Genomate®

DELIVERING ON THE TRUE PROMISE OF PRECISION ONCOLOGY

Evidence-based precision oncology requires reproducible, evidence-based computational solutions that are capable of capturing the large amounts of data presented by complex tumor molecular profiles. Only 14% of NGS tests report an FDA-approved biomarker, and 50% of those harbor co-occurring genetic alterations that make them resistant to the matching molecularly targeted therapy.

Now, we can identify the genetic cause of cancer in 95% of patients, and a vast amount of scientific literature exists about the biological role of these genetic alterations. Although large curated evidence knowledge bases exist, personalized treatment decisions based on multiple parameters and multiple pieces of evidence are subjective and non-reproducible.

To make the true concept of precision oncology clinically feasible, safe, and evidence-based, we need a new class of medical tools: validated and reproducible computational reasoning model-based AI-guided drug assignment tools. That's why Genomate Health has developed its flagship product, the Genomate® Digital Drug Assignment (DDA) system, the first clinically validated computational reasoning system for precision oncology.

Retrospective analysis of SHIVA01's clinical data demonstrated that patients who received a molecular targeted therapy supported by DDA had a fourfold higher disease control rate than patients who received therapies not recommended by the model.

Precision oncology represents a paradigm shift in cancer treatment, aiming to tailor therapies to the unique molecular characteristics of each patient's tumor. By targeting specific genetic mutations or biomarkers driving cancer growth, precision oncology offers the potential for more effective and less toxic treatments.

Despite significant advancements, precision oncology's full potential has yet to be realized. Challenges such as non-utilization of most of the molecular data provided by comprehensive tumor molecular profiling, heterogeneity and inconsistencies of variant databases, low concordance rate of recommendations by different Molecular Tumor Boards (MTBs), and limited access to the expertise provided by MTBs in remote regions and nonacademic centers persist, highlighting the need for innovative solutions to overcome these obstacles.

"With the help of DDA, we can base our decisions on multiple parameters and rare alterations, making the next step toward the full implementation of the concept of precision oncology."

Prof. Dr. Christophe Le Tourneau,
Head of Phase I Unit. Institut Curie, Paris
Principal investigator of SHIVA01, the world's first randomized trial in precision oncology

INTRODUCTION TO PRECISION ONCOLOGY

The concept of precision oncology has its roots in the discovery of oncogenes and tumor suppressor genes in the latter half of the 20th century. It gained momentum with the completion of the Human Genome Project in 2003, which provided a blueprint of the human genome and paved the way for personalized therapies.

The rise of high-throughput sequencing techniques, such as next-generation sequencing (NGS), has enabled comprehensive profiling of tumors at the molecular level, revealing the genomic alterations driving cancer progression. This wealth of genomic data has fueled the development of targeted therapies designed to exploit specific vulnerabilities in cancer cells.

Precision oncology represents a paradigm shift from a one-size-fits-all cancer treatment to a more personalized and targeted approach. By integrating genomic data, clinical information, and computational algorithms, precision oncology enables oncologists to tailor treatment strategies to the unique molecular characteristics of each patient's tumor.

CHALLENGES IN PRECISION ONCOLOGY

Precision oncology entails assigning molecularly targeted treatment to cancer based on the individual genetic alterations of the tumor.[1–3] This concept offers causal therapy by directly interfering with the biological mechanisms underlying tumorigenesis. To this end, the tumor molecular profile, comprising a suite of genetic variants, is revealed by molecular diagnostic testing.[4–8] The need for appropriate variant interpretation based on literature mining has been addressed by the establishment of Molecular Tumor Boards, thus incorporating molecular biologists and geneticists into the clinical decision-making process.[9–16] Expert variant interpretation can be both expensive and time-consuming. To facilitate the process, the current paradigm heavily relies on variant databases to classify the pathogenicity of individual alterations.

The data collected in these knowledge bases vary depending on their final scope, ranging from pre-clinical biological and functional data for translational research applications (e.g., The Cancer Genome Atlas (TCGA), International Cancer Genome Consortium (ICGC), The Jackson Laboratory Clinical Knowledgebase (CKB)) to updated evidence on the clinical benefit obtained from matched drugs that can be used to drive variant-specific treatment recommendations (e.g., OncoKB, MyCancerGenome, CIViC). Other sources are specifically focused on passenger variant curation (e.g., dbCPM). However, one of the major downsides of having multiple knowledge bases is the dispersion of genomic information. In addition, the existence of independent resources with different curators and scopes can lead to inconsistent or incomplete data collection on variants across platforms and to different format presentations and nomenclature, which can generate knowledge gaps and thus hamper the interpretation of variant actionability.[17]

Besides inconsistencies in data collection, the underlying literature can also present inconsistent data due to the complex nature of biological systems, necessitating a comprehensive interpretation approach capable of aggregating various types of evidence. Consequently, there is substantial variability in the pathogenicity assessment of NGS variants and treatment decisions based on molecular markers in solid tumors by annotation services.[18,19]

A key issue identified in using tumor genetic profiling to inform disease management is the prioritization of genetic aberrations by potential impact and contraindications of simultaneously detected aberrations.[13] Accordingly, a recent comprehensive analysis revealed that cancer genomes typically contain 4-5 driver mutations.[20] The current practice of molecular profile interpretation mainly focuses on finding "actionable" mutations or biomarkers associated with specific therapies regardless of the full complexity of the profile.

Nevertheless, it is increasingly evident that the simple assignment of a targeted agent to an actionable mutation results in limited benefit in the majority of patients because of the complexity of the tumor genome.[21–24]

As a consequence of the issues associated with interpreting complex molecular profiles, treatment recommendations provided by Molecular Tumor Boards (MTB) seem to vary widely. A comparison of five independent MTBs from four countries revealed that only two of five MTBs provided similar recommendations for four fictional cases with complex mutational profiles. 25 Similarly, MTBs from twelve cancer institutes in Japan independently recommended a treatment for 50 cases resulting in an adjusted concordance rate of 62%.[26] Moreover, a comparison of the clinical interpretation of high-dimensional molecular data (i.e. WES and RNA-seq) for 46 patients by two MTBs in Germany revealed an overall agreement rate of 44.1%,[27] indicating that more comprehensive tumor molecular profiles present greater challenges in interpretation. Besides, limited access to the expertise provided by MTBs in remote regions and nonacademic centers is another challenge for implementing an evidence-based organizational approach.[28]

Computerized solutions can potentially address the above issues. In fact, the need to incorporate refined computer programs into therapeutic decision-making by molecular tumor boards was already recognized in 2014[14], and their emergence has been anticipated by key opinion leaders.[21,29]

EXPLAINABILITY OF GENOMATE®

Training and testing deep-learning-based artificial intelligence (AI) in the domain of precision oncology is hindered by limitations of appropriate training data, training expertise, experimentation, and simulations.[30] Moreover, the black-box problem of ML systems is a cause for caution; explainability in medicine has a special relevance.[31] A recent study investigating the perspectives of oncologists on the ethical implications of using artificial intelligence for cancer care found that 84.8% of US oncologists reported that AI needs to be explainable by oncologists.[32]

Genomate® is a universal computational reasoning model based on the functional knowledge ("what we already know") available from published experimental data. It uses a network of functional associations connecting mutant driver genes harboring molecular alterations detected by molecular diagnostic tests used in clinical practice (such as SNVs, CNVs, gene/protein expression, tumor mutation burden (TMB), microsatellite instability (MSI)) and druggable targets, MTAs, and tumor type (localization and histology), based on published peer-reviewed evidence (PubMed). Reasoning models are transparent, open-box systems and provide consistent results, where all computational steps and the underlying knowledge used, leading to a specific result, can be retrieved. Thus, the Genomate® system is a fully explainable AI tool providing reproducible results.

THE SCIENTIFIC VALIDATION OF GENOMATE®

SHIVA01 was the first prospective, randomized precision oncology trial. It compared targeted therapies based on tumor molecular profiles vs. chemotherapy treatment by physician's choice.[33] In the experimental arm, patients with diverse types of metastatic cancer that had failed standard-of-care treatment were treated with 11 MTAs, selected following a predefined treatment algorithm according to molecular alteration – MTA pairs. The treatments were selected by the Molecular Tumor Board of Institute Curie, Paris, France. Of the 195 randomized patients, 170 were treated with MTAs, based on SNVs in 50 genes and CNVs in 24 genes by NGS and expression level of three hormone receptors by IHC (including patients after crossover from the chemotherapy treatment arm). Interestingly, the trial was negative for its primary endpoint: there was no significant difference in PFS between the MTA and control arms.

To evaluate the performance of the Genomate® Digital Drug-Assignment (DDA) system, we first processed tumor molecular profiles from SHIVA01, generating individual scores for the drugs received by each patient based on the tumor molecular profile. Then, the relation between the specific drug scores and the efficacy of the corresponding treatments was analyzed. Both outcome data and complete molecular profiles were available for 113 patients.

Overall, 56% of patients responded to personalized therapy, which was a promising result but not better than chemotherapy used in the other arm of the trial. Our results demonstrated that patients treated with therapies supported by Genomate® achieved a 69% benefit rate, better than chemotherapy, while therapies that were indicated to fail achieved only a 17% response rate. Similarly, the mPFS was significantly longer in patients treated with therapies supported by Genomate® than in the patient group indicated to fail.[34] These results demonstrated the clinical predictivity of Genomate. They indicated improved decision by processing the full tumor

molecular profiles provided by clinically used NGS tests, instead of searching for "actionable" alterations.

Besides validating the system by reanalyzing the data of SHIVA01, a large portfolio of validation data sets is analyzed to underscore the predictivity of Genomate® further. These include data from additional clinical trials, RWD, and even preclinical data sets. Two studies describing our results in lung cancer will be presented at ASCO24 (abstracts will be available after May 23, 2024):

- **Algorithmic precision in immune checkpoint therapy response prediction for lung cancer: Evaluating the Digital Drug Assignment model's clinical performance.**
  Vodicska B, et al., https://meetings.asco.org/abstracts-presentations/232329
- **Real-world performance of the digital drug-assignment system for precision oncology in lung cancer.**
  Dirner A, et al., https://meetings.asco.org/abstracts-presentations/237182

More publications highlighting Genomate® results:

- **Lasting Complete Clinical Response of a Recurring Cutaneous Squamous Cell Carcinoma With MEK Mutation and PIK3CA Amplification Achieved by Dual Trametinib and Metformin Therapy.**
  Remenár É et al., JCO Precis Oncol. 2022 Jan;6:e2100344. doi: 10.1200/PO.21.00344. PMID: 35005996. https://pubmed.ncbi.nlm.nih.gov/35005996/
- **Personalized First-Line Treatment of Metastatic Pancreatic Neuroendocrine Carcinoma Facilitated by Liquid Biopsy and Computational Decision Support.**
  Szkukalek J et al., Diagnostics (Basel). 2021 Oct 7;11(10):1850. doi: 10.3390/diagnostics11101850. PMID: 34679548; PMCID: PMC8534772. https://pubmed.ncbi.nlm.nih.gov/34679548/
- **Real-world performance analysis of a novel computational method in the precision oncology of pediatric tumors.**
  Vodicska B, et al., World J Pediatr. 2023. https://pubmed.ncbi.nlm.nih.gov/36914906/

REAL-LIFE IMPACT OF GENOMATE®

Szkukalek et al., Personalized First-Line Treatment of Metastatic Pancreatic Neuroendocrine Carcinoma Facilitated by Liquid Biopsy and Computational Decision Support

In this case study, we presented the case of a 50-year-old female whose metastatic pancreatic neuroendocrine tumor (pNET) diagnosis was delayed by the COVID-19 pandemic. The patient was in critical condition at the time of diagnosis due to the extensive tumor burden and failing liver functions. The clinical dilemma was to choose between two registered first-line molecularly-targeted agents (MTAs), sunitinib or everolimus, or to use chemotherapy to reduce tumor burden quickly.

Cell-free DNA (cfDNA) from liquid biopsy was analyzed by next-generation sequencing (NGS) using a comprehensive 591-gene panel. Genomate® processed the molecular profile for rapid clinical decision support. Everolimus was chosen for first-line therapy based on supporting molecular evidence and the highest DDA ranking among therapies registered in this tumor type. The patient's general condition and liver functions rapidly improved, and CT control revealed partial response in the lymph nodes and stable disease elsewhere.

Remanar et al., Lasting Complete Clinical Response of a Recurring Cutaneous Squamous Cell Carcinoma With MEK Mutation and PIK3CA Amplification Achieved by Dual Trametinib and Metformin Therapy

In this case study, we presented the case of a 70-year-old man with cutaneous squamous cell skin cancer (cSCC) in his right retroauricular region, which recurred aggressively despite repeated surgery and irradiations. Although initial chemotherapy provided transient disease control, gradual disease progression ensued. Tumor molecular profiling revealed, among other alterations, a PIK3CA amplification and an activating MEK1 mutation.

The Genomate® system ranked the MEK inhibitor trametinib as of the highest relevance. Based on the recommendation of the molecular tumor board, metformin plus trametinib combinational therapy was initiated, resulting in a rapid and dramatic tumor response. The tumor clinically disappeared after only one month into the therapy, and complete remission was consequently confirmed by checkups and imaging diagnoses until publication, for about three years.

CONCLUSIONS

Genomate® is the world's first clinically proven computational solution that enables AI-based personalized cancer therapy. It matches targeted therapies to the totality of available molecular information for each patient. By considering 100% of each cancer's mutations simultaneously, Genomate® offers personalized treatment recommendations that optimize patient outcomes:

- **improves therapeutic outcomes**
- **reduces unpleasant side effects**
- **provides better access to targeted therapies**
- **and much more.**

The system is inherently designed to seamlessly integrate emerging diagnostic biomarkers as they gain traction in clinical settings, such as DNA methylation, mutational signatures, RNA signatures, and beyond. As molecular profiling becomes more comprehensive, the volume of data will inevitably surge, posing significant challenges in interpretation and treatment planning. However, our computerized solutions are poised to tackle these issues head-on, offering scalability and adaptability to accommodate the evolving landscape of medical advancements. With our platform, healthcare professionals can confidently navigate the complexities of big data, ensuring optimal patient care and treatment outcomes.

Genomate® operates within the ethical framework of AI augmentation, with the understanding that it does not replace the expertise of medical professionals or the necessity of medical advice. It is a valuable tool for medical professionals and MTBs to make faster and more informed medical decisions.

Join the movement toward a future where every patient recieves the right drug. The first time. Every time.

Genomate®

Learn more about how Genomate's AI-powered precision oncology can be used to help inform your patient's treatment plan at info@genomate.health

More information: www.genomate.health

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