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Advancing Automated Non-Compartmental Analysis with R Shiny

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ABSTRACT

Non-Compartmental Analysis (NCA) is a cornerstone of pharmacokinetic studies, providing critical insights into drug absorption, distribution, metabolism, and elimination. Despite its importance, current workflows are heavily reliant on proprietary tools and manual processes, limiting efficiency, reproducibility and accessibility, particularly in complex and time-sensitive study designs.

To address these challenges, we developed aNCA, an open-source R package with a user-friendly Shiny application, that fully automates NCA calculations and streamlines reporting. Built on the regulatory-aligned PKNCA package, aNCA enables half-life calculations, and exploratory visualizations. A key feature is its ability to generate regulatory-compliant CDISC datasets (PP and ADPP), as well as clinical submission-ready tables, listings, and graphs, dramatically simplifying one of the most time-intensive aspects of NCA workflows.

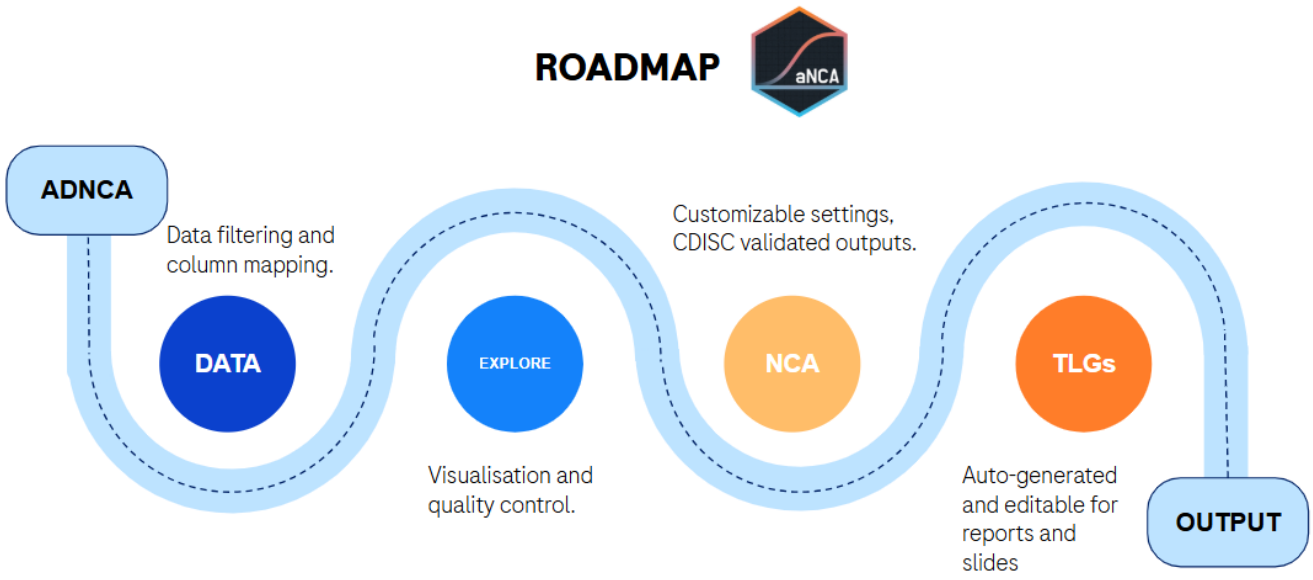

Figure 1. Roadmap of the aNCA application workflow with descriptions of each tab.

INTRODUCTION

Pharmacokinetic studies are central to drug development, quantifying how drugs behave within the body by analyzing absorption, distribution, metabolism, and elimination. NCA, a key methodology for these studies, provides robust estimates of pharmacokinetic parameters such as area under the concentration-time curve (AUC), maximum concentration (Cmax), clearance (CL), and half-life (T½) (1). Unlike compartmental models, which assume specific physiological compartments, NCA relies on fewer assumptions, making it widely adopted in regulatory submissions and early drug development.

While indispensable, NCA workflows often rely on commercial software that comes with high licensing costs and limited adaptability. These tools offer strong primary pharmacokinetic calculations but fall short on secondary functionalities, such as parameter customization, dose-normalized calculations, and custom interval analyses. Such processes frequently require statistical programmers to intervene manually, leading to inefficiencies and heightened risk of error. Additionally, these manual workflows are slow, which is particularly problematic when handling large, complex datasets or complying with tight timelines.

A more critical limitation lies in preparing CDISC-compliant datasets, particularly PP and ADPP, which are required by regulatory agencies like the FDA and EMA. Current tools do not natively produce these outputs, forcing researchers to manually program dataset transformations—a time-consuming task that introduces further bottlenecks. For complex multi-drug or multi-dose studies, this effort often multiplies, delaying critical submissions.

To address these challenges, we have developed aNCA (2), an open-source R package that automates NCA workflows and extends them to include downstream tasks, such as generating CDISC-compliant outputs. Leveraging the PKNCA package (3), aNCA automates study-specific configurations (e.g., dose administration type, analytes, sampling matrices) and incorporates customizable workflows for multi-drug or multi-dose studies. It eliminates manual efforts, accelerates analysis, and provides regulatory-compliant results in a reproducible framework.

aNCA is a product of collaboration among Roche, Lucid Analytics, Appsilon, and Human Predictions, illustrating the power of cross-disciplinary teamwork. Hosted on GitHub under the Pharmaverse (4) initiative, aNCA is completely transparent and accessible to the global scientific community. By integrating automation, standardization, and reproducibility, aNCA empowers statistical programmers, scientists, and pharmacokinetic experts to meet modern regulatory and scientific expectations efficiently and reliably.

PACKAGE OVERVIEW

The aNCA package provides a Shiny application that facilitates an end-to-end Non-Compartmental Analysis (NCA) workflow, utilizing an ADNCA (or similar) dataset as input. The application is organized into four primary tabs:

- **Data**: This tab is dedicated to data upload and processing. Users can map required columns, allowing for flexible data input. Data can also be filtered and reviewed before analysis.

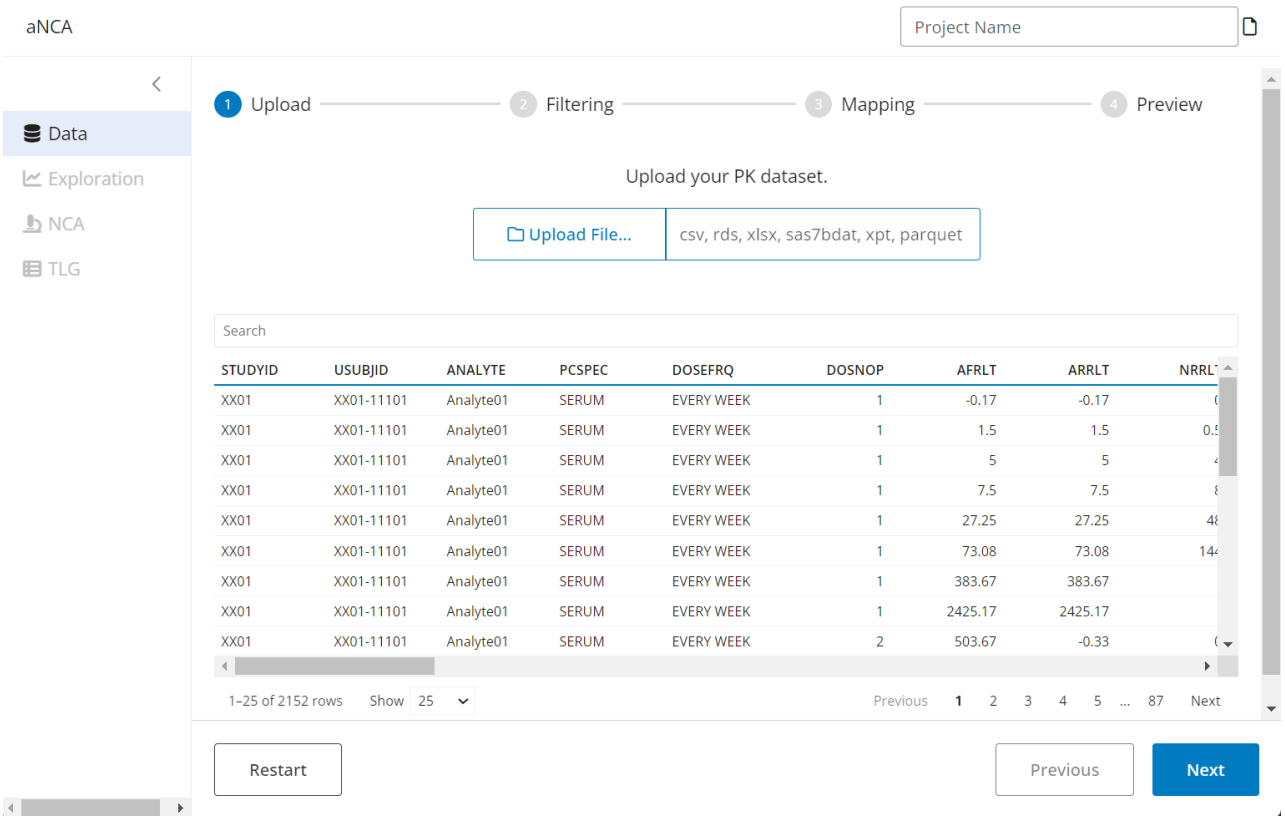

Figure 2: Screenshot of Data tab.

- **Exploration**: This section offers initial data visualization, including concentration-time plots (both mean and individual) and quality control plots, to easily identify errors or inconsistencies in the data.

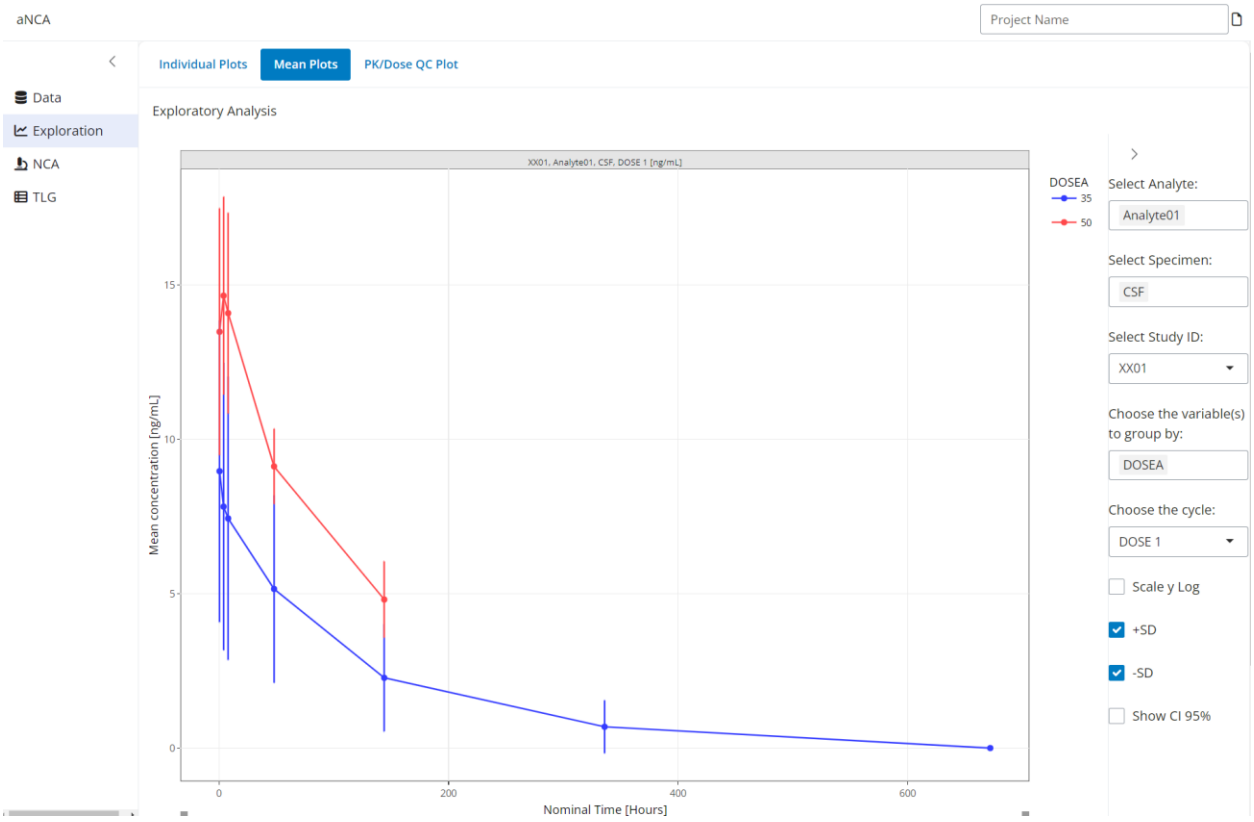

Figure 3: Screenshot of Exploration tab.

- **NCA**: This is the main analysis tab. Here, users can customize the data for analysis, select parameters for calculation, and make any necessary manual adjustments (e.g., half-life customization). Users can then execute the NCA and view results in various formats, including CDISC outputs, summary statistics, and visualization options.

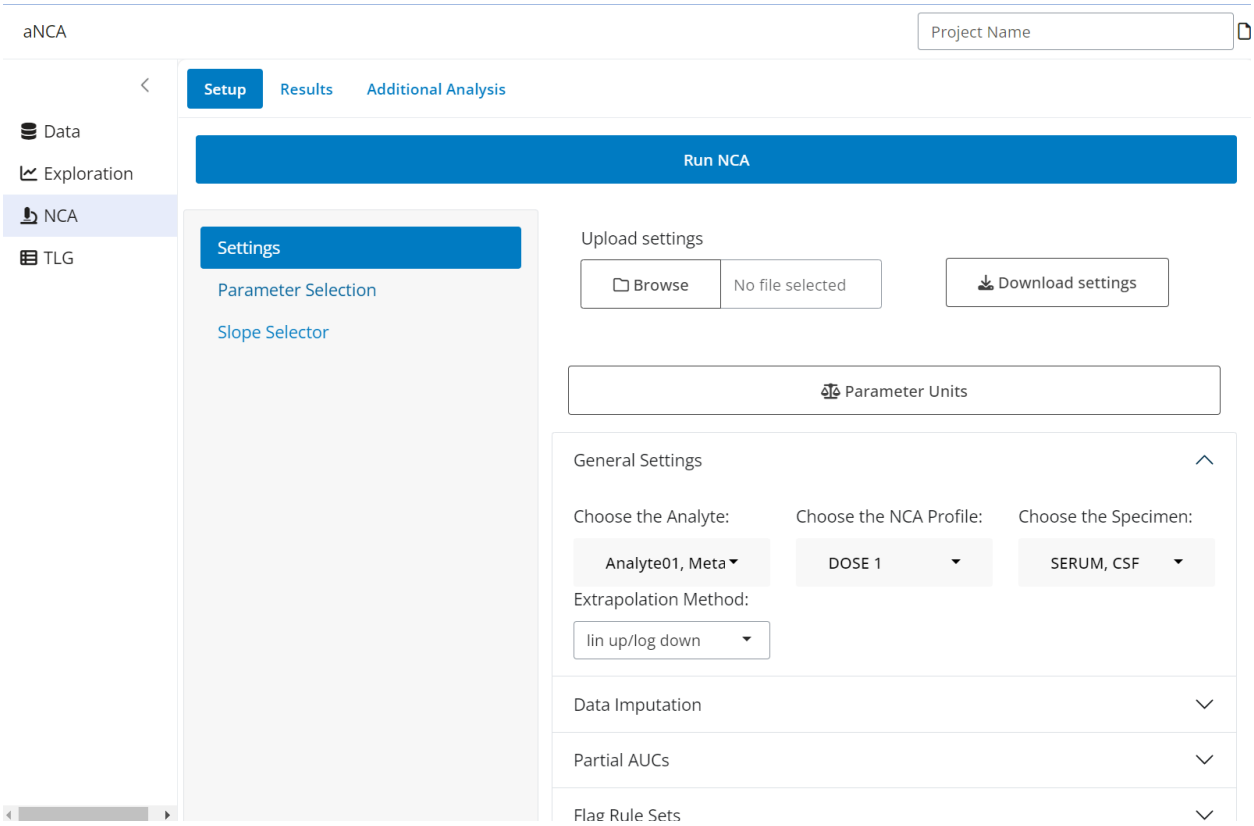

Figure 4: Screenshot of NCA tab.

- **TLGs** (Tables, Listings, and Graphs): This tab is for reporting. Users can select and export desired tables, listings, and graphs for submission to regulatory authorities. This section offers extensive customizable options to tailor plots to user specifications.

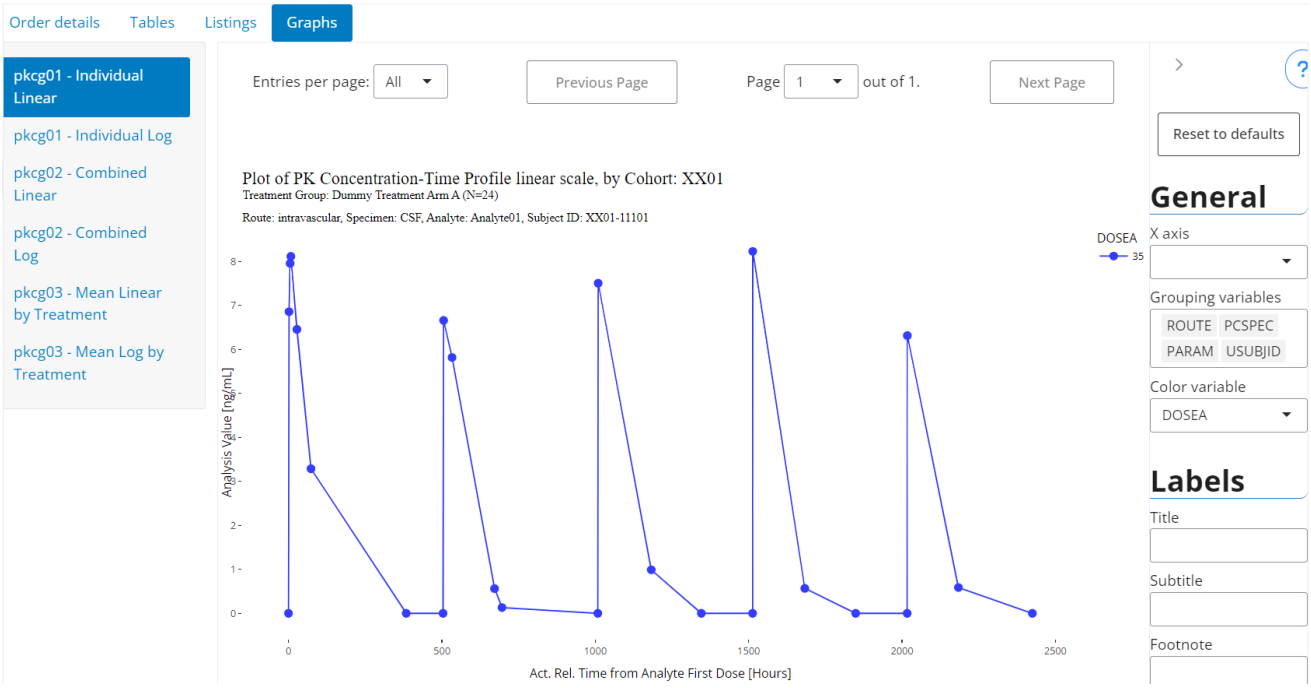

Figure 5: Screenshot of TLGs tab.

AUTOMATION OF NCA WORKFLOWS

Automating Study Configurations and Calculations

aNCA's automation framework sets it apart from traditional tools by automatically identifying and configuring study-specific parameters. This includes the type of dose administration (e.g., IV bolus, infusion, extravascular), sample matrices (e.g., serum, urine), analytes (e.g., drug, metabolite), and dose schedule (single or multiple doses). These inputs guide automated workflows that define imputation rules, calculation methods, and parameter naming conventions, ensuring consistency without requiring manual setup.

This seamless automation eliminates a historically labor-intensive process, empowering researchers to focus on data interpretation. By predefining configurations aligned with regulatory guidelines, aNCA reduces the potential for human error while enhancing reproducibility across studies.

Streamlining Regulatory Compliance with CDISC Standards

One of the most impactful innovations in aNCA is its ability to produce regulatory-compliant outputs, including CDISC PP and ADPP datasets (5). These datasets are formally validated using tools like the P21 review system (6), ensuring alignment with regulatory requirements. Additionally, aNCA facilitates submission-ready Tables, Listings, and Graphs (TLGs), simplifying reporting workflows across clinical trials.

Further validation efforts include:

- Testing Coverage: With nearly 100% functional test coverage, aNCA ensures stability and reliability across its operations.
- Cross-Validation: Core calculations performed within aNCA (using PKNCA) are validated against established tools like Phoenix and PUMA (7), ensuring accuracy.
- Transparency and Recognition: aNCA is open-source, hosted entirely on GitHub, and will soon be available on CRAN. Roche has also recognized and validated the tool, further bolstering its credibility.

By reducing the burden of manual programming and ensuring regulatory compliance, aNCA enables faster, more reliable submissions while fostering confidence among stakeholders.

Enhancing User Experience & Collaboration

Designed with accessibility in mind, aNCA features a Shiny-based interface geared toward non-technical researchers. Collaborating with UX specialists from Roche and Appsilon, the tool ensures ease of use while supporting advanced customization. Features such as settings files allow seamless sharing of analysis methodologies across teams, fostering collaboration and consistency.

To address more complex customization needs, aNCA will soon offer an export feature to generate complete R scripts of analyses. Programming experts can further refine these scripts while benefiting from the foundational automation performed by the tool. This combination of usability and flexibility supports collaboration between technical and non-technical users.

Accelerating Study Timelines

By automating labor-intensive workflows, aNCA can reduce the time required to deliver pharmacokinetic results. Traditional NCA workflows, which often span several weeks, are streamlined into processes lasting days. This time saving is critical for studies under regulatory or project deadlines, ensuring faster decision-making.

CHALLENGES

Developing an open-source R package for a diverse group of scientists from various international companies presents considerable challenges. A significant hurdle involves balancing sufficient customization options for individual research needs with the establishment of automated processes. The objective is to achieve an optimal balance, ensuring package flexibility without introducing excessive complexity in its configuration.

Furthermore, the determination of appropriate default settings is critical. What proves effective in one scientific discipline or corporate environment may be entirely unsuitable for another. To successfully navigate these complexities and foster an inclusive open-source environment, inter-company collaboration is paramount. The establishment of a multi-organizational working group could facilitate the exchange of ideas, best practices, and technical expertise. Such collaboration would contribute to the development of a more robust and adaptable R package, thereby increasing its adoption within the scientific community. Moreover, shared ownership and collaborative development can address intellectual property concerns and ensure the long-term sustainability and support necessary to benefit the broader scientific endeavor.

FUTURE

The aNCA application currently provides a robust foundation for essential non-compartmental analysis. Over the next year, the program will undergo significant enhancements, including the incorporation of new PK parameters through collaboration with the PKNCA team at Human Predictions. Additionally, the automated report generation capabilities will be expanded and diversified to include PDF, HTML, and slideshow formats for both interim analysis and final submission. The team is dedicated to continuous improvement of features and UX design to enhance user satisfaction. Long-term objectives encompass broadening the analytical scope to include toxicokinetics (TK), oligonucleotide analysis, and ultimately, compartmental analysis.

CONCLUSION

aNCA represents a pivotal step forward in redefining NCA workflows, addressing inefficiencies in traditional processes while aligning seamlessly with modern regulatory demands. By automating complex analyses, generating CDISC-compliant outputs, and ensuring reproducible workflows, aNCA solves long-standing challenges in pharmacokinetics.

More than just an analysis tool, aNCA establishes a framework for standardizing and democratizing pharmacokinetic workflows across academia and industry. Backed by thorough validation, open-source transparency, and cross-disciplinary collaboration, aNCA delivers scalable, accessible solutions for modern drug development. With tools like aNCA, pharmacokinetic analyses can be performed with unprecedented speed, accuracy, and confidence, laying the groundwork for the future of pharmacometrics.

REFERENCES

1. Gabrielsson, J., Weiner, D. (2012). Non-compartmental Analysis. In: Reisfeld, B., Mayeno, A. (eds) Computational Toxicology. Methods in Molecular Biology, vol 929. Humana Press, Totowa, NJ. https://doi.org/10.1007/978-1-62703-050-2_16
2. https://github.com/pharmaverse/aNCA. The aNCA GitHub Repository
3. Denney W, Duvvuri S, Buckeridge C (2015). "Simple, Automatic Noncompartmental Analysis: The PKNCA R Package." *Journal of Pharmacokinetics and Pharmacodynamics*, 42(1), 11-107,S65. ISSN 1573-8744, doi:10.1007/s10928-015-9432-2, R package version 0.12.1, https://github.com/humanpred/pknca.
4. Pharmaverse: https://pharmaverse.org/
5. Clinical Data Interchange Standards Consortium. (n.d.). *New Standard Non-Compartmental Analysis*. CDISC Library. Retrieved October 7, 2025, from https://library.cdisc.org/browser/#/mdr/adam/adam-nca-1-0/datastructures/ADNCA/variablesets/NewStandardNonCompartmentalAnalysis
6. Certara. (n.d.). *Pinnacle 21 ADaM Validation Rules*. Retrieved October 6, 2025, from https://standards.pinnacle21.certara.net/validation-rules/ADaM
7. Y.Ma, B. Guglieri-Lopez , J. Gobburu, W. Denney, V.Ivaturi, "Comparison of non-compartmental analysis results between PKNCA, Pumas and Phoenix WinNonlin" https://www.humanpredictions.com/wp-content/uploads/2020/01/ACOP_2019_T102_NCA_performance_evaluation_Yingbo_revised.pdf

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RECOMMENDED READING

PKNCA vignettes and documentation: https://humanpred.github.io/pknca/index.html
Our website for more information: https://pharmaverse.github.io/aNCA/

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