

Commentary

The ADAPT learning cancer treatment system: ARPA-H's initiative to revolutionize cancer therapy

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ADAPT is a nationwide initiative to transform cancer care by detecting and responding to tumor evolution in real time. Integrating multimodal data, interpretable AI, and an evolutionary clinical trial platform, ADAPT predicts emerging resistance traits and guides treatment adjustments as tumors change. A unified national infrastructure enables continuous learning across patients, linking discovery directly to care. By making therapy responsive to tumor changes, ADAPT delivers a scalable model designed to improve outcomes in precision oncology.

As cancer evolves, treatments must adapt and target these changes

Cancer is defined by complex signaling networks and its ability to evolve during treatment and acquire new traits.^{1–4} As tumors mutate and change, they develop resistance to therapies that once were effective. Current translational oncology approaches are not nimble enough to identify these resistance traits as they emerge or to adapt treatment in time. The ARPA-H ADAPT (Advanced Research Projects Agency for Health, Advanced Analysis for Precision Cancer Therapy) program aims to change this by developing biomarkers that capture the dy-

namic nature of cancer and by designing clinical trials that can apply these insights and adjust therapy in near real time. Our ultimate goal is to detect emerging resistance and adapt treatment quickly enough to delay or prevent disease progression.

What would it take to accomplish this goal? First, we must modernize biomarker strategies that have largely relied on limited static measurements that capture only a narrow section of cancer's complexity, such as single gene mutations or baseline pathology. Instead, we must utilize rich multi-modal and longitudinal patient data. Liquid biopsies, for

example, can reveal adaptive tumor reprogramming, including *ESR1* mutations or secondary *EGFR* and *RAS* alterations, and could have even greater impact when integrated into richer predictive models. We need studies that collect measurements before and during treatment, using assays that capture a wide range of disease traits and better characterize tumor phenotypes. We also need dynamic forecasts of tumor evolution that combine clinical and molecular data to create adaptive biomarkers.

Expanding biomarker discovery presents its own challenges, particularly the rigor, speed, and scale needed to

influence treatment decisions in the clinic. To advance the field, we must develop accessible, longitudinal tumor-tracking approaches and biomarkers that capture the full, evolving landscape of resistance across multiple lines of therapy. Achieving this will require a flexible, adaptive clinical trial framework that supports frequent, multidimensional tumor measurements across lines of treatment and within the same platform trial. By embedding biomarker discovery and validation directly into the trial design, such as using Bayesian adaptive N-of-one-like (Bayes-Nano) pilots to accelerate learning from deeply characterized cohorts with shared resistance traits, we can make meaningful progress. These efforts also depend on robust data platforms that enable rapid, secure sharing and analysis of clinical and molecular data across institutions.

ADAPT is designed to meet these needs via three program components (Figure 1A). First, biomarker teams will analyze diverse tumor measurements in near real time to identify treatment-induced changes and build a compendium of predictive biomarkers that guide evolution-based treatment strategies (Table 1). Second, ADAPT will pioneer an evolutionary clinical trial design that incorporates new biomarkers and insights, including AI-guided predictors in one of the first efforts to test such tools in a clinical setting. Patient responses will be assessed across multiple lines of therapy, ensuring that each treatment is informed by resistance traits that emerge during earlier phases. Third, ADAPT will establish a treatment and data platform to accelerate sharing and collaborative learning. Together, these components position ADAPT to advance translational oncology by aligning clinical strategies with the dynamic nature of cancer evolution.

Components of the ADAPT program Predictive drug response models that are dynamic, interpretable, and robust

A core goal of ADAPT is to develop dynamic, interpretable, and robust predictive biomarkers that forecast how a tumor will respond to, or become resistant to, specific therapies. These models will operate on each patient's longitudinal, multimodal data to enable more precise patient-therapy matching (Figure 1B). To create these models, we are applying a range of statis-

tical and machine-learning methods, from classical approaches to advanced computational architectures. Initial model development draws on retrospective datasets from patients and *in vitro* screens, yielding diverse molecular, cellular, and physiological biomarkers. As ADAPT clinical trials begin, these models will be continually refined using real-time longitudinal data from enrolled patients. ADAPT's predictive models will integrate multimodal data, dynamically forecast drug response and tumor evolution, remain biologically interpretable, and deliver reliable predictions even with incomplete or noisy information.

Multimodal integration. Cancer biology is inherently multiscale, spanning nucleotides, proteins, cells, and tissues, with each measured by distinct data types, from genome and transcriptome sequencing to protein pathway maps, histopathology, and radiologic imaging. Traditional predictive models typically analyze only one of these data types at a time, often reducing tumor biology to flat feature lists (e.g., single-gene mutations). Multimodal data fusion offers a transformative alternative. Using unsupervised and self-supervised machine learning, these approaches integrate diverse datasets across scales (Figure 1B). A central opportunity is the creation of patient-specific "embeddings" that convert high-dimensional, heterogeneous data into a unified, lower-dimensional representation. These embeddings can serve as a foundation for many downstream applications. By capturing shared structure across modalities, multimodal models significantly improve predictive power and remain robust even when some data are missing. Through ADAPT, these early proofs of concept will be expanded dramatically in sample size, data depth, and modality diversity.

Prediction of drug response and tumor dynamics. Tumors evolve rapidly under therapy, often acquiring resistance through genetic, epigenetic, or microenvironmental mechanisms. Resistance can emerge from a variety of sources, including target gene mutations, activation of bypass pathways, immune interactions, epithelial-to-mesenchymal transitions, or extrachromosomal DNA (ecDNA). The longitudinal, multimodal datasets collected by ADAPT clinical trial centers, including circulating tumor DNA (ctDNA), biopsies, imaging, and health records, will be essential to forecast tumor trajectories. Leveraging these data, ADAPT

will develop models that anticipate resistance, detect early warning signals, and recommend adaptive treatment strategies, preventing disease progression before it becomes clinically apparent.

Biological interpretability. Black-box predictions are insufficient for oncology, where clinical decisions require mechanistic understanding. Interpretability ensures models not only forecast outcomes but also reveal biological processes underlying drug response. Our team has developed several strategies to make predictive models biologically interpretable, including SHapley Additive exPlanations (SHAP) (which attributes feature contributions using game-theoretic principles⁵), logic-based models, and visible neural networks that align network structure with known molecular pathways. These approaches have already yielded interpretable models of resistance to chemotherapy and CDK4/6 and BRAF inhibitors.^{6,7} In ADAPT, we will extend these methods to map patient-specific resistance pathways and inform rational combination therapies. Mechanistic transparency will be essential for building trust and accelerating clinical adoption.

Robustness to partial information. Real-world oncology data are often incomplete, and predictive models must function reliably despite missing modalities. To address this, we are developing approaches ranging from data interpolation to transfer learning and cross-context modeling. Tools like OncoPredict⁸ can impute missing drug-sensitivity values during model training, while TCRP⁹ (transfer of cellular response prediction) enables models trained in data-rich settings to be adapted to contexts with very limited samples, including, for example, transferring models from large cell-line screens to small breast cancer cohorts with fewer than ten cases. Foundation models further enhance robustness by learning cross-modal relationships from large, heterogeneous biomedical datasets, enabling stable predictions even when specific data types are absent or noisy. By integrating these strategies, ADAPT will deliver predictive systems resilient to the practical constraints of clinical data.

Evolutionary clinical trials

Personalized cancer care has long been a goal but has been limited by slow, static trial designs and the inability to adapt treatment as tumors evolve. ADAPT will

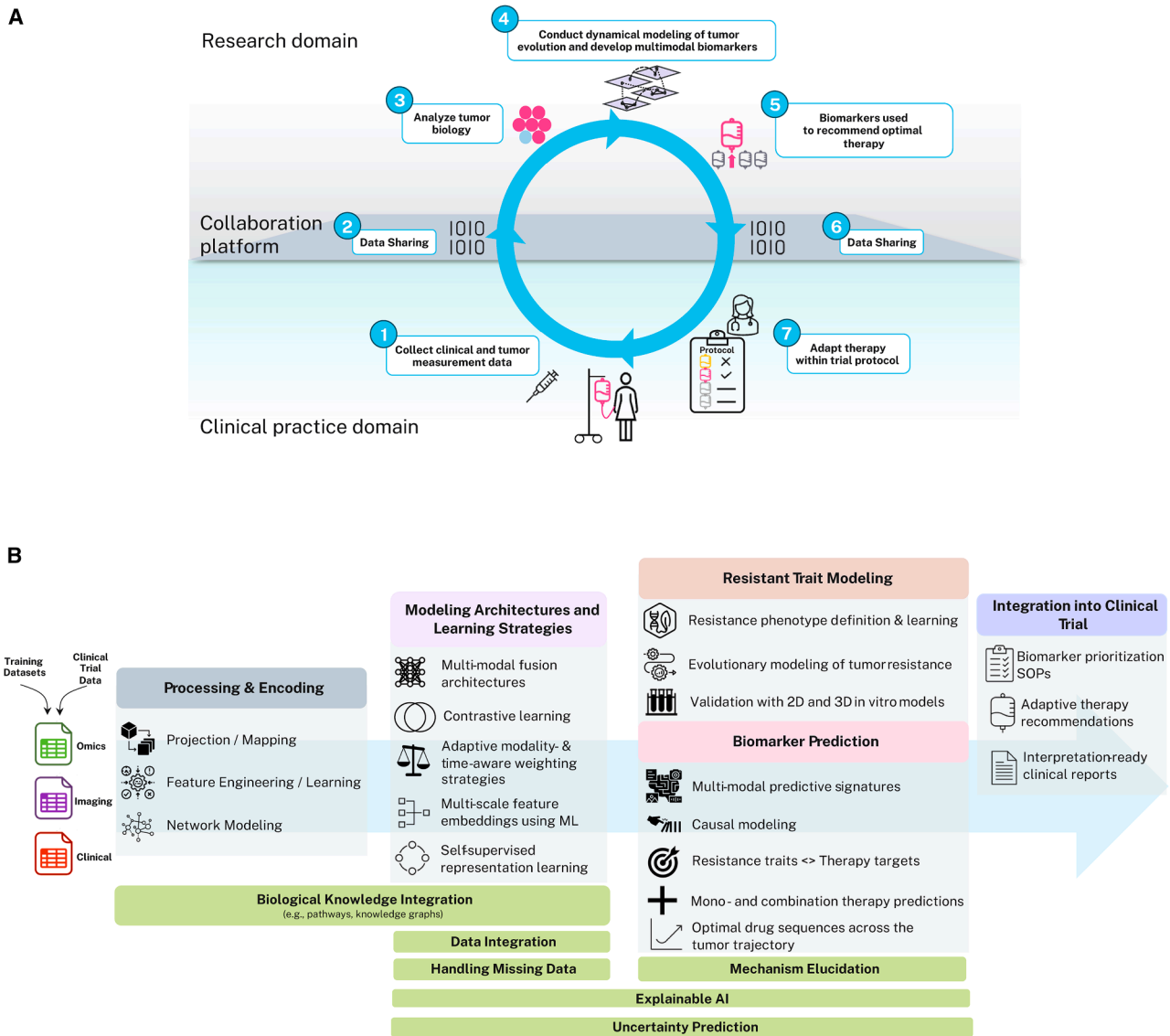


Figure 1. Key transformative components of the ADAPT program

(A) ADAPT will develop, test, share, and refine multimodal biomarkers within an adaptive clinical trial to optimize treatment selection by (1) collecting comprehensive clinical and laboratory data, including electronic health record (EHR), biopsy when feasible, blood-based assays, digital imaging/pathology, and tumor biology measurements such as DNA/RNA sequencing and circulating tumor DNA/methylome profiling; (2) sharing data on the collaboration platform in near real time; (3) integrating multimodal inputs through analytical pipelines to detect tumor traits; (4) using dynamical modeling to build longitudinal, multimodal biomarkers; (5) generating treatment recommendations based on tumor evolution and emerging traits; (6) coordinating biomarker implementation through close collaboration between research and clinical teams; and (7) assigning patients to trial arms using biomarker-stratified adaptive randomization to dynamically adjust therapy and overcome resistance. This continuous loop, from measurement to analysis, biomarker development, testing, and trial deployment, enables a data-driven approach where evolving patient information directly informs care. (B) ADAPT's integrated computational pipeline processes heterogeneous data (omics, imaging, and clinical records) through feature engineering, projection, and network modeling to create structured representations, which are combined using multimodal fusion, contrastive and self-supervised embeddings, and time-/modality-aware weighting to handle missing or asynchronous data. Downstream resistance modeling defines phenotypes and characterizes tumor evolution. Biomarker prediction uses biologically interpretable, multimodal signatures and causal modeling to map resistance traits to therapeutic targets, forecast responses to single or combination therapies, and optimize drug sequencing. Outputs include prioritized biomarkers, adaptive therapy recommendations, and clinician-ready reports for integration into ADAPT trials.

address this gap by launching a centralized, modular, open-source evolutionary clinical trial protocol across multiple US sites. This trial introduces several innovations: the ability to test multiple therapy sequences within a single protocol, rapid incorporation of newly discovered bio-

markers, and iterative treatment selection informed by real-time tumor evolution. Biomarkers identified by ADAPT researchers will be prospectively evaluated within the same framework, eliminating the need for separate trials for each biomarker. Metastatic tumors will be as-

sessed and treated in cycles, with therapy adjusted as new resistance traits arise.

The adaptive clinical trial will enroll patients with metastatic breast, colorectal, and non-small cell lung cancers, which are three of the most common malignancies, all marked by frequent primary

Table 1. Types of biomarkers developed in the ADAPT program

Biomarker category	Biomarker description/features	Purpose	Decision point	Application examples (not comprehensive)
Predictive drug response biomarkers	multi-modal predictors of response to standard-of-care (SOC) therapies (targeted and immunotherapies) and novel therapeutics in metastatic breast, lung, and colon cancers	predict optimal next-line therapy	pre-treatment or at baseline (after progression on prior therapy)	<p>breast cancer: ER+ HER2– patients: predict benefit from ER-targeting therapy and other 1st-, 2nd-, or 3rd-line treatments TNBC patients: predict who benefits from immunotherapy and other targeted therapies</p> <p>lung cancer: Predict benefit of SOC treatments STK11 or KEAP1 mt NSCLC: predict benefit of PD1 antibody + CTLA4 antibody combination therapy KRAS G12Cmt NSCLC: predict benefit of KRAS inhibitor + VEGF inhibitor combination therapy</p> <p>colon cancer: Predict benefit from SOC therapies Predict benefit of PDL1/VEGF bispecific antibody therapy</p>
Early biomarkers of “universal” drug response (“delta Biomarkers”)	multi-modal changes in tumor state shortly after treatment initiation reflecting early adaptive evolution that can forecast longer-term therapeutic success or failure across therapies	predict whether patients should continue their current first-choice therapy or, alternatively, switch to a second-choice regimen if the delta biomarker indicates a low probability of response	shortly after therapy initiation at early follow-up evaluation (~3 weeks)	rapid assessment of tumor response to first- and second-line SOC treatments in colon, lung, and breast cancer patients; early detection of non-response by delta biomarkers can guide prompt implementation of add-on therapies or switching the patient to an alternative treatment regimen
Dynamical biomarkers for optimal drug sequences	forecast tumor growth and molecular trajectories to identify resistance as tumors evolve	predict optimal drug sequences from tumor trajectory data and guide selection of therapy regimens that provide optimal patient outcomes	throughout treatment (serial imaging/liquid biopsy) and following progression	models will identify molecular changes over time that predict tumor growth under specific treatments, enabling forecasts of tumor trajectories across different therapies; models link molecular evolutionary patterns to patient outcomes and support selection of personalized therapy tailored to each tumor’s unique evolutionary profile (for example, in breast cancer, a tumor may evolve from a state of initial endocrine resistance, followed by compensatory EGF/ERBB pathway activation and increased proliferation, and finally enter an immune cold IL-low signaling driven refractory state; such a model could recommend sequential endocrine therapy, adding ERBB-targeted agents, chemotherapy, and finally

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Table 1. Continued

Biomarker category	Biomarker description/features	Purpose	Decision point	Application examples (not comprehensive)
Tumor growth rate biomarkers	monitoring and optimized assessment of disease state changes (e.g., tumor doubling time, growth curves, and trajectory patterns) to assess ongoing or predict continued therapeutic response	detect emergence of drug resistance earlier in treatment, through optimized monitoring of tumor growth, and improve accuracy of drug response evaluation (substantially beyond RECIST)	throughout treatment (serial imaging)	including IL-targeting therapy, e.g., IL-15 activating therapy) integrate radiologic and clinical measurements across modalities to monitor tumor growth over time, accounting for biases and uncertainties, to evaluate ongoing disease progression, predict continued tumor growth rate dynamics, support translational links to molecular evolution and therapeutic response, and enable faster, more reliable decisions about a patient's response to therapy
Prognostic biomarkers	indicates an increased or decreased likelihood of a future clinical event or disease outcome	estimate the likelihood of disease progression or death	pre-treatment or at baseline	identification of patients at high risk of recurrence or progression during SOC treatments, such as markers of proliferation or cancer aggressiveness

ADAPT is developing several categories of biomarkers to meet patient needs. Predictive drug response biomarkers use multimodal data to recommend effective therapies before treatment begins. Early efficacy, or “delta,” biomarkers quickly indicate whether a therapy is working, allowing timely treatment adjustments. Dynamical biomarkers track tumor growth and response patterns over time to guide optimal therapy sequencing. Acquired resistance biomarkers identify molecular changes that signal emerging resistance and inform targeted treatment choices. Biomarkers of novel therapeutic vulnerabilities highlight new drug targets and help match patients to investigational therapies. Together, these biomarker types aim to improve accuracy; expand clinical utility; and support highly personalized, adaptive cancer care.

and acquired resistance despite multiple available treatments. ADAPT will uncover biomarkers that guide optimized regimens for both standard and emerging therapies. Within the trial, rapid-turn-around biomarker modeling and collaboration with drug developers will launch biomarker-driven sub-trials, enabling the rapid identification of promising biomarker-drug pairings for diverse patient cohorts.

Breast cancer. Most participants will have estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative disease progressing after first-line endocrine therapy plus cyclin-dependent kinase 4/6 (CDK4/6) inhibition and will receive optimized next-line treatments based on each tumor's traits. A subset with triple-negative breast cancer (TNBC) will receive innovative chemotherapy-based regimens, androgen receptor-targeted therapies, or novel agents. Serial blood biopsies and imaging across treatment lines will guide biomarker-driven treatment selection and Bayes-Nano sub-trials targeting acquired resistant traits as they emerge.^{10,11}

Colorectal cancer. The ASCEND colon cancer trial is further detailed in a commentary published in the same issue.¹² Participants will have metastatic microsatellite-stable disease and will undergo serial tissue and plasma profiling across first through third lines of therapy. Early treatment-induced changes (“delta biomarkers”) will be correlated with outcomes in phase one. In phase two, biomarker-defined sub-trials will evaluate novel therapeutics using adaptive randomization and synthetic controls. Early paired biopsies will be assessed as predictors of long-term benefit to support adaptive switching. Pilot N-of-one and N-of-few studies will explore multimodal signatures in smaller subsets of patients with treatments tailored to individual tumor traits.

Lung cancer. Participants with advanced non-small cell lung cancer (NSCLC) will begin first-line immunotherapy and be monitored with serial ctDNA/cell-free DNA (cfDNA) and CT/MRI imaging. Tumor biopsies will be obtained at baseline and at progression. Multimodal data will be used to develop biomarkers predicting immunotherapy response and

guide subsequent treatment selection. Patients who progress will enter biomarker-matched sub-trials testing novel therapies targeting resistance mechanisms identified through ADAPT's modeling efforts.

As an ARPA-H program, ADAPT is committed to broad dissemination. The trial will use a modular, scalable design that can be implemented at diverse institutions within ADAPT and adopted by external clinical teams. Open protocols and shared infrastructure will ensure that the innovations developed here can extend across cancer types and settings.

Treatment and analysis platform

The ADAPT program unifies insights from researchers and clinicians through the creation of the ADAPT Treatment and Analysis Platform (TAP), an informatics system that hosts a suite of tools. This platform enables near-real-time availability of integrated patient data and evolutionary trial protocols and supports the design, testing, and standardization of newly developed biomarkers and drug targets. TAP fosters a close community of researchers and clinicians, building a collective knowledge base where each

patient's data contributes to the treatment of others with similar tumors.

ADAPT TAP is built on two integrated components: the DNAnexus Managed Cloud Platform and The Extensible Neuroimaging Archive Toolkit (XNAT).¹³ The DNAnexus platform enables scalable multi-omics data storage, management, and analysis with robust, contextualized metadata. Its native features, combined with ADAPT-specific customizations, support secure data sharing, harmonization, and processing as well as visualization of clinical, imaging, and molecular datasets generated in the trials. XNAT provides imaging-centric workflows, including automated image quality control, processing, visualization, annotation, and high-throughput feature extraction. These imaging features can then be integrated with molecular and clinical data on DNAnexus, creating a unified resource for multimodal biomarker discovery. By keeping data and analysis in a standard platform, the ADAPT program ensures that as performers collaborate and benchmark biomarker development, the results can be definitively traced back to the source in a reproducible manner.

Achieving near-real-time decision-making

The success of ADAPT relies on seamless coordination between biomarker teams and clinicians to rapidly analyze patient data and support real-time treatment decisions without disrupting care. To enable this, all biological assays and data processing are centralized with a single vendor operating under strict turnaround times. The cloud-based, interoperable TAP platform will link clinical sites and research teams, ensuring fast data flow, real-time collaboration, and timely delivery of interpretable results to providers and patients. Frequent, minimally invasive monitoring—primarily blood-based assays and radiologic imaging—will reduce patient burden while generating the longitudinal datasets needed for dynamic modeling. Finally, ADAPT will develop a regulatory and reimbursement roadmap to support the approval and adoption of multimodal biomarkers and decision-support tools, ensuring their sustainable integration into clinical practice.

Conclusions

Novel tumor measurement technologies and advanced computational methods

are opening unprecedented windows into tumor biology, offering new opportunities to guide patient care. The ability to track how tumors change during treatment highlights the need for clinical approaches that are both personalized and longitudinal. The ARPA-H ADAPT program is designed to meet this need by embedding real-time biological and computational insights into the design and conduct of clinical trials, with a focus on the metastatic cancer setting where resistance emerges most urgently. By establishing an evolutionary trial infrastructure, ADAPT creates a flexible platform for testing a diversity of therapies in direct response to tumor adaptation, accelerating the translation of discovery into care. Ultimately, this program seeks to transform cancer treatment by uniting cutting-edge science with clinical decision-making, mapping and targeting tumor evolution in ways that improve outcomes and bring tangible benefits to patients and their families.

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DECLARATION OF INTERESTS

T.I. is a co-founder and member of the advisory board of and has an equity interest in Data4Cure and Serinus Biosciences. T.I. is a consultant for and has an equity interest in Ideaya Biosciences and Eikon Therapeutics. The terms of these arrangements have been reviewed and approved by the University of California San Diego in accordance with its conflict-of-interest policies. L.C. serves on the scientific advisory board for the Breast Cancer Research Foundation (BCRF), a philanthropic organization that provides support for the Translational Breast Cancer Research Consortium (TBCRC), the organization in which the ADAPT breast cancer trials will be run. This role is uncompensated, and L.C. is not involved in decisions related to funding TBCRC or the ARPA-H trials. S.K. is a consultant for Arvinas, DeBiopharm, Larkspur, Janssen, Kivu, Genentech, Merck, Boehringer Ingelheim, Bayer Health, Pfizer, Mirati Therapeutics, Flame Biosciences, Carina Biotech, Frontier Medicines, Replimune, Bristol-Myers Squibb-Medarex, Amgen, Tempus, Harbinger Oncology, Zentalis, AVEO, Tachyon Therapeutics, Agenus, Revolution Medicines, Kestrel Therapeutics, Roche, Arcus Biosciences, AstraZeneca Pharmaceuticals, BeiGene, Clasp Therapeutics, Cytovation, Dewpoint Therapeutics, Marengo Therapeutics, SageMedic, Servier, Sibylla, T-Cypher Bio, XAIRA, AmMax Bio, and Ikena and receives research funding from Guardant Health, Genentech/Roche, EMD Serono, Amgen, Lilly, Daiichi Sankyo, Pfizer, Boehringer Ingelheim, BridgeBio, Zentalis, BioMed Valley, Johnson & Johnson, BMS, Cardiff, Jazz Pharmaceuticals, and Frontier Medicines. A.G. has consulted for Ci-

bermed Inc. F.M. is a co-founder and advisor for Modella AI and an advisor for DanaHER. A.H.B. is a founder of Unravel Genomics.

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