Genedata Profiler®

Fact File — Using Precision Medicine Concepts To Improve Clinical Trials

Substantial improvements in drug development methods and technologies have resulted in considerable gains in efficacy, safety and tolerability of therapeutic products, although these improvements are often contingent on certain factors for each patient. Analysis of variability in patients' genes, environment and lifestyles enables researchers and ultimately, clinical physicians, to adopt a precision medicine approach to disease treatment or prophylaxis, matching selected patients with optimal pharmaceutical therapies to achieve the best outcome for those patients, while minimizing adverse reactions[1]. A precision medicine approach, focusing on the application of pharmaceutical compounds for targeted patient populations, displays benefits in drug research and development as well as in the clinic.

Processing and analysis of these vast quantities of clinical data requires sophisticated, automated software to complete processes that would require weeks or months of work by research scientists in just hours, with a highly significant reduction in errors. **Genedata Profiler®** is the leading enterprise software platform for precision medicine research, dramatically accelerating the process of analyzing large, complex sets of study data and providing valuable, accurate reports.

Benefits of precision medicine concepts in clinical trials

Analysis of large-scale clinical data can help research scientists target therapeutic compounds under investigation to determine their most effective application, accelerating clinical trial results and significantly reducing associated financial costs[2] (Figure 1). With drug research and development costs from discovery to market launch potentially exceeding $5 billion[3], pharmaceutical companies are exploring all avenues to save R&D costs.

Precision medicine concepts applied to clinical trials are instrumental in reducing the investment required to bring new drug candidates to market. These techniques enable annual worldwide drug development costs to be reduced significantly through:

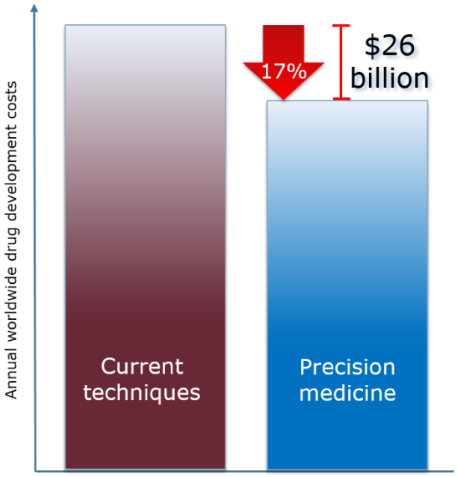


Figure 1: Estimate of cost savings in drug development when precision medicine concepts are applied.

Early success: accelerating the clinical application of candidate compounds, qualified in or prior to clinical trials;

Early failure: saving research costs by terminating unsuccessful drug candidates as early as possible;

Enhanced speed to market: dramatically improving drug efficacy and tolerability profiles to accelerate regulatory approval.

Genedata solutions in silico

Using biomarkers for precision medicine concepts in clinical trials

The identification and application of biomarkers is key to the effective application of precision medicine concepts in clinical drug trials. The use of biomarkers has increased substantially in recent years; historically, genomic, proteomic and metabolomic biomarkers have been key to many cancer therapy trials. While oncology remains the greatest area of focus, analysis of biomarker data is becoming commonplace across many therapeutic areas, including metabolics and endocrinology, reproductive and urologic disease, cardiovascular disease, neuroscience, gastroenterology, and rare diseases.[4]

Early success

Knowledge of how certain biomarkers are affected by a therapeutic compound under specified conditions allows those biomarkers to be used to predict the efficacy and safety of the compound. These predictions may be made early in the assessment of a therapeutic candidate, accelerating the decision to investigate it for clinical applicability.

Early failure

Examination of biomarker data can also flag early warning signs that indicate with high confidence the probable failure of a candidate compound, even in the early stages of clinical trials. These indicators enable an early decision to terminate clinical investigation of failing compounds before substantial resources are committed.

Enhanced speed to market

The presence of a biomarker or a combination of biomarkers may correlate with improved response to a given therapy and decreased toxicity, manifested as improved tolerance of the therapy. Once biomarkers for efficacy and tolerability have been identified, patients eligible for treatment may be enrolled in a clinical trial on the basis of presence of the required biomarkers (Figure 2). Clinical trials in which subject patients are selected, or stratified, in this way demonstrate an improved response rate to the therapy under investigation and reduced time taken to achieve trial endpoints.

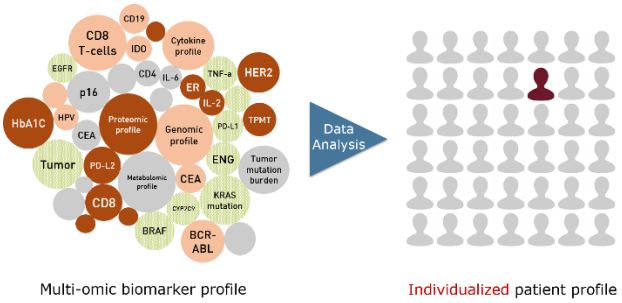


Figure 2: Multi-omic biomarker analysis allows stratification of patients and ultimately the provision of individualized therapy.

Meta-analysis of clinical trials that use biomarkers to stratify patients indicates that the probability of successful transition from Phase I to approval of the drug is almost twice that of trials that do not use biomarkers to select patients. In oncology trials, for example, the probability of success can rise from 1.6% for trials that do not use biomarkers to stratify patients to 10.7% when biomarkers are used[5] (Figure 3).

Biomarkers											
		Phase 1 to Phase 2			Phase 2 to Phase 3			Phase 3 to approval			Overall
Therapeutic group		Total phase transitions	$POS_{1,2}$, %	(SE, %)	Total phase transitions	$POS_{2,3}$, %	SE, %	Total phase transitions	$POS_{3,APP}$, %	(SE, %)	POS, % (SE, %)
Oncology	No biomarker				4773	17.4	(0.5)	1159	33.6	(1.4)	1.6
	With biomarker				742	38.8	(1.8)	77	63.6	(5.5)	10.7
	All				5515	20.3	(0.5)	1236	35.5	(1.4)	
	No biomarker				1438	33.9	(1.2)	1086	52.0	(1.5)	
	With biomarker				2	50.0	(35.4)	15	20.0	(10.3)	
Cardiovascular	All	1539	44.6	(1.3)	1440	34.0	(1.2)	1101	51.6	(1.5)	7.8 (0.8)
	No biomarker	1241	39.6	(1.4)	1027	37.9	(1.5)	962	62.2	(1.6)	9.3 (1.0)
	With biomarker	7	85.7	(13.2)	5	100.0	(0.0)	2	100.0	(0.0)	85.7 (13.2)
CNS	All	1248	39.9	(1.4)	1032	38.2	(1.5)	964	62.2	(1.6)	9.5 (1.0)
	No biomarker	2181	40.4	(1.1)	2050	30.2	(1.0)	1141	51.1	(1.5)	6.2 (0.6)
	With biomarker	42	54.8	(7.7)	42	28.6	(7.0)	15	53.3	(12.9)	8.3 (6.4)
Autoimmune/ inflammation	All	2223	40.7	(1.0)	2092	30.2	(1.0)	1156	51.1	(1.5)	6.3 (0.6)
	No biomarker	2506	38.9	(1.0)	2106	25.4	(0.9)	964	63.7	(1.5)	6.3 (0.6)
	With biomarker	9	55.6	(16.6)	14	35.7	(12.8)	5	60.0	(21.9)	11.9 (16.8)
Genitourinary	All	2515	39.0	(1.0)	2120	25.5	(0.9)	969	63.7	(1.5)	6.3 (0.6)
	No biomarker	359	34.3	(2.5)	287	28.9	(2.7)	212	66.5	(3.2)	6.6 (1.5)
	With biomarker	5	80.0	(17.9)	0	N.A.	N.A.	0	N.A.	N.A.	N.A. N.A.
Infectious disease	All	364	34.9	(2.5)	287	28.9	(2.7)	212	66.5	(3.2)	6.7 (1.5)
	No biomarker	1961	39.7	(1.1)	1453	34.7	(1.2)	1069	75.1	(1.3)	10.4 (0.9)
	With biomarker	6	66.7	(19.2)	27	44.4	(9.6)	9	100.0	(0.0)	29.6 (16.8)
Ophthalmology	All	1967	39.8	(1.1)	1480	34.9	(1.2)	1078	75.3	(1.3)	10.5 (0.9)
	No biomarker	180	52.2	(3.7)	274	34.7	(2.9)	207	74.9	(3.0)	13.6 (2.8)
	With biomarker	1	0.0	(0.0)	3	33.3	(27.2)	0	N.A.	N.A.	N.A. N.A.
Vaccines	All	181	51.9	(3.7)	277	34.7	(2.9)	207	74.9	(3.0)	13.5 (2.8)
	No biomarker	733	40.8	(1.8)	761	32.9	(1.7)	609	85.4	(1.4)	11.4 (1.3)
	With biomarker				5	0.0	(0.0)	0	N.A.	N.A.	N.A. N.A.
Overall	No biomarker				766	32.6	(1.7)	609	85.4	(1.4)	5.5
	With biomarker				14 169	26.8	(0.4)	7409	59.0	(0.6)	10.3
	All				840	38.6	(1.7)	123	60.2	(4.4)	
					15 009	27.4	(0.4)	7532	59.0	(0.6)	

Figure 3: Biomarkers improve the success rate of clinical trials

In the regulated, clinical environment, genomic data may be combined with epigenomic, proteomic, and other omic data, along with clinical data, laboratory test results from patients and imaging data to provide more information to inform endpoint analysis of a clinical study. This combined analysis facilitates accurate decision-making about whether to advance compounds under investigation to the next clinical phase of the study (Figure 4).

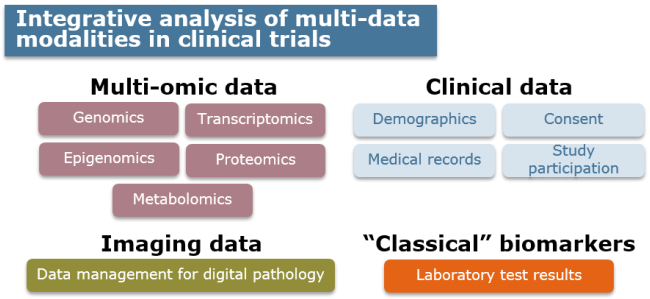


Figure 4: Clinical trial analysis requires integration of multi-omic and other data and translation of NGS, MS, and digital pathology research pipelines into clinical practice, while ensuring full regulatory compliance.

Genedata Profiler for multi-omic data integration and analysis

Drug research teams using multi-omic data in clinical trials face three critical challenges:

- integration and analysis of distributed omic, other biomarker & clinical data;
- translating NGS, MS, and digital pathology research pipelines into clinical practice;
- ensuring full data governance, chain of custody, and reporting in regulatory-compliant analysis pipelines.

Genedata Profiler is the solution to overcome these challenges, while reaping the time and financial benefits of using powerful, automated software to accelerate and improve data analysis. The software platform provides a secure, study-centric data management infrastructure to integrate and analyze omic and clinical data while maintaining compliance with regulatory requirements (Figure 5). The software allows users to:

- import and validate clinical and phenotypic subject data;
- query & filter subject data, and create cohorts;
- link omic (e.g. NGS) data to subjects and samples to establish and maintain the chain of custody between clinical and omic data.

Genedata Profiler allows NGS, mass spectrometry data and digital pathology research data to be translated into clinical practice, producing data reports in CDISC SDTM-PGx format that are ready for submission to regulatory authorities. The software incorporates processes to ensure security in the highly regulated environment of clinical trials, and its method lifecycle management includes checks to ensure data quality:

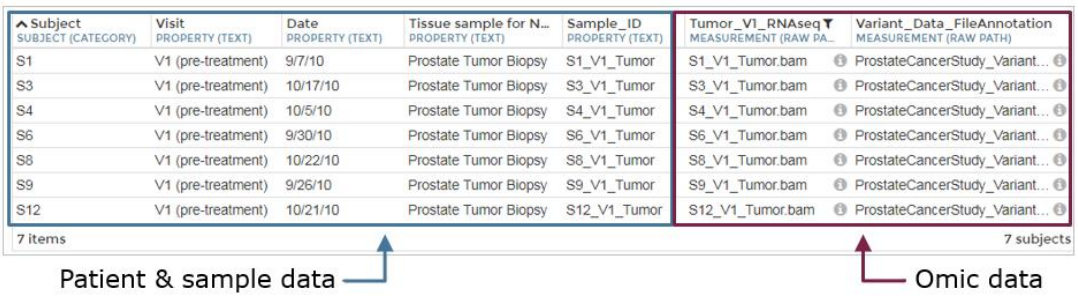
- data analysis workflows, including version and access control, are standardized throughout the organization;
- research workflows can be easily transferred and locked down for clinical use;
- quality control and auditability are ensured with a visual "traffic light" system and detailed quality reports and metrics (Figure 6).

		Name	Quality	Quality (Paired Samples)	Factor
1	☑	sample1			Pho4
2	☑	sample2			Pho4
3	☑	sample3			Pho4
4	☑	sample4			WT
5	☑	sample5			Pho4
6	☑	sample6			Pho4
7	☑	sample7			WT

Sample	Overall QC	Mapping Quality
sample1	Pass	60
sample2	Pass	60
sample3	Pass	60
sample4	Warn	60
sample5	Pass	60
sample6	Pass	60
sample7	Fail	60
sample8		

Figure 6: Sample quality classification and reported metrics in Genedata Profiler are shown in a "traffic light" format.

Figure 5: Genedata Profiler integrates and analyzes subject data from multiple sources and maintains the links between all data.



Subject SUBJECT (CATEGORY)	Visit PROPERTY (TEXT)	Date PROPERTY (TEXT)	Tissue sample for N... PROPERTY (TEXT)	Sample_ID PROPERTY (TEXT)	Tumor_V1_RNAseq MEASUREMENT (RAW PA...	Variant_Data_FileAnnotation MEASUREMENT (RAW PATH)
S1	V1 (pre-treatment)	9/7/10	Prostate Tumor Biopsy	S1_V1_Tumor	S1_V1_Tumor.bam	ProstateCancerStudy_Variant...
S3	V1 (pre-treatment)	10/17/10	Prostate Tumor Biopsy	S3_V1_Tumor	S3_V1_Tumor.bam	ProstateCancerStudy_Variant...
S4	V1 (pre-treatment)	10/5/10	Prostate Tumor Biopsy	S4_V1_Tumor	S4_V1_Tumor.bam	ProstateCancerStudy_Variant...
S6	V1 (pre-treatment)	9/30/10	Prostate Tumor Biopsy	S6_V1_Tumor	S6_V1_Tumor.bam	ProstateCancerStudy_Variant...
S8	V1 (pre-treatment)	10/22/10	Prostate Tumor Biopsy	S8_V1_Tumor	S8_V1_Tumor.bam	ProstateCancerStudy_Variant...
S9	V1 (pre-treatment)	9/26/10	Prostate Tumor Biopsy	S9_V1_Tumor	S9_V1_Tumor.bam	ProstateCancerStudy_Variant...
S12	V1 (pre-treatment)	10/21/10	Prostate Tumor Biopsy	S12_V1_Tumor	S12_V1_Tumor.bam	ProstateCancerStudy_Variant...

Genedata Profiler is the single enterprise software system offering a complete solution to the challenges of integration and analysis of multi-omic data in clinical trials (Figure 7), and like all Genedata products, may be operated in the cloud, offering scalable compute-on-demand flexibility to precision medicine research teams.

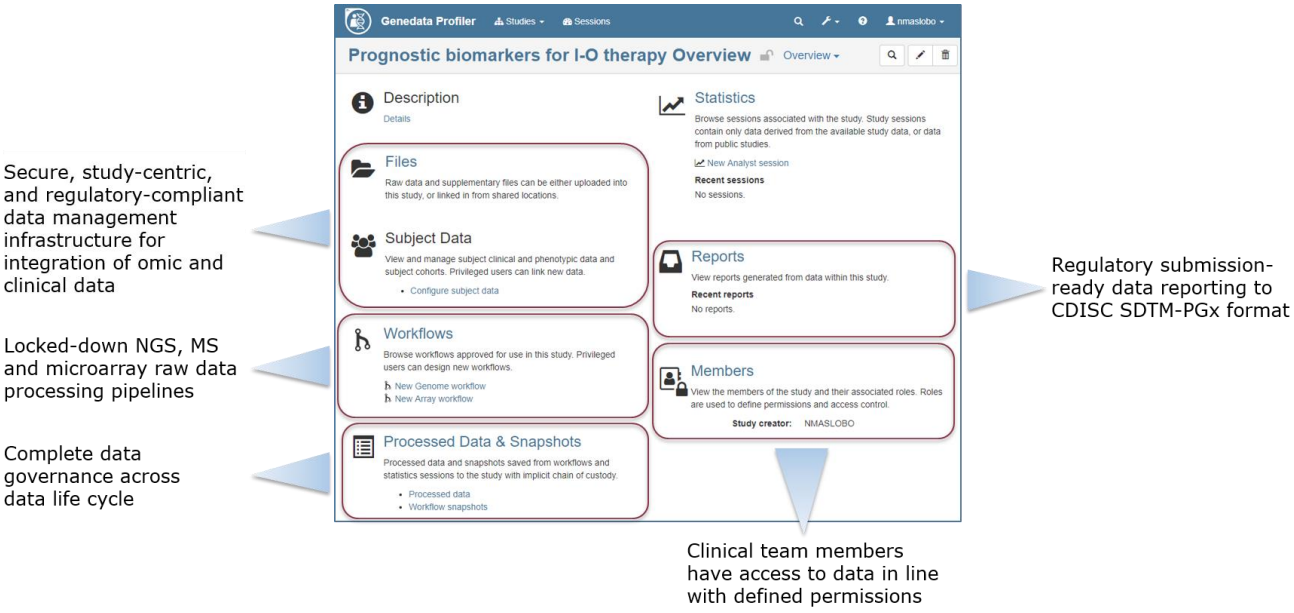


Figure 7: Genedata Profiler meets the challenges of integrating multi-omic data in clinical trials.

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