



# Advancing Precision Medicine - Challenges And Opportunities





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**P**recision medicine has broad applications in optimizing the design and execution of clinical trials. It will play an increasingly important role as pressure grows on the pharmaceutical and medical device industry to run more efficient, cost-effective and productive trials. And, ultimately, precision medicine will help deliver measurable value from therapeutic interventions across health systems.

The biomarkers, patient records and advanced data analysis used in clinical studies help identify and recruit more viable, stratified and potentially responsive patient populations. Then, as trials unfold, each of these tools or sources can be used to track disease progression or treatment responses more accurately. But precision medicine is also about taking steps to ensure patient engagement, retention and treatment adherence over the course of a study, raising the odds of successful outcomes.

To determine where and how precision medicine supports these objectives, and to pinpoint the drivers for further adoption of it in clinical trials, Informa Pharma Intelligence conducted an online

survey for NTT DATA between November 20, 2019, and December 3, 2019. It used the Informa Pharma Intelligence database to recruit participants.

Among qualifying respondents, 63% were senior IT executives in pharmaceutical companies, while a further 25% worked in research and development (R&D). Commercial operations was the most prevalent job function, accounting for 63% of all respondents, with another 11% engaged in clinical operations. Geographically, 75% of respondents were based in North America and 24% in Europe.

The results and conclusions were based on 323 completed surveys. By analyzing key questions in

terms of both first and mean rankings, the survey highlighted not only the degree of consensus around crucial issues and challenges in applying precision medicine to clinical trials, but also how much views and perspectives may vary within those parameters. NTT DATA uses insights such as these to better inform our current and future solutions and to leverage the full benefits of precision medicine.

## STUDY HIGHLIGHTS

Oncology was, by some margin, the therapy area in which survey participants saw precision medicine having the greatest impact. In the NTT DATA and Informa Pharma Intelligence survey, 67% of respondents selected oncology as the seedbed for precision medicine. This result compared with 13% of respondents who opted for neuroscience, 6% each for cardiovascular and diabetes, and 5% for respiratory disease.

Precision medicine strategies are particularly applicable to oncology because each cancer patient is unique. This is evidenced by the current trend toward individualized treatment based on genetic status and the emergence of “tumor-agnostic” therapies. Moreover, the same cancer and its health effects can mutate over time in a single patient.

One reason for the growing influence of precision medicine in drug development is that designing clinical trials and then identifying and recruiting suitable patients is highly challenging — all the more so with the increasing prevalence of molecular profiling. Problems can arise with both patient characteristics and the physical distribution of trial populations. Too often, study participants are narrowly defined but geographically diffused.

In the NTT DATA and Informa Pharma Intelligence survey, patient awareness, access and enrollment

were identified (by 49% of respondents) as the most significant obstacles to the pursuit and implementation of precision medicine in clinical trials, followed by availability of/access to patient data (12%), payer funding and reimbursement for patients (11%), technology investments (10%) and lack of enabling infrastructure/tools (9%).

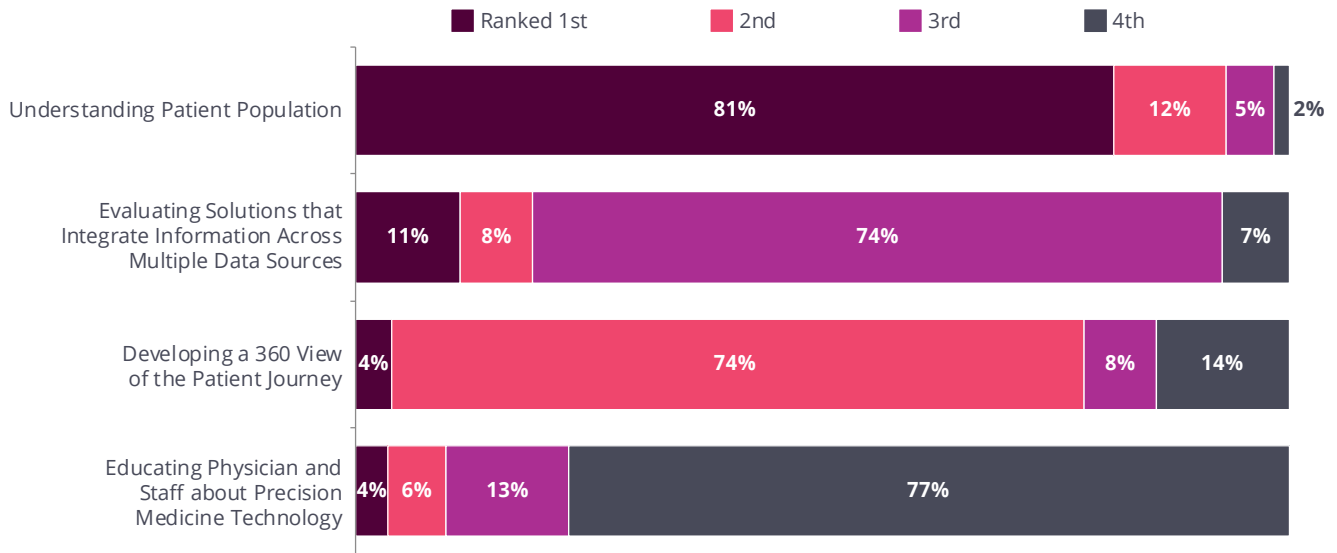
Understanding the patient population was seen, by far, as the most important step in developing a precision medicine program, followed by evaluating solutions to integrate information across multiple data sources. These measures were ranked first by 81% and 11% of respondents, respectively. Only 4% chose “developing a 360-degree view of the patient journey” and “educating physicians and staff about precision medicine technology” as pivotal steps.

On a mean basis (the sum of all rankings divided by the number of responses), a 360-degree view of the patient journey was considered the second most important development step (mean ranking 2.32, versus 1.27 for understanding the patient population). Evaluating solutions that integrate information across multiple data sources was in third place (mean ranking 2.77).

Geographical location was convincingly the most significant factor in defining inclusion/exclusion criteria for trial recruitment, with 66% of first rankings and the top mean score of 1.64. The second most important factor in the first rankings was medical/disease condition or progression (24%), followed by recruitment duration (7%) and patient visits (3%). The mean rankings gave a different picture, with patient visits coming in second at 2.29, above recruitment duration (2.84) and medical condition/progression (3.13).

Failure to recruit sufficient numbers of patients remains a significant obstacle to successful trial

**Figure 1: Precision Medicine Development Steps**



*Question: Please rank the most important steps in developing your precision medicine program?*

*Base: All respondents (n=310). <sup>1</sup>Mean Rank: Sum of rankings divided by number of responses counted.*

completion. Often, this is down to short enrollment periods, staff shortages that limit recruitment opportunities, or difficulties integrating and managing disparate research sites.

### TECHNOLOGY DRIVERS

Among the emerging technology drivers for precision medicine, statistical analytics were a strong priority, ranked first by 70% of participants and also significantly favored in the mean rankings (1.74). Integration of data sources, such as laboratory results, claims data or electronic medical / health records (EMR/EHRs), was the number one priority for 9% of respondents (mean ranking 3.64) and patient-population repositories for 8% (mean ranking 4.47).

Mean scores also gave some precedence to digital health applications and interoperable EMRs. The former (for example, Fitbit activity trackers) were placed first among technology drivers by only 3% of respondents yet achieved the second-highest mean

ranking — 2.83. Interoperable EMRs were ranked first by just 4% of respondents yet came in third in the mean rankings (3.23).

In the NTT DATA and Informa Pharma Intelligence survey, EMRs were seen as the key source for identifying clinical trial populations, cited by 58% of respondents. On the same parameter, physician referrals, laboratory diagnostics and health care claims scored a more modest 17%, 14% and 10%, respectively. When survey participants were asked about specific analytics capabilities used to find clinical trial candidates, they decisively (71%) favored statistical packages such as cluster or regression analyses, followed by Excel-based modeling tools (17%) and artificial intelligence (AI)/ machine learning (ML) (9%).

Another crucial factor in clinical trial performance is data. Statistics are the bedrock of every study, from design through execution, analysis and reporting. They enable sponsors to control for biases or confounding

factors, as well as to pick up and measure any random errors that may occur as the trial progresses.

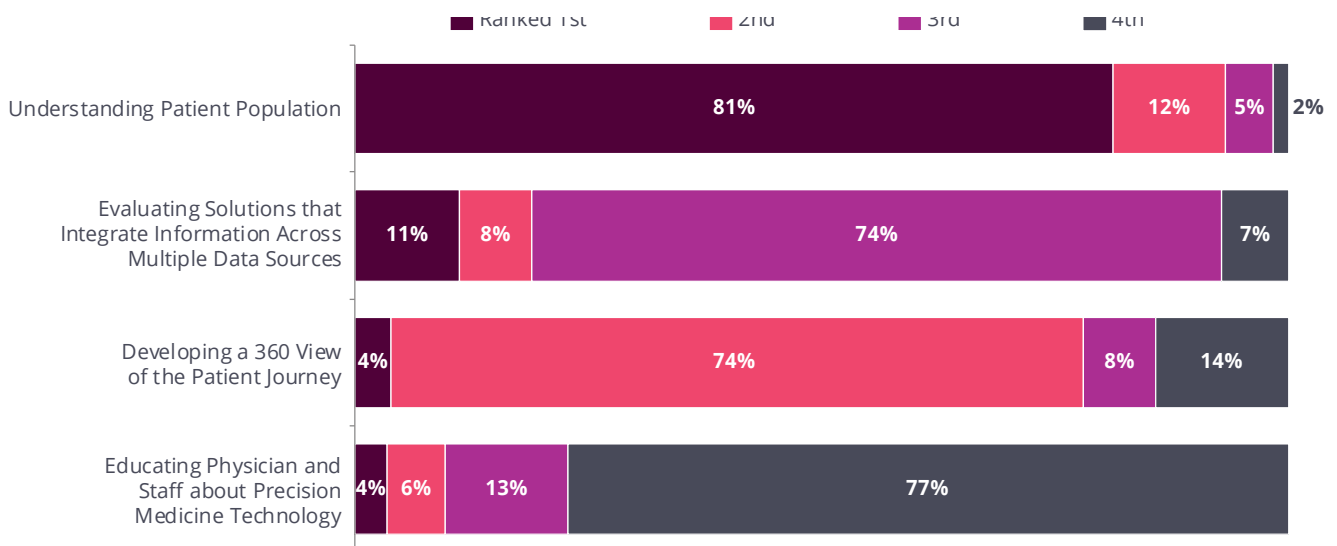
### PATIENT RETENTION

Once clinical trials are underway, the focus of precision medicine strategies is likely to be on patient retention, tracking and measuring disease progression using biomarkers and other analytical tools, and tapping data sources to inform decisions on treatment continuation or cessation. In the NTT DATA and Informa Pharma Intelligence survey, patient behavior was considered (by 50% of respondents) the characteristic with the most impact on patient retention in clinical trials, substantially more than disease stage and progression (17%), travel hardships and social circumstances (both 12%), or financial hardships (8%).

Questioned on specific technologies they used to improve patient retention, 83% of respondents referred to more traditional communication channels, such as email, text or voicemail messages. There was some evidence of emerging digital technologies coming into play, with virtual digital assistants (Alexa from Amazon and Google Assistant) scoring 6% and social robots (Jibo, Pepper and Aibo) 1%.

Patient behavior initiatives employed as retention strategies in clinical trials included support and education (counseling, communities and family coordination), communication (text/ email messages and patient feedback), resource provision (accommodation, meals, transport and visiting nurses) and database management (information and preselection). Among patient retention activities related to disease stage

**Figure 2: Patient Retention**



*Question: Please rank the most important steps in developing your precision medicine program?*

*Base: All respondents (n=310). <sup>1</sup>Mean Rank: Sum of rankings divided by number of responses counted.*

and progression, respondents cited criteria review (broadening eligibility), communication (marketing, specialist doctors and patient information), project re-evaluation (treatment modification and realigning the trial plan) and direct monitoring (local or home visits).

Travel and financial hardships affecting patient retention were mitigated through reimbursement (travel expenses, accommodation, loss of income and meals), travel assistance (accommodation and transport), financial incentives (parking/taxi vouchers and free treatment) and other types of assistance programs (fees, meal vouchers and stipends). Respondents tackled retention issues associated with social circumstances through support and education (counseling, communities and family), resource provision (hotels, meals, transport and visiting nurses), social media (apps, awareness and socialization), database management (information and preselection) and other incentives (stipends).

Another precision medicine strategy that can enhance both patient retention and outcomes in clinical trials is using biomarkers, whether to pinpoint stratified populations at the recruitment stage or to clarify treatment responses, disease progression and endpoints during the trial itself. Identifying the salient features of biomarkers is an important component of precision medicine in clinical development. The survey found that linear discriminant analyses (35% of respondents) and support vector machines (32%) were favored as the most effective technologies to identify biomarker features, ahead of random forests (27%) or other methods (5%).

## **TRACKING DISEASE PROGRESSION AND TREATMENT CESSATION**

Precise measurement of disease progression is a critical driver of trial outcomes. Any two patients

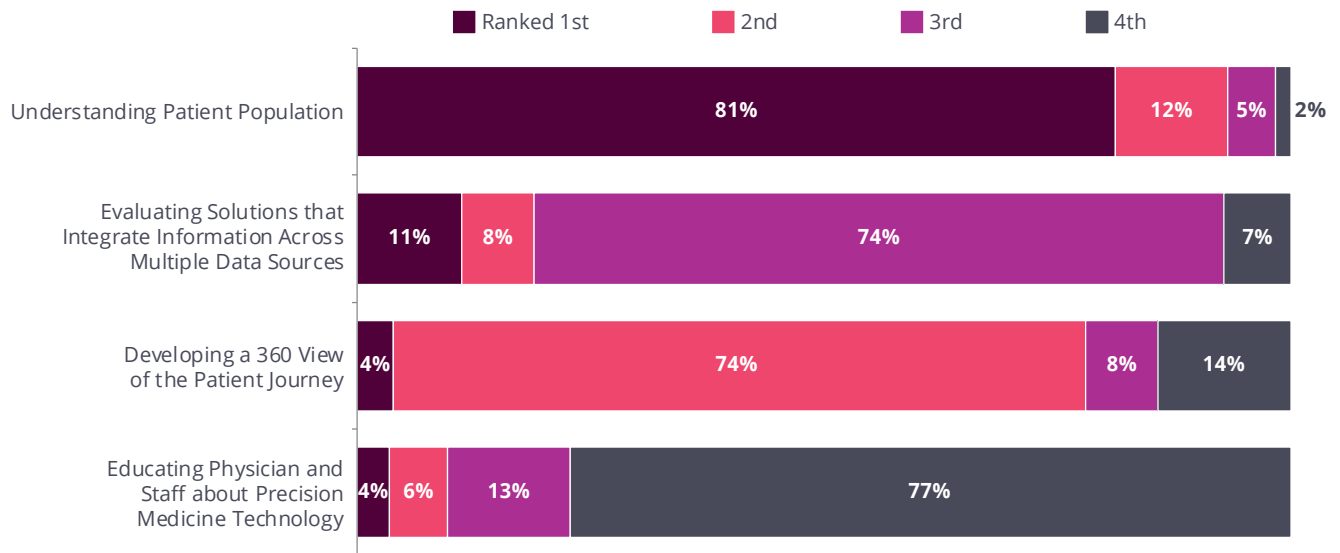
with the same disease can vary symptomatically. Their disease may progress at different rates and respond differently to the same therapy. Understanding how to anticipate and manage patient variation is a fundamental objective of precision medicine, both within clinical trials and in the wider health care environment.

ML techniques have spawned computer models of disease progression that help to iron out patient heterogeneity in clinical development. One associated precision medicine strategy is to track biomarkers using longitudinal algorithms that incorporate the trial subject's screening history and model biomarker activity from disease onset through clinical presentation.

The NTT DATA and Informa Pharma Intelligence survey found that a patient's genetic composition is easily the biggest impact on disease progression (61% of respondents). Otherwise, participants cited disease pathogenesis (19%), patient behavioral characteristics (12%) and social circumstances (8%). Empirical and system-progression models (both 41%), followed by semi-mechanistic models (16%), were most often used to quantify disease progression by respondents in data management and analytics roles. Among clinical operations specialists, clinical (33%), laboratory (27%), pathology (20%) and radiographic (19%) methods prevailed.

Data managers regarded empirical, system-progression and semi-mechanistic models as all important techniques for measuring disease progression in clinical trials. However, empirical models had the edge, with 82% of respondents regarding them as either "extremely" or "very" important in quantifying progression, compared with 76% for system-progression and 67% for semi-mechanistic models.

**Figure 3: Measuring Disease Progression**



*Question: Please rank the most important steps in developing your precision medicine program?*

*Base: All respondents (n=310). <sup>1</sup>Mean Rank: Sum of rankings divided by number of responses counted.*

Among the data sources used to determine whether patients should continue or cease treatment during clinical trials, there was marked preference for the number of lines of therapy, in terms of both first (68%) and mean (1.86) rankings. On a first-rankings basis, patient responsiveness to therapy was the second most important consideration (22%), followed by clinical data sources such as EMRs, laboratory tests or genomics (7%), and then by radiology (2%) and pathology (1%) data, respectively.

In the mean rankings, clinical data (2.20) moved up to second place, ahead of pathology data (3.12), responsiveness to therapy (3.17) and radiology data (4.65). Other data sources that respondents would like to see used to improve decision-making on treatment continuation/cessation included academic, patient feedback, biomarker, AI, pharmacy and health insurance, genetic analysis and metadata.

Survey participants were also asked what factors they monitored to determine whether treatment

cessation was warranted in a clinical trial. On a first-ranking basis, susceptibility (to recurrence or remission) was the overriding factor, with a score of 69%, followed by safety (20%), pharmacodynamic response (5%), risk of recurrence/remission (3%), and biopsy test results (tumor size and shrinkage at 2%).

Once again, though, the mean rankings showed a somewhat different picture, with susceptibility still — by some margin — the key factor (mean score 1.68) but with risk (2.27) and pharmacodynamic response (2.97) taking on more weight. The mean rankings for safety and biopsies were 3.32 and 4.62, respectively.

### IT SERVICES DRIVERS

As the NTT DATA and Informa Pharma Intelligence survey findings make clear, it is imperative that pharmaceutical companies and their IT partners use the full range of available technologies and data sources to take proactive decisions on implementing precision medicine strategies in clinical trials. That

way, they can ensure trials are better designed, focused and populated, as well as more tightly managed and monitored, from the outset.

Regulatory agencies have encouraged pharmaceutical companies to explore alternative clinical trial designs, such as basket, umbrella or various adaptive studies, that “simultaneously evaluate multiple drugs and/or disease populations in multiple sub-studies, allowing for efficient and accelerated drug development.”<sup>1</sup> These newer types of trial take advantage of the real-time flexibilities offered by emerging AI and ML technologies.

For example, sponsors can profile enrolled patients with the help of DNA sequencing, metabolomics or proteomics. Study drugs can then be matched to identified pathologies based on real-world data derived from AI and ML analyses of large data sets. Another use for AI and ML as precision medicine tools in clinical trials is to facilitate electronic data monitoring, whether in ensuring the accuracy of study data or maintaining patient safety.

If the results of the NTT DATA and Informa Pharma Intelligence survey illustrate just how important precision medicine techniques are to pharmaceutical companies looking to get the most out of clinical trials, they also indicate how much implementation relies on capabilities outside the industry mainstream. In terms of first rankings, survey respondents saw traditional IT vendors, such as NTT DATA and others, as by far (74%) the most important IT organizations in enabling industry-wide progression and adoption of precision medicine.

Academic research laboratories were way behind, with 10% of first rankings, followed by industry consortia (9%) and data aggregators (8%). In the mean rankings, on the other hand, industry consortia were the second most important driver,

with a score of 2.14, lagging traditional IT vendors (1.54) but ahead of data aggregators (2.87) and academic research labs (3.45).

Data storage management is expected to be, by some distance, the largest cost component in implementing precision medicine, with first-ranking and mean-ranking scores of 72% and 1.53, respectively. Advanced analytics picked up 10% of first rankings, while AI/ML scored 8%, infrastructure management (cloud and data lake) 7% and the internet of things (IoT) 2%. On a mean basis, data storage management remained in first place (1.53) but infrastructure management came second (2.35), in front of advanced analytics (2.89), IoT (3.94) and AI/ML (4.29).

The two most significant obstacles to adopting IT solutions that drive precision medicine in clinical trials are likely to be knowledge of available data sources (39%) and access to IT skillsets (38%), survey participants believe. Obstacles regarded as less daunting were lack of data aggregation/integration capabilities (10%), lack of global regulatory awareness (7%) and shortage of analytics tools (5%).

## **HOW NTT DATA AND EVERIS IS EMBRACING AND EVOLVING PRECISION MEDICINE**

As the survey results show, individualized care is at the center of tomorrow's health delivery systems. Precision medicine brings that prospect to fruition. It cannot evolve, though, without the right technology infrastructure to support data storage and usage across a wide range of applications. That includes integrating, tailoring and interpreting data from diverse sources, such as clinical trials, medical imaging, patient records, insurance claims or genomic profiling, as well as from multiple organizations and geographies.

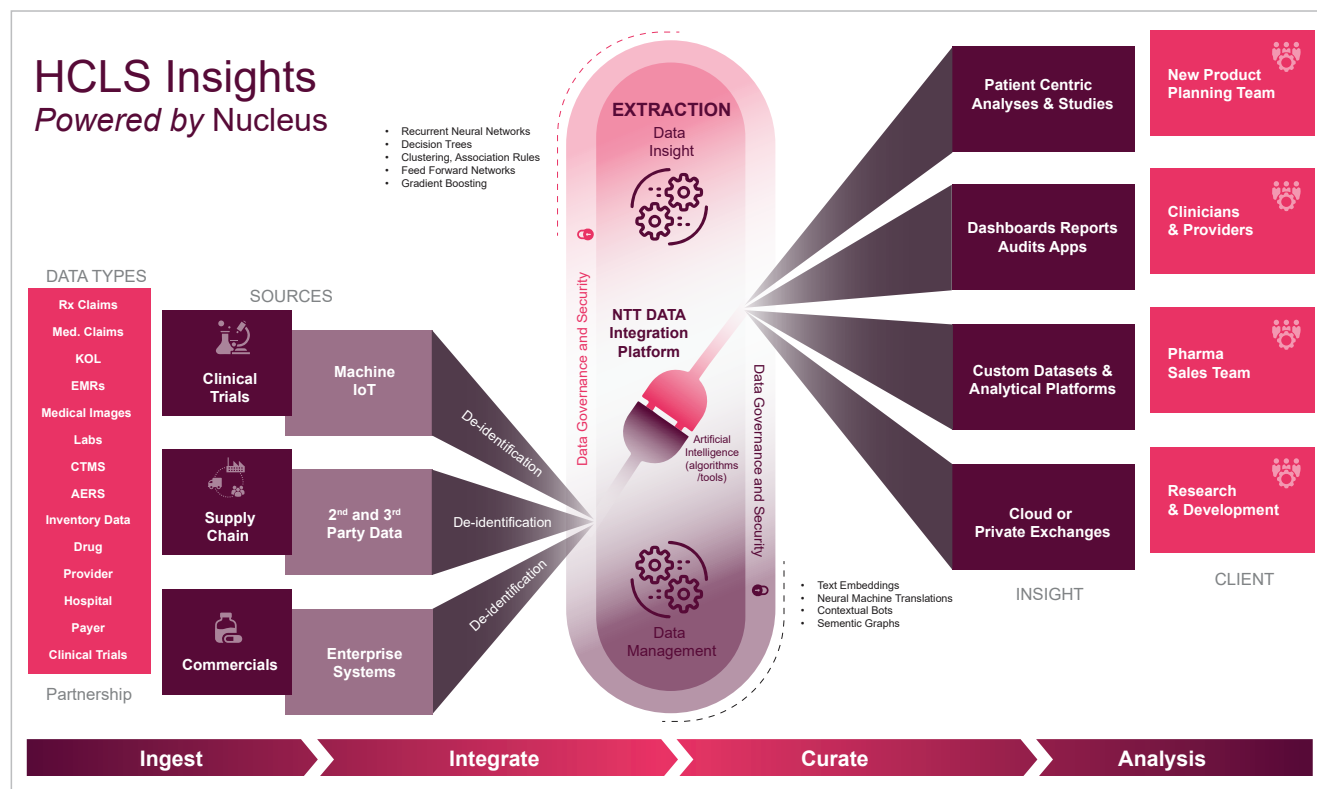


NTT DATA and everis draws on a wide range of data sources, as well as tools for data integration, analysis and presentation, to embed precision medicine strategies in the design and execution of clinical trials. We currently offer several use cases through NTT DATA's HCLS Insights *Powered by* Nucleus solution. For example, patient-analysis use cases give an overview of patient demographics by therapeutic area (breast or pancreatic cancer). Each area then characterizes patients as prospective, in-trial or real-world, and according to their distribution across oncology practices by ZIP code. A dashboard, developed as part of the HCLS Insights *Powered by* Nucleus solution, also provides information from EMRs on patients' interactions with health care systems and on diagnostic status (affected body sites) by integrating laboratory and EMR data.

The SRT solution, Smart Remote Treatment, of everis is made up of a set of AI algorithms that determine the ideal dose of lithium to be prescribed from a predictive model that calculates literacy (reference value in lithium treatments that measures the concentration lithium in blood at 12 hours of intake) based on multiple clinical incidence parameters, including real-time data related to lifestyle, diet and sleep quality. The solution is developed by BIOEF / Bioaraba, which provides leadership and clinical knowledge, Tecnalía, a reference partner in offering the necessary technology for the administration and control of lithium in blood through a transdermal patch and everis, responsible for the development of the artificial intelligence of the solution.

In NTT DATA's patient-cohort and trial-site use cases, the client uses the HCLS Insights *Powered*

**Figure 4: NTT DATA HCLS Insights *Powered by* Nucleus solution diagram**



## ADVANCED ANALYTICS TECHNIQUES

NTT DATA is adding to its portfolio of clinical-trial solutions advanced analytics techniques that will employ ML algorithms. These algorithms will play a significant role in cleaning the large volumes of real-world data generated during drug development, as well as in prioritizing molecules based on their known biological properties. Both existing and new supervised and unsupervised learning approaches will apply our ML algorithms. NTT DATA will also leverage a cloud infrastructure to better manage the multidimensional nature of emerging omics data.

Given the still evolving role of precision medicine in clinical trials and the advances in next-generation sequencing, NTT DATA's algorithms and patients' genomic profiles will be increasingly valuable for risk prediction, disease diagnosis and the development of targeted therapies.

by Nucleus platform to track the performance of trial sites based on patient dropouts and the final distribution of enrolling versus non-enrolling sites. The solution also includes a detailed ranking of trial sites, mapped across the study investigators.

The regimen-analysis use cases integrate diagnostic laboratory and EMR data by disease type and chart the patient journey in terms of disease stage, therapeutic area, diagnostic distribution of laboratory results and type of drug regimen (pre- or post-trial). HCLS Insights can categorize test results by therapeutic area, laboratory test, medical imaging and result value.

The NTT DATA HCLS Insights *Powered by Nucleus* solution extends throughout the life sciences value chain, integrating AI approaches such as ML, deep learning and natural language processing to tackle the health care data challenges of scalability and high dimensionality while transforming big data into clinically actionable knowledge.

## NEW PARADIGMS IN PRECISION MEDICINE

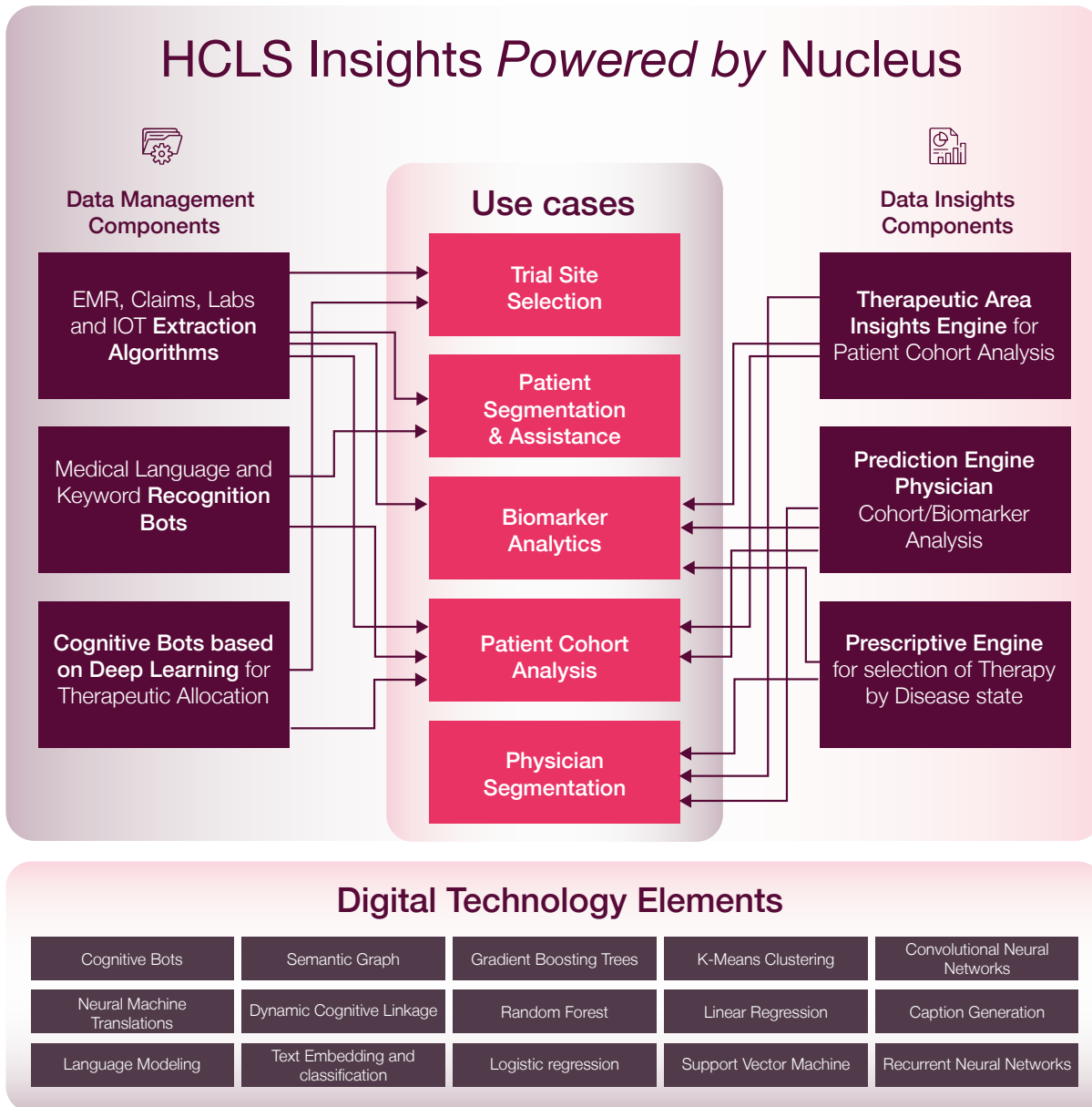
The benefits of precision medicine strategies, such as in the NTT DATA use cases, can be seen in the clinical

validation of increasingly complex diagnostic tests, as well as the development of innovative methods for evaluating drug efficacy and the re-assessment of standards of evidence. With new paradigms like rapid-learning precision medicine, every patient encounter is regarded as an experiment, in which all available data is continuously gathered and analyzed to inform each subsequent encounter with the same or similar patients.

In the future, the adoption of precision medicine will be driven by issues such as genomics diversity, integration with the concept of precision public health and the need for cost efficiencies in health care. By incorporating precision medicine strategies into clinical trials and other health care settings, pharmaceutical companies will be able to sustain a continuous cycle of feedback.

The results of the joint survey conducted by NTT DATA and Informa Pharma Intelligence show that ongoing efforts to achieve even more precision and individualization in these settings will depend on analytics and AI adoption, as well as the availability of data sources, data requirements, algorithmic transparency, reproducibility and real-world assessments.

Figure 5: Use cases and components of the HCLS Insights Powered by Nucleus solution



Specialist providers, such as NTT DATA, are raising the bar for sourcing, integrating, analyzing and customizing valuable data assets to support precision medicine strategies in clinical trials. For all stakeholders in clinical development, the long-term benefit of these and other precision medicine tools should be more efficient, cost-effective trials that bring real value and innovation to the therapeutic landscape.

#### SOURCES

1. U.S. Food and Drug Administration. "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics." Draft Guidance for Industry. October 2018. <https://www.fda.gov/media/120721/download>

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