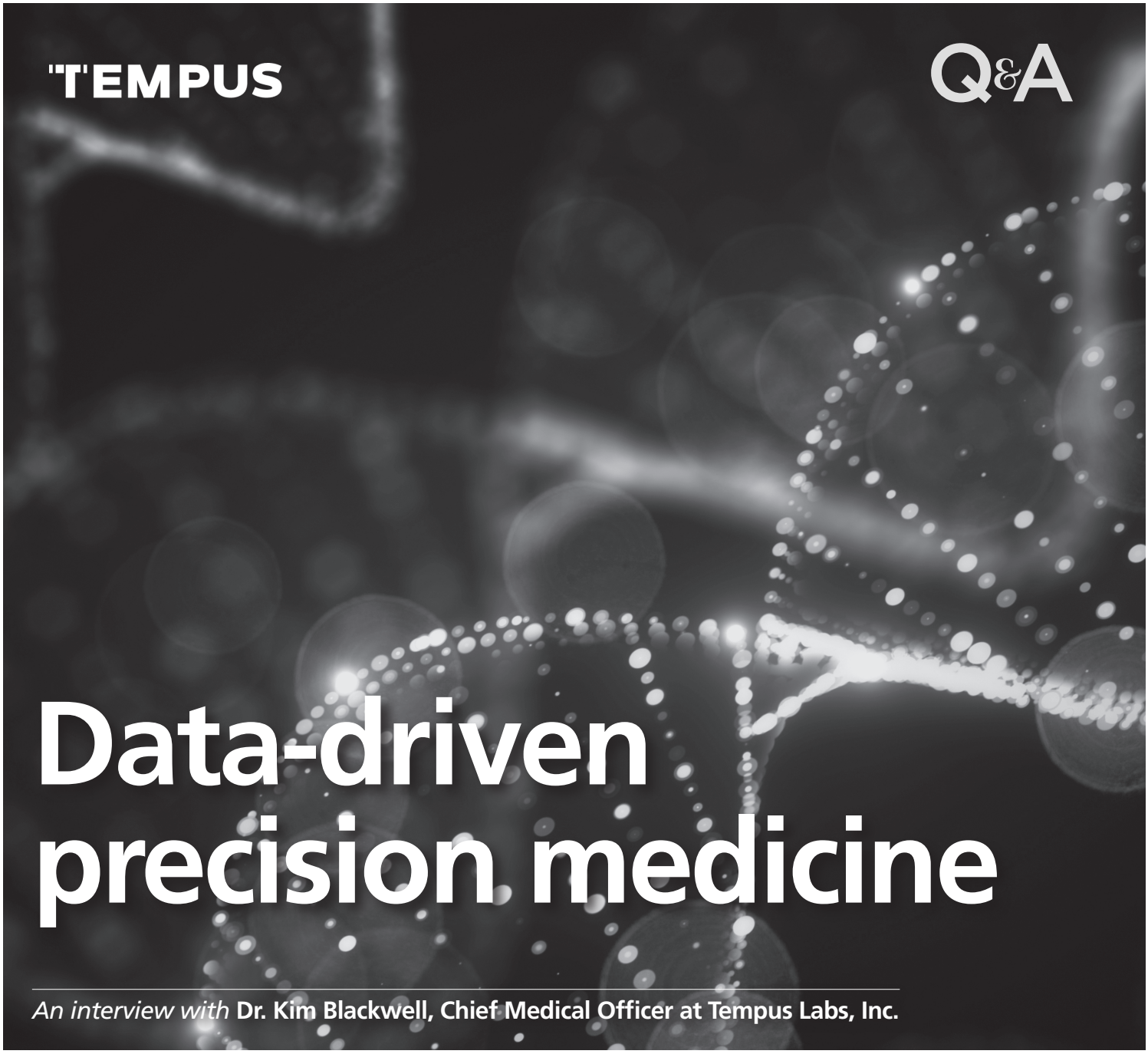


Data-driven precision medicine

An interview with **Dr. Kim Blackwell, Chief Medical Officer at Tempus Labs, Inc.**

Introduction

Over 75% of U.S. oncologists use NGS tests to guide treatment decisions. Of those oncologists, 29.1% reported to use NGS to determine eligibility for clinical trials (Freedman *et al.*, 2018). It is expected that this number will continue to rise. Further, a recent publication in Nature Biotechnology demonstrated comprehensive genomic analysis of clinical data and paired tumor-normal genomic data is capable of matching over 90% of cancer patients to targeted therapies and over 75% of patients to biomarker-based clinical trials (Beaubier *et al.,* 2019).

Given this increasing use of genomic and clinical data for developing or prescribing therapies, the need for large libraries of clinical and molecular data will grow apace. Of equal utility will be operating systems to make that data accessible to physicians for real-time, data-driven decisions to deliver personalized patient care. Many groups are now engaged in the discovery, development, and delivery of precision medicine options for physicians through distinctive solution sets.

One such company is Tempus, a precision medicine and artificial intelligence company. Tempus has a CAP/CLIA-certified next-generation sequencing (NGS) lab and advanced analytics platform capable of identifying biomarker targets. Leveraging integrated analyses of clinical and molecular data can help overcome some of the challenges of modernization. In 2019, Tempus launched its TIME Trial™ program to match patients to trials and bring those trials to them using a just-in-time activation model. This patient-centric program enables a trial site activation on behalf of an identified patient within two weeks (see Case Study).

Dr. Blackwell discusses Tempus and its robust and growing menu of offerings below.

Brief history and background on Tempus

Q. How does Tempus' approach, platform, data, and results differ from others in precision medicine and artificial intelligence?

A. Tempus has developed a platform to ingest and analyze data points across all major disease types, allowing us to derive personalized insights on patients. We leverage this data to empower our researchers, better characterize and understand diseases, and to drive better outcomes through precise, individualized care. Tempus also offers multiple services to pharma and biotech companies across the drug development process. We use our data, NGS assays, and partnerships across healthcare to support biomarker discovery, patient sequencing, clinical trial recruitment, and companion diagnostic development, making us the most comprehensive partner for pharma and biotech companies.

Generating and acquiring data, database design

Q. Data selection criteria and database design are critical to the quality of analysis, e.g., the types of questions and queries covered and the confidence in outcomes. Does Tempus build its database from public and client data, patient samples or both?

A. Tempus is differentiated from other private data sources in its ability to offer full multimodal data collected across the spectrum of oncology practices (academic and community) to be representative of the totality of cancer patients. Additionally, the Tempus de-identified database is complementary to and differentiated from publicly available data sources such as The Cancer Genome Atlas (TCGA) in its coverage of the patient stage. TCGA is focused on early-stage, treatment-naive tumors whereas Tempus is sequencing patients during the entirety of their cancer journey. Thus, the Tempus database provides coverage of late-stage patients, where most drug development efforts are focused, allowing teams to interrogate the effects of stage and prior treatments as well as understand the biology of non-primary lesions. Tempus also integrates de-identified data directly from ASCO's CancerLinQ dataset.

Q. What are Tempus' criteria for data selection and qualification? Please discuss how Tempus designs and/or selects its genomic (DNA, RNA) and proteomic data.

A. We designed our panels through a mix of inputs including business needs, clinician feedback, papers, National Comprehensive Cancer Network (NCCN) guidelines, druggable targets, open clinical trials, and other factors to provide comprehensive coverage for oncogenic pathways. This is achieved with a broad panel of genes, covering single-nucleotide variants (SNVs), insertions and deletions (INDELs), fusions and select gene rearrangements. At Tempus we strive to be best in class, and as a result we perform a tumor-normal DNA match to obtain high levels of specificity. Additionally, Tempus offers a full RNA transcriptome which we have shown to increase the likelihood of therapeutic targets versus DNA alone (Beaubier *et al*., 2019). Our databases are designed to ensure efficient analysis of this genomic data coupled with clinical information.

"At Tempus we strive to be best in class, and as a result we perform a tumor-normal DNA match to obtain high levels of specificity"

Q. Please provide background on how Tempus generates broad panel assays for recruitment in clinical trials and diagnosis; that is, how patients were matched to specific clinical trials (anonymized patients, trial name).

A. We believe that breadth and depth are fundamental to developing a comprehensive suite of assays. Tempus' broad panel assays include our 648 gene tissue assay (the xT assay), our 105 gene liquid biopsy assay (the xF assay), and our whole exome assay (the xE assay). We are also in the process of developing a novel minimal residual disease assay (MRD, the xM assay) to monitor disease recurrence via liquid biopsy and we have recently started to offer a germline assay (the xG assay).

Supporting pharma/biotech across the drug development process

Q. Tempus has a reputation as a healthcare technology company, but recently started working with pharma/biotech. What services does Tempus provide to these companies?

A. Tempus provides three core services to pharma/biotech: 1) Sequencing; 2) Real-World Data; 3) Trial Matching. Tempus sequences for clinical trials both retrospectively and prospectively. We have three core NGS assays that support trial recruitment and companion diagnostic development. On the data side, Tempus has been generating a massive clinical-genomic dataset that can be leveraged to answer biopharma research questions across the development life cycle, by bringing together de-identified clinical data, molecular data, and imaging data with our analytic tools and services. Finally, through the clinical and molecular data we are generating in the clinic, we are able to use that data to accurately match patients to clinical trials, reducing testing at large to find patients.

Q. What is it about your pharma offerings which differentiates you from the competitors?

A. Tempus has focused on generating RNA data, collecting germline DNA, and immuno-profiling from day one, which has allowed us to build a robust dataset for biopharma to use for research, and has allowed us to maintain a lead in the market on these capabilities. This all comes together to benefit our sequencing, data products, and ability to match to trials accurately.

Q. Tempus is moving towards becoming a companion diagnostic provider. Can you speak more to the strategic decision here and what Tempus' approach will be to CDx development and commercialization?

A. Tempus has built relationships with over 6,000+ oncologists in the United States and increasingly, these services have been ordered globally. Through the relationships we have built with oncologists, we believe that we can leverage that commercial advantage to be widespread and ensure that patients can access and physicians order companion diagnostics. In addition, Tempus' advantages in RNA, cfDNA and Immunotherapy allow us to play in areas of CDx development that others in the market cannot.

Tempus leverages both artificial intelligence (AI) and machine learning (ML)

Q. Could you please explain how Tempus differentiates between AI and ML in the context of its platform – e.g., decision making (AI) vs data classification (ML)?

A. In its original definition, "AI" refers to systems that look as if they had intelligence (in the 70s that

could have been an ATM machine), whereas "ML" refers more specifically to algorithms that can learn from data. In the past 4-5 years, however, the two terms have been used very interchangeably in the industry, and we have adopted that as well in our terminology. None of our algorithms are doing actual clinical decision making, although in low-risk operational settings (e.g., document routing for abstraction), we do use ML systems to de facto make decisions about which documents should be seen by abstractors with priority.

Q. Explain how Tempus leverages AI and algorithms to provide more value to panels? For example, are the panels selected by the AI programs and algorithms more flexible and robust to allow more comprehensive testing? Are these panels able to tease out finer differentiation at the individual level?

A. Great question. ML was used to optimize some operational parameters, such as thresholds, for some panels, and we have also used it to try to identify what sample parameters are indicative of sequencing success or failure, tumor percentage, and how much tissue needs to be scraped etc. In addition, some of our tests like Tumor Origin (TO) and Homologous Recombination Deficiency (HRD) use ML on top of our sequencing data to generate clinically actionable insights that are used by providers for diagnosis and treatment decision making.

Q. On its website, Tempus highlights importing and organizing unstructured data to understand the clinical context for each patient case. Do these datasets include EHR/EMRs, too? Are these EHR/EMR datasets integrated with genomic, proteomics, and clinical data, or do they provide for a separate, parallel report?

A. Internally, from the technical side, we use ML to structure information both from clinical notes as well as information from EHRs. We are prioritizing full data integration with EMRs so that clinical data can be updated as necessary. We also bring that data together internally with genomic and imaging data. Tempus has a secure clinical portal which provides a report incorporating relevant clinical, genomic and imaging data for each sequenced patient,

CASE STUDY – TIME Trial

A biopsy sample from a patient with colorectal cancer being treated at an academic center was sequenced and analyzed using Tempus' xT assay. A clinically actionable gene fusion was reported, and an open biomarker-based clinical trial was identified through the TIME Trial™ program. Using Tempus' referral network, a notification was sent to the treating physician that a nearby TIME site could open up the trial. Tempus connected the referring physician to the TIME site's principal investigator (PI) to discuss the potential trial for that patient. The patient's records were then transferred, and the patient had an initial consult visit with the PI. After the consultation, the decision was made that the best treatment option for this patient was the TIME trial. The timeline from when the Tempus xT report was delivered to the primary physician until the patient's consult visit at the TIME site was 10 business days (**Figure 1**).

The Rapid Activation Request was completed by the TIME site's PI and the TIME trial sponsor. This action represents Day 1 of the rapid activation timeline. The pre-negotiated CTA and budget exhibit were executed on Day 2. It was quickly noted that the patient's insurance was not accepted at the TIME site. The sponsor and site agreed to an all-inclusive budget for study procedures that were not covered by the patient's insurance. The CTA and budget were executed accordingly within a day. The site-specific CIRB submission was approved by Advarra within 48 hours of submission (Day 5). This approval process was expedited because the site strictly adhered to the ICF template and onboarding process. By the end of the first week, the site had completed all essential documents and submitted them to the CRO. The essential documents were completed and approved by the CRO prior to the site initiation visit (SIV). This also resulted in the approval to release investigational products (IP). The SIV was conducted remotely on Day 8 due to COVID-19 travel restrictions. After the SIV, all activation items were completed, and the site activation letter was sent the following morning. The total time from the receipt of the Rapid Activation Request to the clinical trial site activation was 9 business days (**Figure 2**). The patient consented and completed all screening procedures four days following activation.

Lastly, this TIME site was activated in the midst of the coronavirus (COVID-19) pandemic. Several actions were taken to accommodate the changing clinical trial landscape at this time. For example, an initial feasibility assessment was conducted to evaluate the site's remote monitoring capabilities. Telemedicine was utilized to conduct the initial consult visit at the TIME site and was investigated as an option for any future study visits to limit the patient's public exposure. Documents were routed to the PI/sponsor for signature via DocuSign. All these actions supported the rapid site activation timelines and patient safety during the COVID-19 pandemic restrictions.

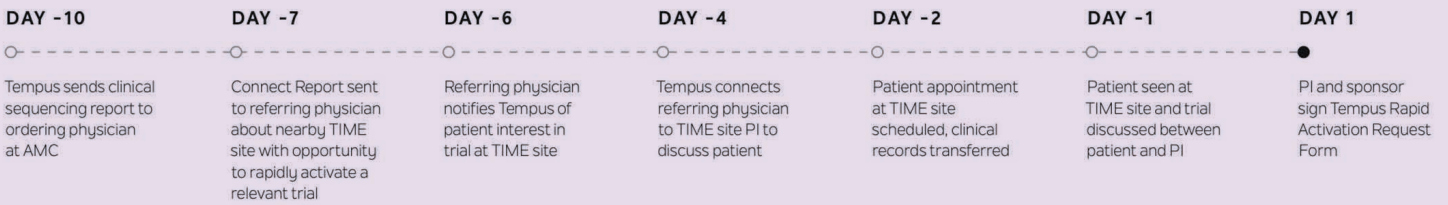


Figure 1: TIME Patient Pre-screening and Referral Process - Case Study Timeline: Timeline showcases Tempus' xT report delivery to the referring physician up through the rapid activation request at the TIME site. The patient was identified as a potential candidate, referred, and consulted within 10 business days.

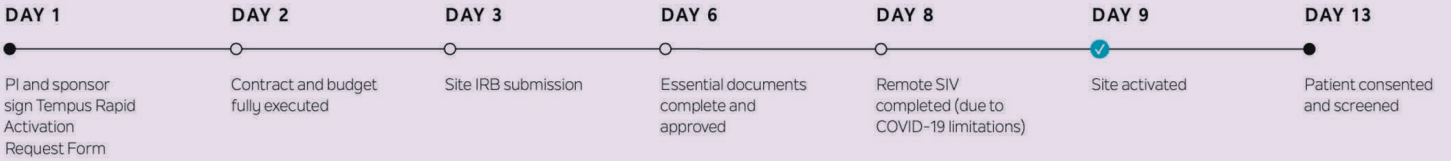
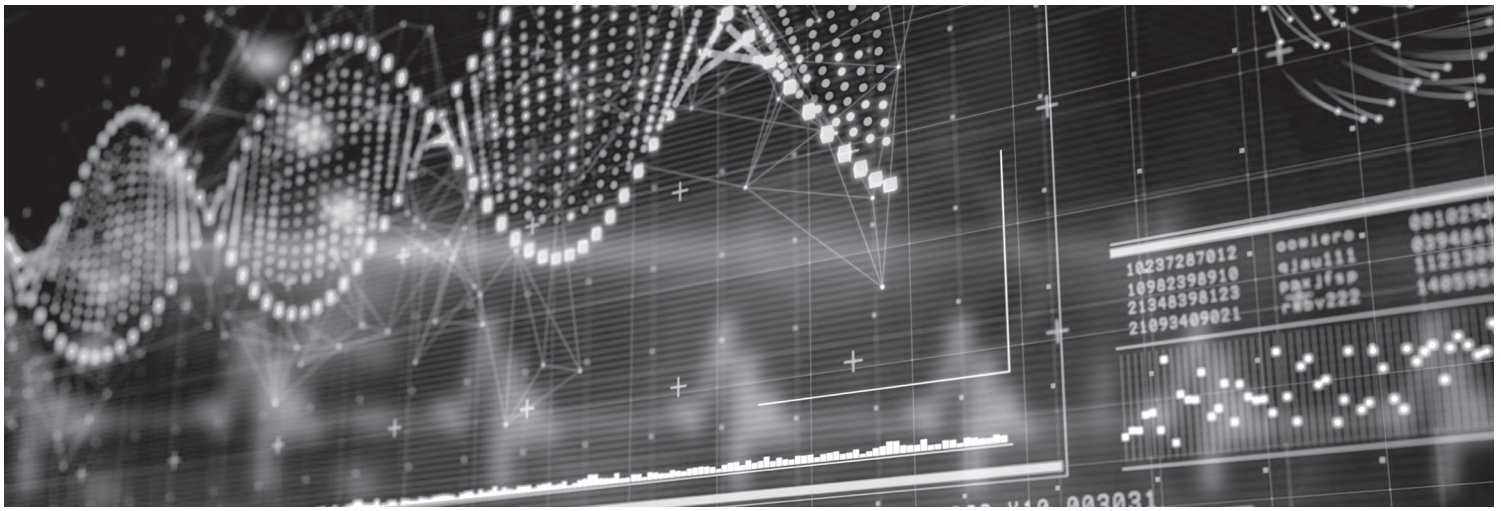


Figure 2: TIME Rapid Activation Process - Case Study Timeline: Timeline showcases Rapid Activation Request form submission through patient consent.



including findings related to treatment options and important genetic variations.

AI/ML Use in clinical settings

Q. How does Tempus data, sequencing and analysis lend itself to identifying eligible patients for clinical trials?

A. Drug Development in the precision medicine era has allowed for the creation of powerful therapies for specific, molecularly defined patient populations. The clinical trials for these therapies have to focus on narrow inclusion and exclusion criteria to properly define the targeted patient population. Identification of eligible patients for precision medicine studies has special challenges and requires all the clinical and molecular data routinely Tempus collects as part of the standard of care. Tempus supplements this data with AI/ML algorithms, such as Homologous Recombination Deficiency (HRD) and Tumor Origin (TO), to further discern the disease characteristics of a patient's tumor so that patient trial matching can be done more robustly and help all involved avoid screen failures.

Q. How does Tempus support biopharma sponsors once a patient is identified?

A. Tempus has found that patient trial matching services are more effective for biopharma sponsors when awareness and access activities are incorporated as it helps increase physician and patient engagement. Tempus raises awareness of the matched clinical trial option with the treating physicians by supplying an output that shows how the patient matches the key inclusion and exclusion criteria for the study. In other words, we do quite a bit of eligibility work before even engaging the treating physician. Then this output comes with a concise write up about the science and design of the study, which physicians have told us helps them understand the additional options early.

In addition to identifying patients, Tempus has built a just-in-time clinical trial site network called the TIME Trial Program which allows studies to be activated in less than 14 business days if a patient is identified. Pretty much everyone – sponsors, physicians, research staff and patients, have been surprised how fast things move in this program and recognize the value of increasing access for underrepresented and remote patient populations.

"Tempus has found that patient trial matching services are more effective for biopharma sponsors when awareness and access activities are incorporated"

Q. How is actionable guidance for informed decisions (connecting physicians with up-to-date treatment options and relevant insights for patients) conveyed to physicians? Are physicians provided with a query-able interface? Are rank-ordered options for treatment provided to physicians for assessment and selection of treatments?

A. One of Tempus' core priorities is empowering physicians with easy-to-use tools that embed our machine learning capabilities. Physicians have access to these tools in the Tempus Physician Portal and Tempus objectively displays therapeutic options based on the patient characteristics. Tempus does not rank or recommend any assessments or treatments and tries to be as comprehensive as possible in identification of treatment options, including identification of best-fit clinical trials that are nearby.

Closing comments/summaries

We hope these replies provide your readers with a useful overview of the Tempus mission and flywheel of activities we are performing. We have developed a technology-supported system that not only helps physicians and patients understand their cancer but also makes appropriate molecularly-driven therapies available and more easily explainable to them. Every day at Tempus, we see how technology can optimally support genomic and clinical science to improve the lives of patients facing cancer and other chronic diseases, this is what inspires us to continue innovating. JoPM

Dr. Kim Blackwell

Blackwell serves as Tempus' Chief Medical Officer. She joins Tempus from Eli Lilly, where she was Vice President of Early Phase Oncology and Immuno-oncology. Prior to that, she was a Professor of Medicine and Assistant Professor of Radiation Oncology at Duke University, where she directed the Women's Cancer Program, Strategic Collaborations, and the Precision Medicine Initiative for the Duke Cancer Institute.

References

Beaubier N., Bontrager M., Huether R. *et al.* (2019). Integrated genomic profiling expands clinical options for patients with cancer. Nat Biotechnol 37, 1351–1360.

Freedman A.N., Klabunde C.N., Wiant K., *et al.* (2018). Use of next-generation sequencing tests to guide cancer treatment: Results from a nationally representative survey of oncologists in the United States. JCO Precis Oncol. DOI: 10.1200/PO.18.00169. The study used data from the National Survey of Precision Medicine in Cancer Treatment mailed to a nationally representative sample of oncologists.