CASE STUDY

DNAnexus®

With a Scalable Cloud Foundation, City of Hope's POSEIDON Powers a *Sea Change* in Personalized Cancer Care

City of Hope's POSEIDON precision oncology platform leverages the DNAnexus technology stack to ensure a consistent analytical workflow for breast cancer biomarkers in clinical trials

Key Takeaways

- Robust biomarker protocol allows for uniform analysis of samples collected at multiple clinical trial sites
- Cloud-based solution enables reports to be accessible from anywhere with appropriate permissions
- Analysis pipeline can be locked down for standardized analysis and reporting
- Secure and compliant environment streamlines clinical trial design and implementation and provides a detailed audit trail for regulators
- Sophisticated biomarker analysis workflow slashes timelines from three days to less than two hours

City of Hope, one of the largest cancer research and treatment organizations in the United States and a leading research center for diabetes and other life-threatening illnesses, emerged from humble beginnings: two tents set up in the California desert in 1913 to help patients suffering from tuberculosis. Today, with nearly 600 physicians and more than 1,000 scientists across the nation, the National Cancer Institute-designated comprehensive cancer center is a crown jewel in the American healthcare system. It operates facilities across California, Arizona, Illinois, and Georgia, bringing cutting-edge care to patients with cancer through advanced treatments, clinical trials, and a precision medicine approach.

Recently, City of Hope's research informatics team, led by Samir Courdy, Senior Vice President of Informatics, significantly expanded its capabilities through a scalable cloud-based precision oncology system built on the DNAnexus technology stack. This foundation was designed to support cutting-edge clinical research and precision medicine by empowering scientists and clinicians to explore and analyze omics and clinical data in a unified data and analysis environment.

At City of Hope, the outcome of this design is POSEIDON, the Precision Oncology Software Environment Interoperable Data Ontologies Network. This sophisticated environment is built on a data model incepted by Samir Courdy and developed by City of Hope's research informatics team. The model is known as the POSEIDON Common Data Model (PCDM). One clear differentiator of this model is it incorporates clinical, biospecimen, genomic results, and claims data into a single relational data model. Another unique feature of POSEIDON is the ingestion of de-identified electronic medical record data on a daily basis. It also incorporates DNAnexus features to allow researchers to explore, analyze, and visualize de-identified clinico-omic data from patients and public data sources. Capabilities made available through the POSEIDON platform support drug development, empower informed treatment selection for cancer patients, provide clinical decision support for molecular tumor boards, generate data for numerous publications and grant applications, and facilitate clinical trials.

The POSEIDON system has been so successful that City of Hope scientists are now looking for ways to open up access to researchers at other organizations.

The Challenge: Implementing Complex, Multi-modal Biomarkers Across Clinical Trial Sites

About four years ago, scientists at City of Hope comprehensive cancer center were on a quest to improve outcomes for patients with advanced estrogen-receptor-positive (ER+) / human-epidermal-growth-factor-receptor-2-negative (HER2-) breast cancer. Most patients with ER+ breast cancer are still treated with endocrine therapy and have excellent five-year survival rates[1], even without the use of adjuvant chemotherapy. However, treatment response rates tend to be lower in patients with metastatic disease, with only 30% of patients displaying tumor regression[2] on endocrine therapy. This outcome has been attributed to primary or acquired endocrine resistance in progressive tumors. Despite this, endocrine therapy continues to be used as the primary systemic therapy for all advanced ER+ breast cancers. Drugs such as alpelisib, a PIK3CA inhibitor, and everolimus, an mTOR inhibitor, target the pathways often used by the cancer to endocrine develop resistance, but unlike PIK3CA inhibitors, there were no known biomarkers to guide use of mTOR inhibitors just a few years ago. That meant patients who might benefit from these potentially life-saving treatments were left to make a choice based on gut-instinct rather than guidelines.

City of Hope's research team, led by Dr. Andrea Bild and Dr. Aritro Nath in the Department of Medical Oncology and Therapeutics Research, set out to identify and validate the missing biomarkers. Dr. Nath mined gene expression data from nine ER+ breast cancer cell lines and from 23 patients treated with everolimus[3]. They developed an integrative machine learning biomarker that can successfully distinguish mTOR inhibitor responders from non-responders, and can therefore be applied in the clinic to guide use of everolimus therapy.

Subsequently, Dr. Nath used data from 833 ER+ breast cancer tumors to develop a new prognostic model for endocrine therapy, employing a systems biology approach. They developed a machine learning biomarker model known as ENDORSE to distinguish likely responders to endocrine therapy from non-responders, and then validated the biomarker by retrospectively using it in data from five clinical trials. "[We] demonstrated superior and consistent performance of the model over clinical covariates, proliferation markers, and multiple published signatures," Dr. Nath and his collaborators wrote in a peer-reviewed publication[4] in Molecular Systems Biology.

Confident that the biomarkers could accurately identify patients most likely to benefit from the use of endocrine or combination therapies, the scientists locked down the machine learning code and implemented it in the SPOCK clinical trial (Systems Biology Guided Therapy for Breast Cancer Positive for Oestrogen Receptor After Aromatase Inhibitor and CDK Inhibition).

The scientists could now move forward with a Phase II clinical trial to implement the biomarkers for patients with ER+ breast cancer, but they also had a new challenge. "We wanted to create something that could be used at multiple clinical sites, without needing our team to perform the analysis for the biomarkers each time," Nath says. "That's when we started looking at cloud-based solutions to help make that possible."

The Solution: Streamlining and Standardizing Complex Biomarker Data Analysis in the Cloud with POSEIDON

What Dr. Nath and his colleagues didn't know at the time was that City of Hope's Research Informatics team led by Samir Courdy was already working with DNAnexus to design and develop the company's scalable cloud-based system as POSEIDON for scientists and clinicians at the comprehensive cancer center. Containing de-identified electronic medical record, genomic, and imaging data from nearly 1 million patients, and growing rapidly, the platform had already been used to support a clinical trial, multiple publications, and grants worth millions of dollars in research funding from the National Institutes of Health.

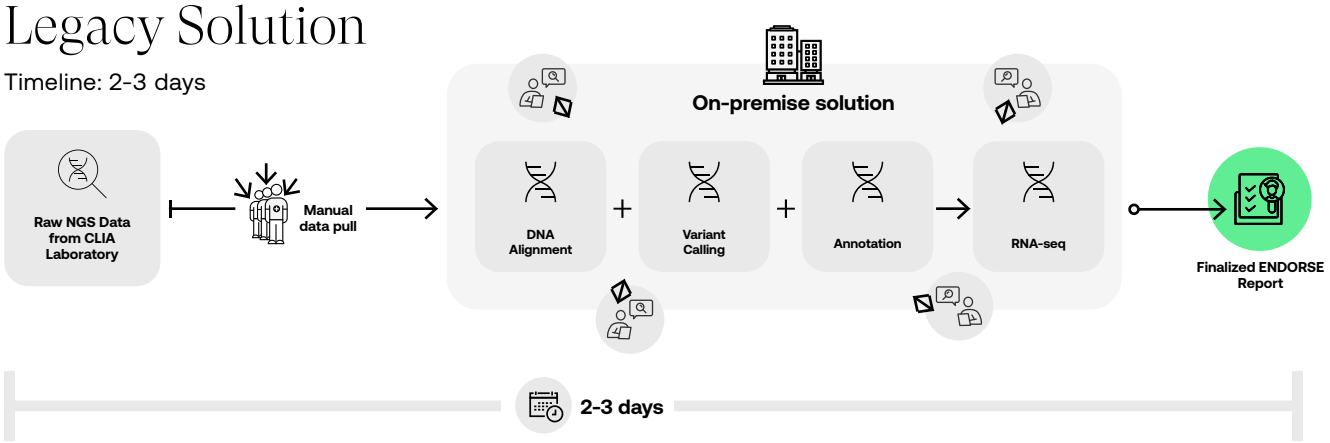
Dr. Nath went to the informatics team looking for certain capabilities that would allow him to share the SPOCK biomarker pipeline across clinical sites. From the start, he saw that the DNAnexus-enabled POSEIDON system was exactly what was needed. "We realized that our informatics work could be easily translated to the capabilities of the DNAnexus platform," he says. "There were several prebuilt apps we could incorporate into the biomarker pipeline for processing genomic and multi-omic data that were really helpful." *(Figure 1)*

Dr. Nath and his collaborators created a biomarker analysis workflow within POSEIDON and worked with the research informatics team to generate a report at the end of that pipeline to show treatment recommendations based on those results. The process was straightforward: they wrote R scripts, and the research IT team wrapped them into apps that could be configured and executed through a graphical user interface within the cloud-based platform. Now, samples sequenced anywhere can be uploaded into POSEIDON and analyzed through a consistent, vetted pipeline to produce reliable data.

Based on the success of the SPOCK biomarker pipeline, Dr. Nath has also used the POSEIDON platform for other projects. With a single-cell sequencing study, for example, he worked closely with DNAnexus software engineers to set up the features he wanted.

Legacy Solution

Timeline: 2-3 days



POSEIDON

Timeline: 2-3 **hours**

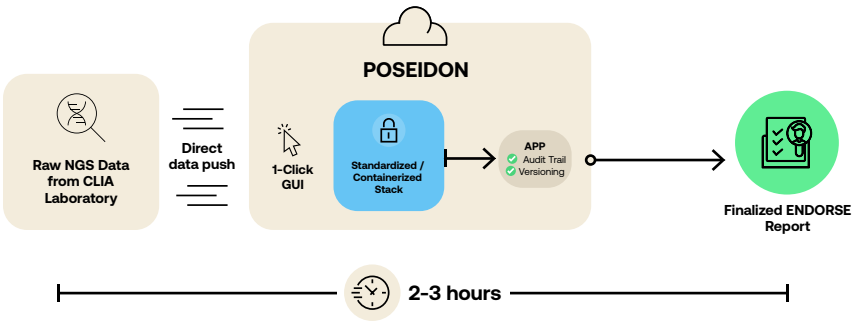


Figure 1. Streamlined multi-modal biomarker data analysis with POSEIDON

The "Legacy Solution" involved coding individual next-generation sequencing (NGS) data analysis steps in R, manually linking inputs and outputs for each step, and deploying on in-house servers. This workflow required manually pulling the NGS data from the CLIA sequencing lab, monitoring the process at multiple steps, and addressing software-hardware issues as they arose. The process generally took 2-3 days to complete and required close human supervision. By contrast, the same data analysis workflow, when implemented on POSEIDON in the cloud, yielded a 2-3 hour turn-around time, automated data flows that were monitored and audited, and a secure, locked-down process that was tracked from end-to-end. The POSEIDON workflow was also more easily accessible to external clinical sites under the appropriate security and governance controls.

Of particular interest to Dr. Nath was DNAnexus' commitment to providing a secure and compliant environment. Because the platform adheres to HIPAA and other clinical and business regulations, "it makes it very easy for us to talk to IRBs or anyone else who wants to know how data will be stored and shared," he adds.

The Result: Enabling Additional Clinical Trial Sites with Faster Results

Implemented through the POSEIDON platform, the SPOCK biomarkers for ER+ breast cancer were just the beginning of the story for Dr. Nath's team. Since adopting the cloud-based pipeline, they have developed and validated additional biomarkers that allow them to report a patient's likely sensitivity to four different drugs for breast cancer *(Figure 2)*. "That report tells us which patients would likely benefit from these drugs so providers can select between standard-of-care treatments," Dr. Nath says. The three additional biomarkers used in this process were developed with help from City of Hope's POSEIDON platform, which made it easy for scientists to explore gene expression and whole genome sequencing data.

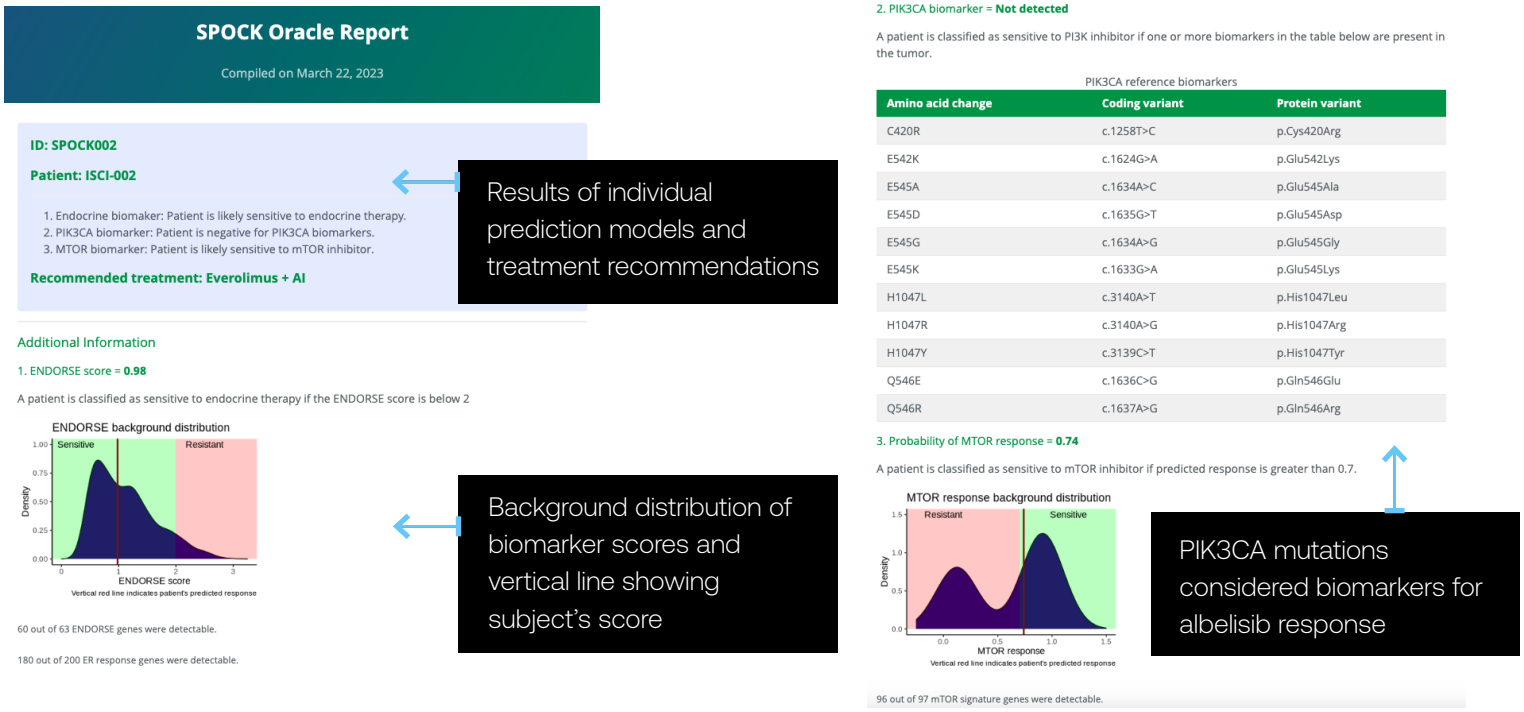


Figure 2. Example of the SPOCK biomarker-based treatment recommendation report.

City of Hope's POSEIDON workflow generates an easy-to-interpret PDF report based on each subject's biomarker results, including a treatment recommendation. The report is returned automatically to the ordering physician at the clinical trial site and includes the following specific information: results of individual prediction models; treatment recommendation; background distribution of ENDORSE and MTOR biomarkers, with subject's score indicated; list of PIK3CA mutations that are considered biomarkers for alpelisib response.

Thanks to its scalability, City of Hope's POSEIDON has made it possible to analyze patient data and return results much faster. Before Dr. Nath deployed his analysis pipeline on the platform, his team used local compute clusters and their own scripts to analyze the whole exome sequencing and RNA-seq data from patient samples. "If we were super-efficient, that process took us two to three days and required manual intervention at multiple points," he says. "But after moving to POSEIDON, the amount of time required to do the whole analysis and generate the report is now less than two hours. It's very efficient and requires absolutely no intervention." From start to finish, that means ordering physicians can get results for their patients just two weeks after the biopsy procedure.

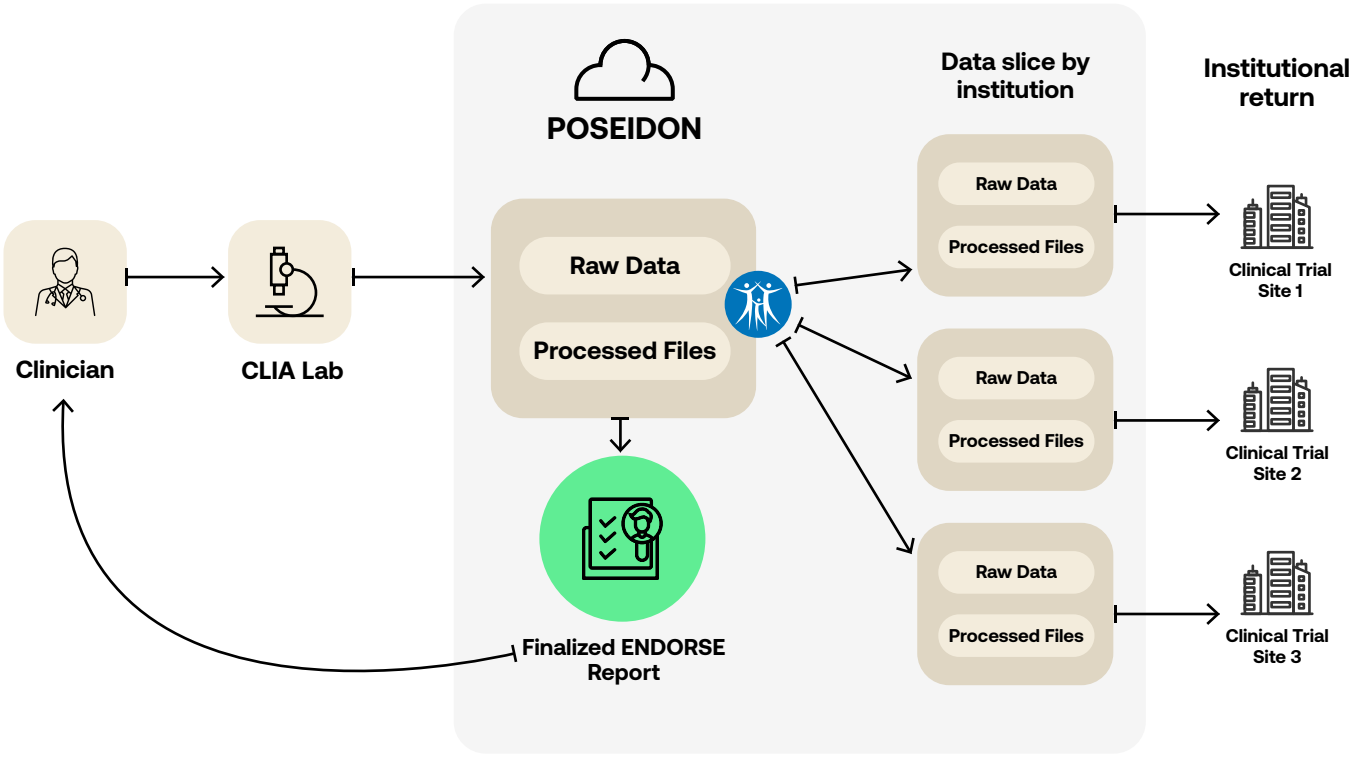


Figure 3. Flow of data and results across SPOCK clinical trial sites

Clinicians at trial sites order the ENDORSE biomarker test through City of Hope, which processes biopsy samples through their wet-lab, obtains clinical-grade NGS results in a CLIA-certified lab, and processes those results through City of Hope's POSEIDON data analysis workflow. The ENDORSE biomarker report is then returned to the ordering physician. Clinical trial sites also have access to the raw and processed files through the cloud under appropriate security, privacy and governance controls.

That automation and speed have been particularly attractive to City of Hope's clinical partners, such as pharmaceutical companies and healthcare systems looking to incorporate the approach into their own clinical trials (Figure 3). "You really don't have to do anything except upload the data and click a button," Dr. Nath adds. The cloud-based approach allows for access from anywhere with appropriate permissions, and also provides a detailed audit trail that can be used to demonstrate adherence to regulatory guidelines whenever needed.

What's Next

The ENDORSE biomarker is now being implemented in the SPOCK clinical trial conducted by Inova Health System at a clinical site in Virginia, where it will be evaluated in a larger patient population. The City of Hope team can analyze bulk tissue or individual cells as needed; all wet-lab processing is performed at the same facility to ensure consistency. Clinical samples are sent to a City of Hope partner for sequencing, and analysis and reporting are conducted through City of Hope's POSEIDON system. Additional trial sites run by Cleveland Clinic and MD Anderson Cancer Center will be added in the future and will follow the same procedure for sample processing and analysis *(Figure 3)*. The study is slated for completion in 2025.

Meanwhile, Dr. Nath and his colleagues are hoping to expand access to the POSEIDON environment to researchers and clinicians at other institutions. This would give other teams the same capabilities that City of Hope has, and also ensure consistent analysis and reporting. "We are working with the Research Informatics team to develop portals that will allow more external users to gain access to these software tools," says Dr. Nath, who has applied for NIH funding to make this possible.

And, of course, Dr. Nath's own biomarker development projects continue. He is currently working with Trey Ideker at the University of California, San Diego, to identify and validate DNA-based biomarkers using deep neural network models for drugs that will be included in planned clinical trials. "Our goal is to implement more of these models on City of Hope's POSEIDON platform so we can process clinical samples from any of our clinical trial partners, analyze the data, and eventually improve patient outcomes," Dr. Nath says.

To learn more about the POSEIDON platform, please visit

cityofhope.org/research/beckman-research-institute/precision-medicine

ascopubs.org/doi/10.1200/JCO.2021.39.15_suppl.e18813

ashpublications.org/blood/article/142/Supplement%201/7177/505569/Poseidon-a-Collaborative-Environment-for-the

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References:

[1] Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2012) 'Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100 000 women in 123 randomised trials', The Lancet, 379(9814), pp. 432–444. doi:10.1016/s0140-6736(11)61625-5.

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[3] Nath, A. et al. (2022) Predicting clinical response to everolimus in ER+ breast cancers using machine-learning, Frontiers. Available at: https://www.frontiersin.org/articles/10.3389/fmolb.2022.981962/full (Accessed: 11 December 2023).

[4] Nath, A., Cohen, A.L. and Bild, A.H. (2022) 'Endorse: A prognostic model for endocrine therapy in estrogen-receptor-positive breast cancers', Molecular Systems Biology, 18(6). doi:10.15252/msb.202110558.

ABOUT DNANEXUS

DNAnexus is a leading provider of secure, scalable, and intuitive biomedical data analysis software and bioinformatics applications for the life sciences and healthcare industries. We actively manage and support more than 80 petabytes of complex genomic, multi-omic, and clinical datasets on behalf of a growing network of collaborations with large-scale biobanks, as well as leading pharmaceutical, clinical diagnostic, academic research, and government organizations. Scientists across 48 countries are now using our platform to gain data-driven insights that can advance scientific discovery, accelerate precision medicine, and improve patient care.