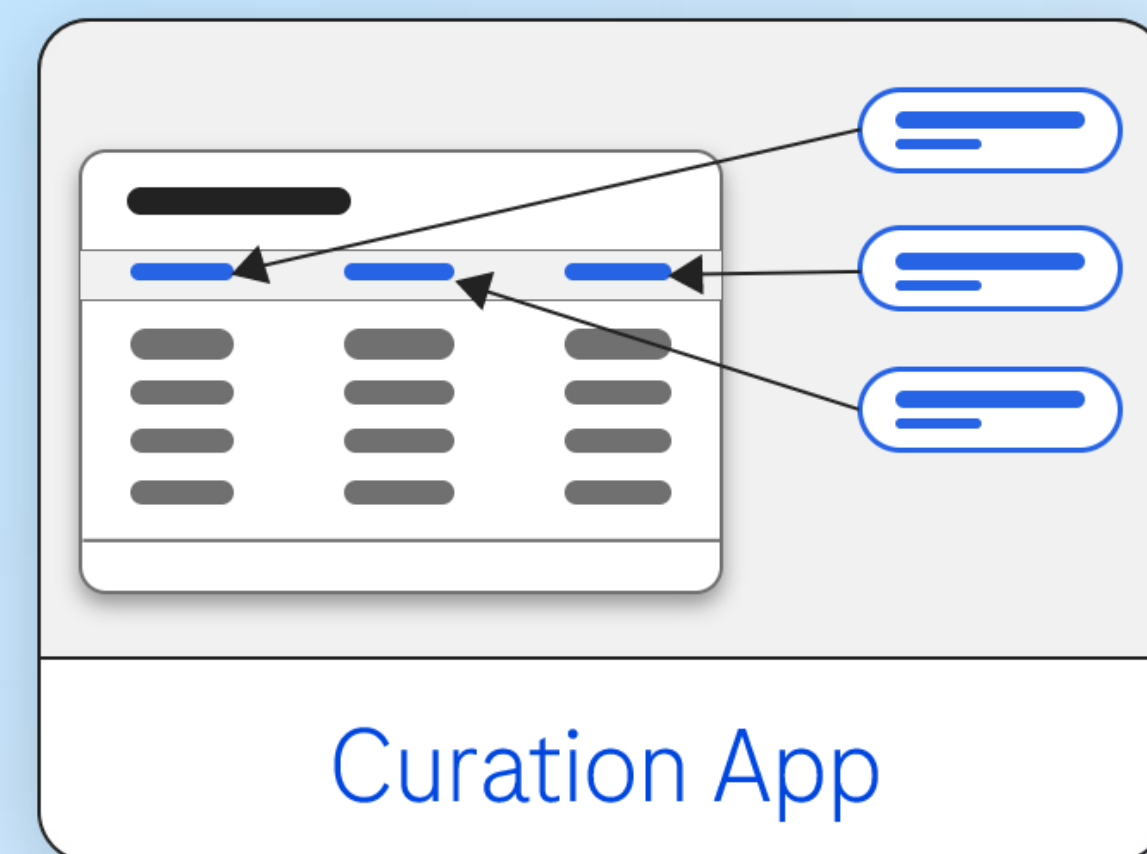


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Apps

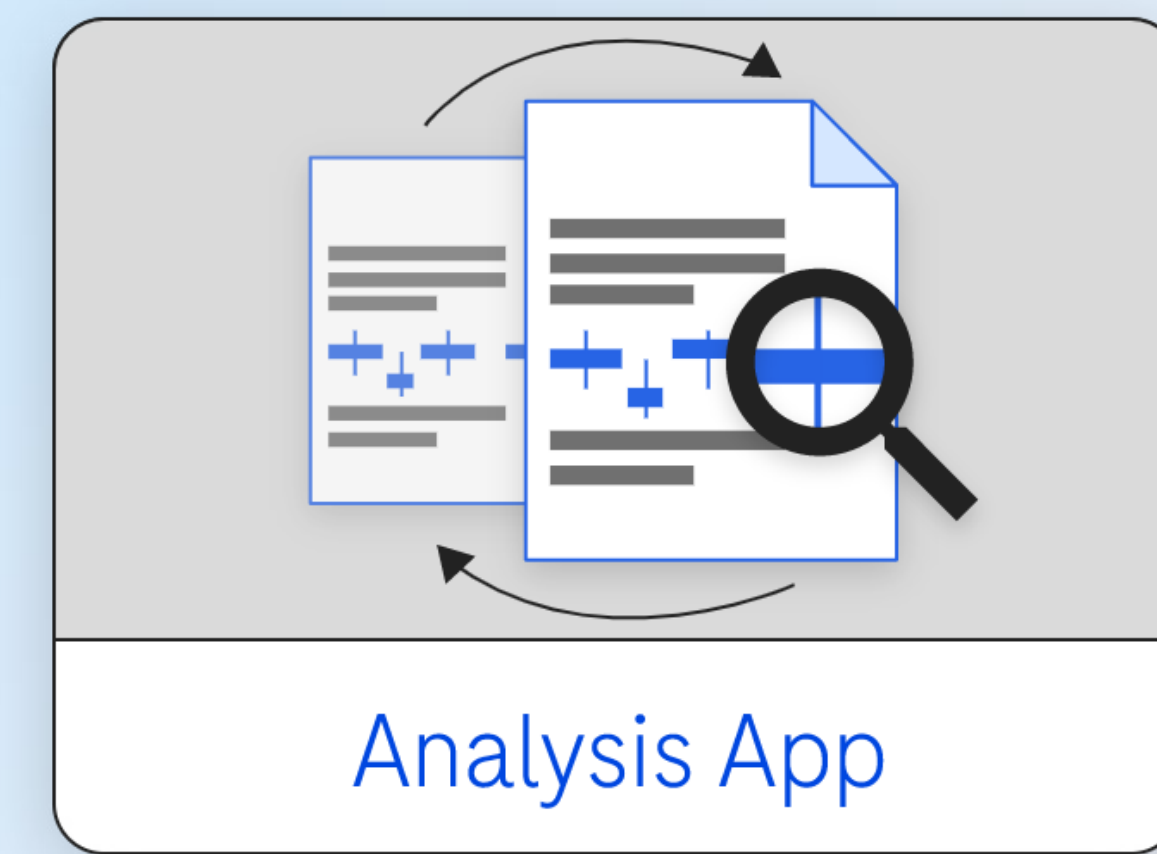
From the Workbench, access to the user-friendly Apps allows curation, analysis and comparison of data across cohorts, clarifying the clinical utility of biomarkers for a better understanding of which biomarkers deserve further IVD development.



Curation App

Curation

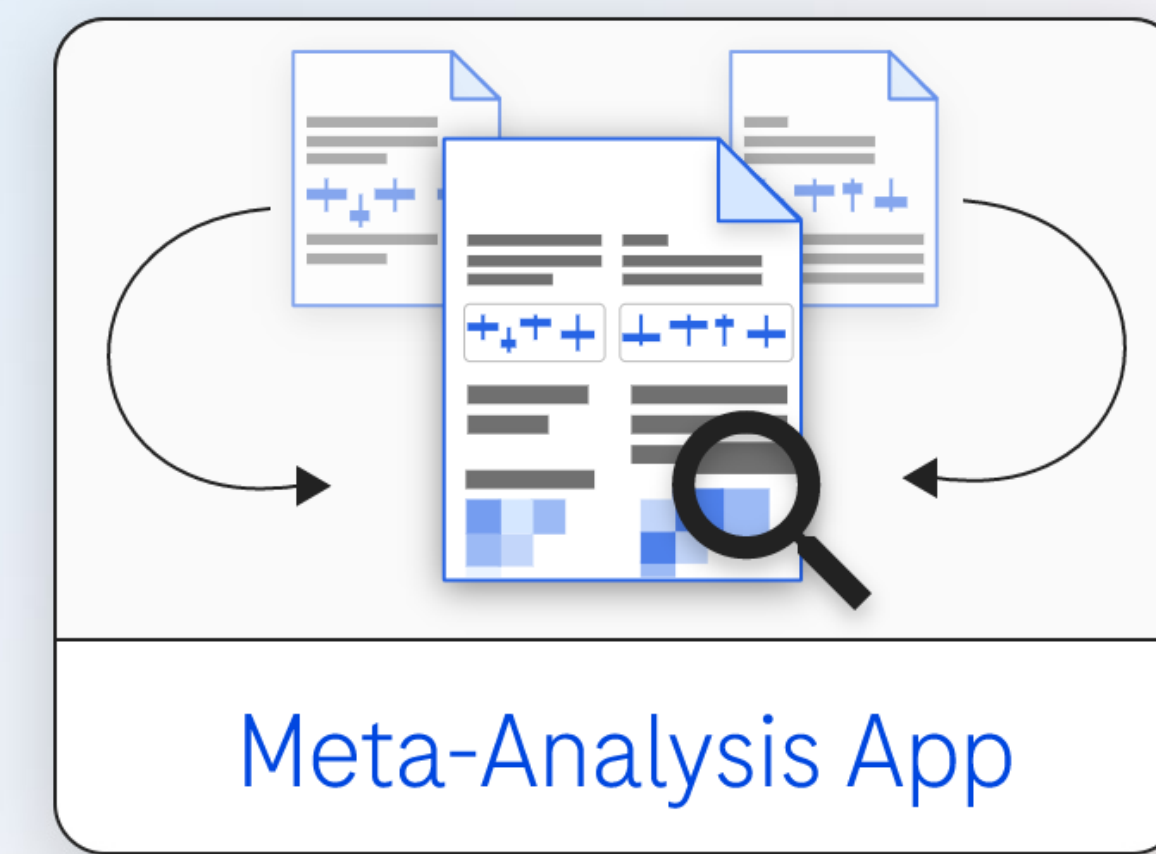
Translate variables within a cohort to a common data dictionary so that datasets are harmonised and comparable.



Analysis App

Analysis

Select from a suite of statistic analysis to gain insight into data.

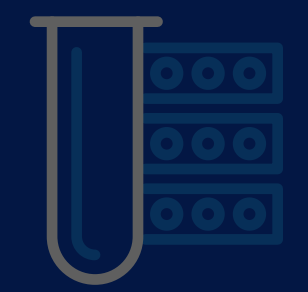


Meta-Analysis App

Meta-Analysis

Enables results comparison across cohorts.





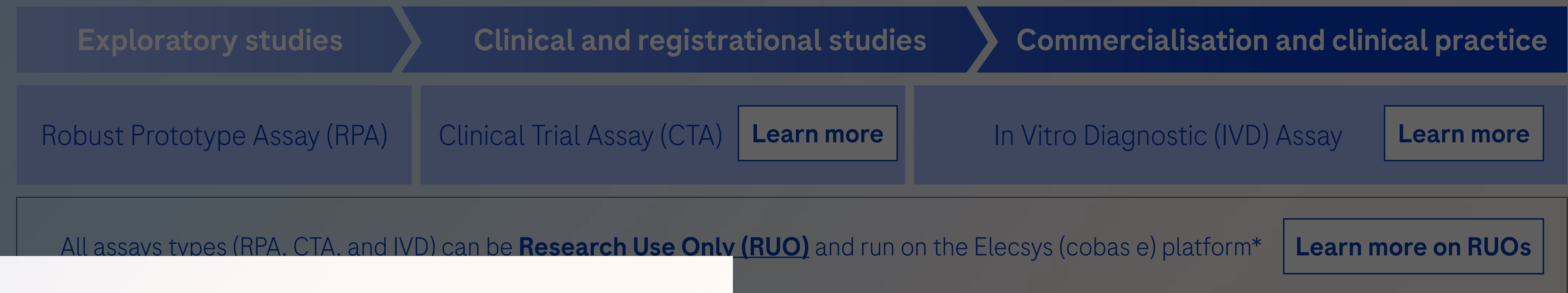
Assay advancement

During Robust Prototype Assay (RPA) development phase, it is ensured that assays are designed with a special focus on performance, quality, and robustness. This includes a rigorous assay validation, for example, including precision, interference, stability and different sample type testing. As a result, only assays that meet the high quality standards are implemented in the NTK.

Not only biotech and pharmaceutical research development teams, but also academic partners rely on RPAs when conducting early clinical or research studies to explore the potential value of specific biomarkers.

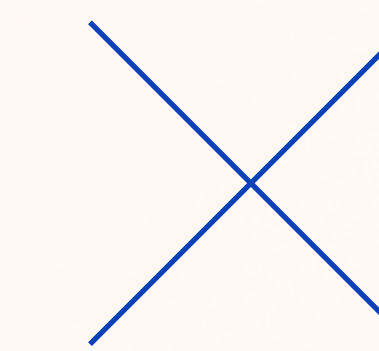
RPAs are implemented to analyse samples from early clinical and research studies collected by industry and academic partners.

Assay evolution beyond RPAs



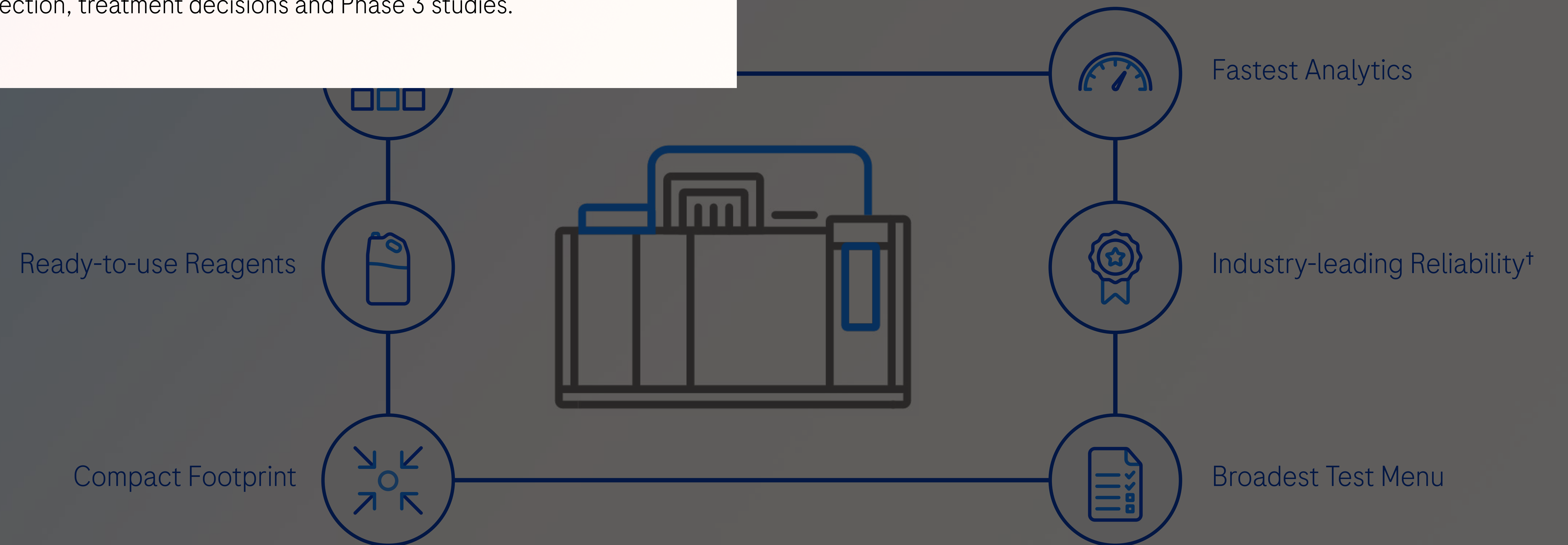
What is a CTA?

While RPAs cannot be used for patient decisions, they can be further developed and validated as clinical trial assays (CTAs) and potentially also as in vitro diagnostics (IVDs) to support patient selection, treatment decisions and Phase 3 studies.



Elecsys® (cobas® e) platform

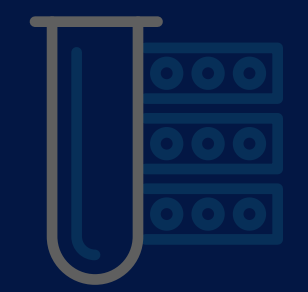
Same core values, delivers standardisation



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*cobas® e modules include e 411, e 402, e 601/602, and e 801

†Competitive mean time between failure rate published by CAP Today: Chemistry and Immunoassay Analyzers for Mid- and High-Volume Laboratories, July 2022. Internal Roche MTBF data on file.



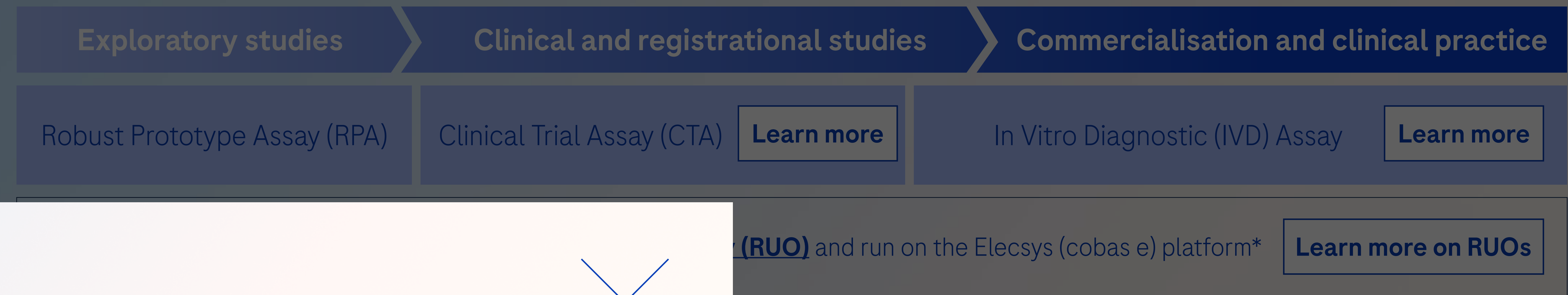
Assay advancement

During Robust Prototype Assay (RPA) development phase, it is ensured that assays are designed with a special focus on performance, quality, and robustness. This includes a rigorous assay validation, for example, including precision, interference, stability and different sample type testing. As a result, only assays that meet the high quality standards are implemented in the NTK.

Not only biotech and pharmaceutical research development teams, but also academic partners rely on RPAs when conducting early clinical or research studies to explore the potential value of specific biomarkers.

RPAs are implemented to analyse samples from early clinical and research studies collected by industry and academic partners.

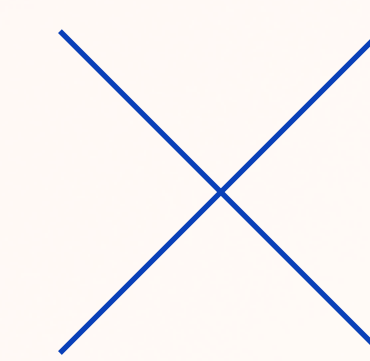
Assay evolution beyond RPAs



What is an IVD?

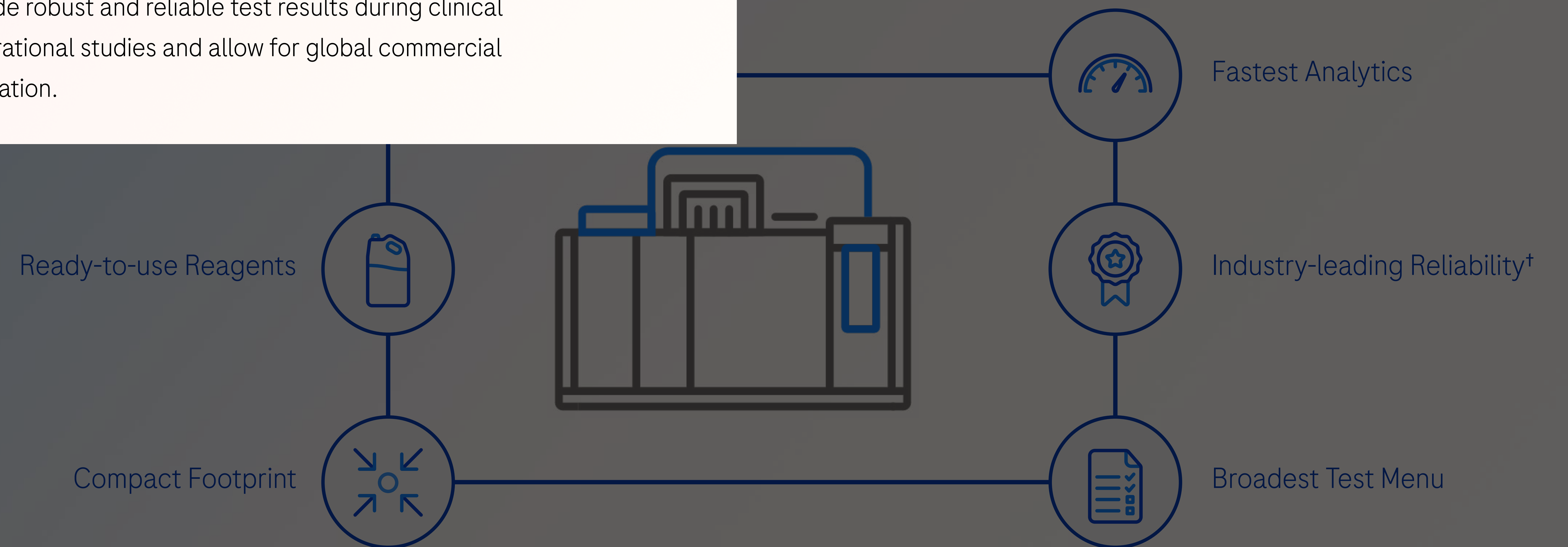
In vitro diagnostic (IVD) assays are commercially available and are intended to be used in clinical practice with a specific intended use. IVDs have undergone extensive regulatory review to obtain approval by regulatory bodies.

IVDs provide robust and reliable test results during clinical and registrational studies and allow for global commercial implementation.



Elecsys® (cobas® e) platform

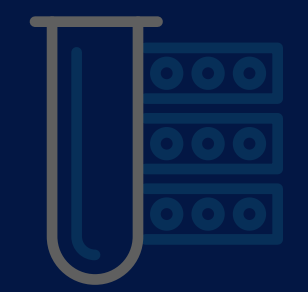
Same core values, delivers standardisation



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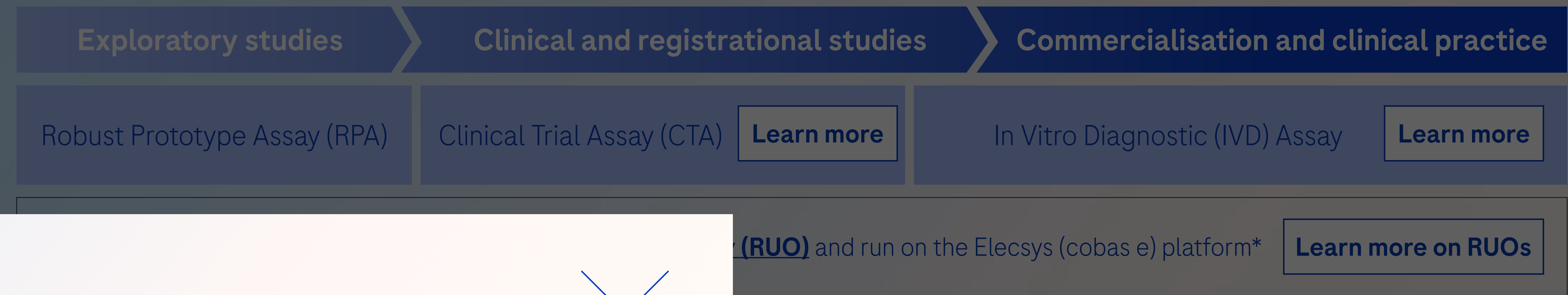
Assay advancement

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Not only biotech and pharmaceutical research development teams, but also academic partners rely on RPAs when conducting early clinical or research studies to explore the potential value of specific biomarkers.

RPAs are implemented to analyse samples from early clinical and research studies collected by industry and academic partners.

Assay evolution beyond RPAs



What is an RUO?

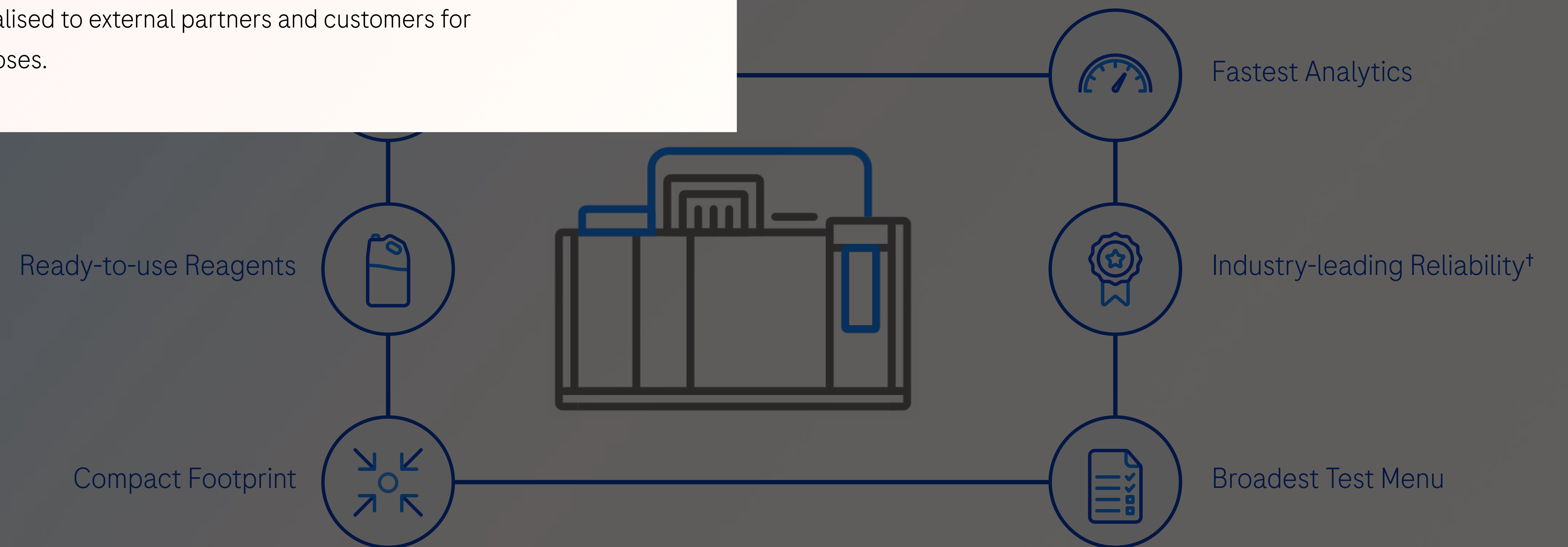
Research use only (RUO) assays are in the laboratory research phase of development and cannot be used for clinical decision-making or diagnosis.

RPAs, CTAs and IVDs can be labeled as RUO assays and commercialised to external partners and customers for their purposes.

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Elecsys® (cobas® e) platform

Same core values, delivers standardisation



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Partnership

Diagnostic

Roche Diagnostics provides precise measurement of reliable biomarkers

Academic

Academia collects patient data for the NTK biomarker portfolio, performs the assays in the various assays, and uses statistical analysis models to determine clinical utilities around

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