Computer-Assisted Treatment Decision in Precision Oncology

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Innovation in Precision Oncology:
Genomate Health – A European Tech Spin-out in the US

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2003: Foundation of a precision oncology company (Budapest, Hungary)

2005: One of the first successful targeted therapies in lung cancer*

2008: Introduction of NGS into molecular testing

2016: Introduction of the first version of a digital drug assignment system

2021: First clinical validation of the system**

2023: Foundation of the spin-out (Boston, MA, USA)

*J Clin Oncol. 2005 23(30):7736-8.

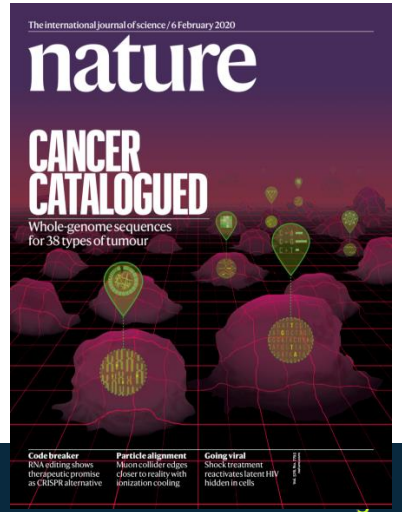
**NPJ Precis Oncol. 2021 5(1):59.

Precision Medicine in Oncology

May 28, 2001

- Assigning molecularly targeted treatment to cancer, based on the **individual genetic alterations of the tumor**. **Causal therapy**, directly interfering with the biological mechanisms underlying tumorigenesis.
- The current practice mainly focuses on finding "actionable" mutations or biomarkers associated with specific therapies regardless of the full complexity of the profile.
- Potential impact and contraindications **of simultaneously detected alterations are usually not considered.**

Feb 05, 2023



- Cancer genomes typically contain **4-5 driver mutations.***
- **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.**

*Nature. 2020 578(7793):82-93.

**e.g. Cancer J. 2019 25(4):300-4; J Clin Oncol. 2020 38(33):3883-94; JCO Precis Oncol. 2018 2018:10; Ann Oncol. 2022 33(2):143-157.

Highly discordant treatment recommendations by Molecular Tumor Boards

- Comparison of **5** independent MTBs (4 countries)*
- **4** fictional cases with complex mutational profiles
- **only 2 of 5 MTBs provided similar recommendations**

- MTBs from **12** cancer institutes (Japan)**
- independently recommended a treatment for **50 cases**
- **adjusted concordance rate of 62%**

- Comparison of the clinical interpretation of high-dimensional molecular data by **2** MTBs (Germany)***
- **46** patients (WES and RNA-seq)
- 51,610 aberrations (median, 393 per patient)
- **overall agreement rate: 44.1%**

An interpretation, drug assignment crisis?

*JCO Precis Oncol. 2018 2:1-14. **Ann Oncol. 2021 32:5 _suppl: S588-S589 ***J Clin Oncol. 2020 38:15_suppl: 3564-3564

A solution in the future?

REVIEW ARTICLE

Future Approaches to Precision Oncology–Based Clinical Trials

Arjun Mittra, MD, and Jeffrey A. Moscow, MD†*

Abstract: The last 2 decades have seen a rapid advance of the precision oncology paradigm—from its early singular successes to becoming the prevailing model of cancer therapy. As the treatment of cancer moves away from traditional chemotherapy, so too will oncology clinical trials have to move away from the traditional model of phase I to phase III progression of drug development. Achieving this goal of individualized care will involve a concerted effort by the entire cancer care community to fundamentally change the design and implementation of oncology clinical trials. We envision that the next 2 decades will be a period of evolution in precision oncology clinical trials through scientific and technologic advances, transformation of clinical trial infrastructure, and changes in the kind of evidence required for regulatory approval.

Key Words: Clinical trial design, ePRO, precision medicine, precision oncology

(*Cancer J* 2019;25: 300–304)

”It is the year 2039”

It is the year 2039, and a young woman with non-Hodgkin lymphoma first learns of her diagnosis. This diagnosis was made through an annual blood test that she obtained at her local pharmacy. The test separates multiple blood components, performs an initial screen, and then reflex tests for hundreds of medical conditions using the various components based on initial screening to her and her disease characteristics. However, although the treatment would be personalized exactly to the molecular features of the cancer and her body's ability to metabolize the drugs, he really could not tell her with any certainty what the chances of a successful treatment would be for her, or what the chances would be that she would have a significant ill effect of the treatment plan, because her treatment plan may be a relatively unique prescription.

Our patient chooses the personalized, precision medicine clinical trial. As the first step on this study, she has another blood sample drawn, which is subject to an extensive high-throughput molecular, epigenetic, and phenotypic testing, carried out from her circulating tumor cell characterization and circulating tumor DNA (ctDNA). Her digitized imaging data and germline pharmacogenomic profile are also entered into a research database to be analyzed by an artificial intelligence (AI) system.

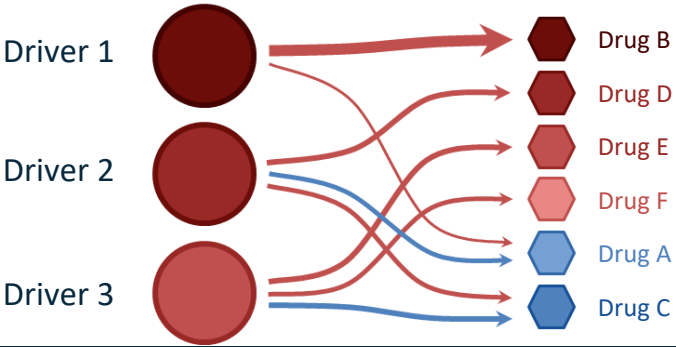
The patient and doctor review the informed consent. They are happy to learn that there are no specific treatment arms, as all patients are receiving a personalized therapy plan. The study is not comparing one drug against another, or even one regimen against another. Rather, it will compare one AI-based treatment assignment algorithm against another. Both proprietary algorithms were devised by an AI algorithm from private international databases of the clinical experience of millions of patients, the molecular char-

”The study …will compare one AI-based treatment assignment algorithm against another”

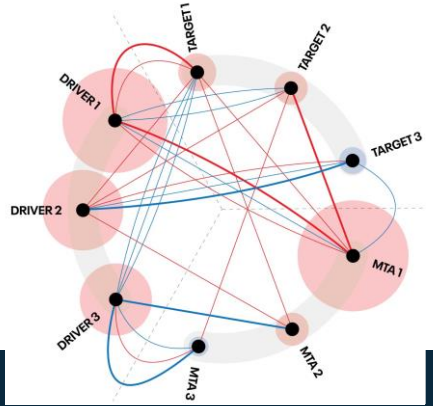
Mittra, A. & Moscow, J. A. Future approaches to precision oncology-based clinical trials. Cancer J. 25, 300–304 (2019).

From single associations to evidence network

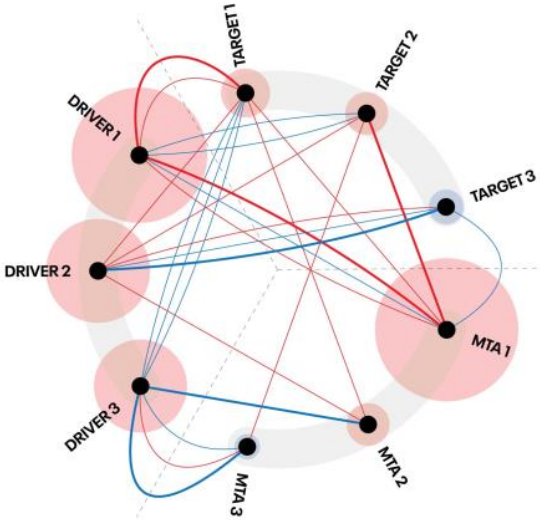
Current paradigm

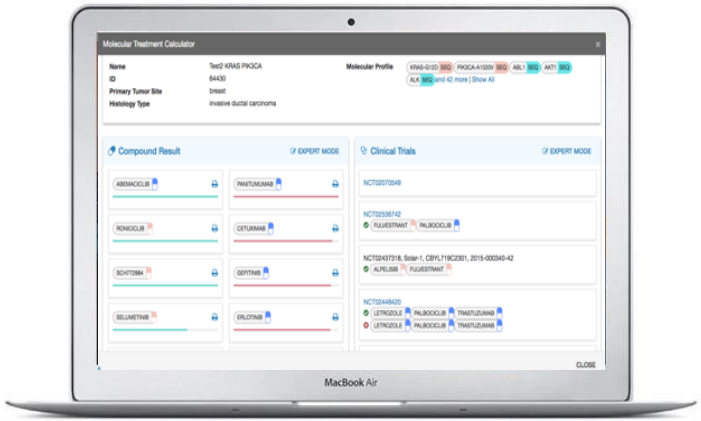


A computable network of evidence associations
for each individual molecular profile



AI-based (automated evidence-based reasoning framework) SaMD for precision oncology





Built on experience with **10,000+ cases**

Linking

- **700+ driver cancer genes** to
- **600+ molecularly targeted agents (MTA)** with
- **34,000+ evidence relations**

CLINICAL VALIDATION

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sebastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators

Lancet Oncol 2015

Published Online
September 3, 2015
http://dx.doi.org/10.1016/S1470-2045(15)00188-6

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(15)00224-7

SHIVA01, the first prospective, randomized precision medicine trial

- comparing **targeted therapy** based on tumor molecular profile **vs.** treatment by **physician's choice**
- patients with diverse types of metastatic cancer that had failed standard-of-care treatment
- **11 MTAs**, selected following a predefined treatment algorithm, molecular alterations–MTA pairs
- 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)
- both outcome data and complete molecular profiles were available for **113 patients**
- **negative for its primary endpoint**: no significant difference in PFS between the MTA and control arms

Lancet Oncol. 2015 16(13):1324-34.

CLINICAL VALIDATION

npj | precision oncology

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Article | Open Access | Published: 23 June 2021

A computational method for prioritizing targeted therapies in precision oncology: performance analysis in the SHIVA01 trial

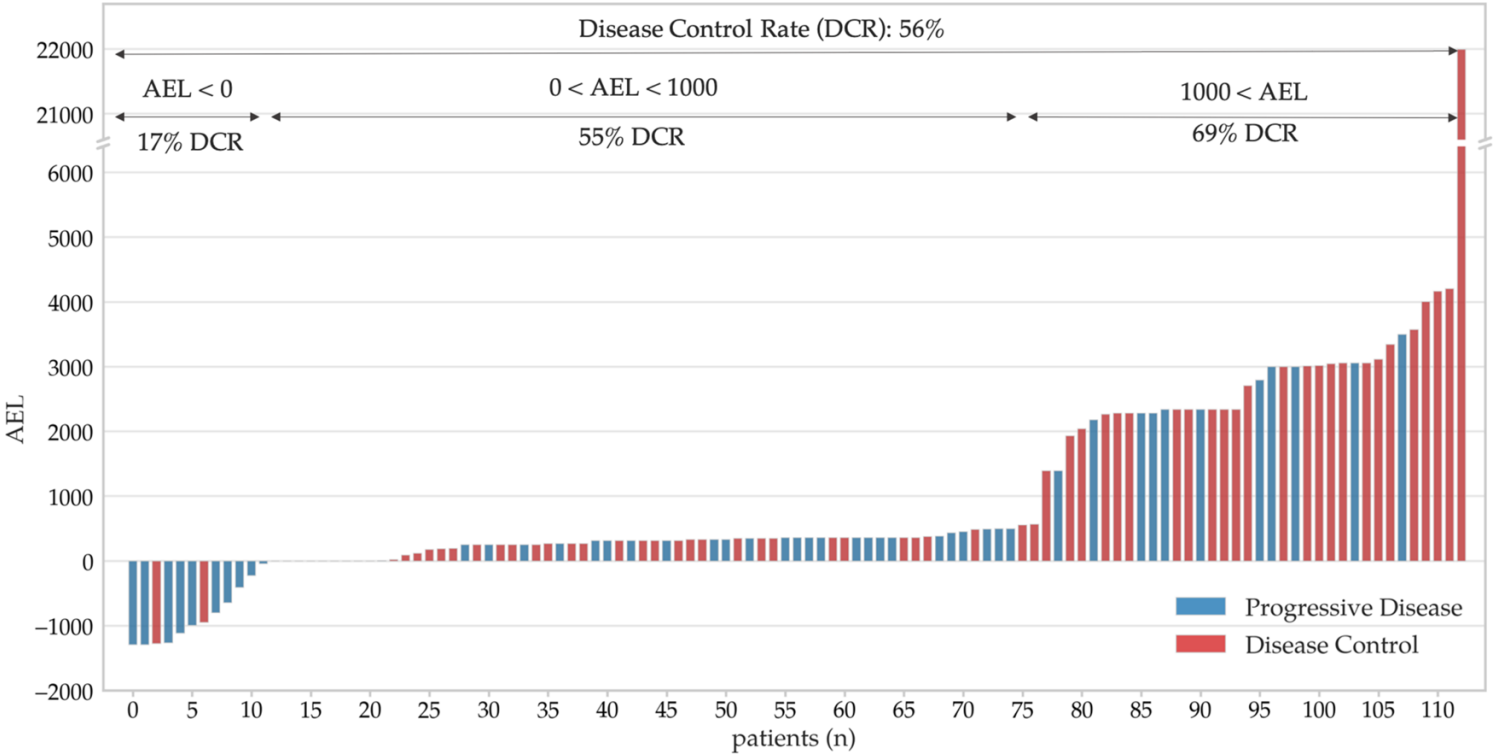
Istvan Petak ✉, Maud Kamal, Anna Dirner, Ivan Bieche, Robert Doczi, Odette Mariani, Peter Filotas, Anne Salomon, Barbara Vodicska, Vincent Servois, Edit Varkondi, David Gentien, Dora Tihanyi, Patricia Tresca, Dora Lakatos, Nicolas Servant, Julia Deri, Pauline du Rusquec, Csilla Hegedus, Diana Bello Roufai, Richard Schwab, Celia Dupain, Istvan T. Valyi-Nagy ✉ & Christophe Le Tourneau ✉

npj Precision Oncology **5**, Article number: 59 (2021) | Cite this article

- Molecular profiles of the 113 patients were uploaded into the DDA system
- DDA assigned an **AEL scores** to all MTAs used for **each patient** in SHIVA01

AEL: Aggregated Evidence Level, a **computed compound evidence score** according to the digital drug assignment system

CLINICAL VALIDATION – DDA score is predictive of clinical benefit



Summary

- At the detailed molecular level, **each tumor** can be considered as an **individual** disease type
- The **depth of molecular diagnostic tests** is rapidly increasing, just as the **number of approved and experimental targeted therapies**
- It is highly **challenging** to keep up with this pace of progress by constantly amending **guidelines**, making them overwhelmingly complex
- Personalized **MTB treatment recommendations** are highly subjective and **discordant**
- The amount of data and level of complexity requires **computational solutions**
- **DDA** aggregates and weights evidence in a relation network associated with the individual tumor molecular profile and **prioritizes dugs based on a computed score**
- Reanalysis of the SHIVA01 trial data demonstrated that **DDA score is predictive of clinical benefit**
- Further clinical and real-world validation studies are in the **Genomate pipeline**

International Innovation Awards, Recognition

American Society of Clinical Oncology

Breakthrough innovations (AI) in Oncology Conference Award 2019

Get In the Ring start-up competition

Global champion

(109 counties, 25,000 applicants)

2021

DIGITALEUROPE

Most promising technology company in Europe 2021

Mayo Clinic Platform_Accelerate

Selected as a partner company for the 2023 cohort

Thank you!

AI-powered precision oncology.
The right drug. The first time. Every time.