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OCTANE (Ontario-wide Cancer Targeted Nucleic Acid Evaluation): a platform for intraprovincial, national, and international clinical data-sharing

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ABSTRACT

Cancer is a genetic disease resulting from germline or somatic genetic aberrations. Rapid progress in the field of genomics in recent years is allowing for increased characterization and understanding of the various forms of the disease. The Ontario-wide Cancer Targeted Nucleic Acid Evaluation (OCTANE) clinical trial, open at cancer centres across Ontario, aims to increase access to genomic sequencing of tumours and to facilitate the collection of clinical data related to enrolled patients and their clinical outcomes. The study is designed to assess the clinical utility of next-generation sequencing (NGS) in cancer patient care, including enhancement of treatment options available to patients. A core aim of the study is to encourage collaboration between cancer hospitals within Ontario while also increasing international collaboration in terms of sharing the newly generated data. The single-payer provincial health care system in Ontario provides a unique opportunity to develop a province-wide registry of NGS testing and a repository of genomically characterized, clinically annotated samples. It also provides an important opportunity to use province-wide real-world data to evaluate outcomes and the cost of NGS for patients with advanced cancer.

The OCTANE study is attempting to translate knowledge to help deliver precision oncology in a Canadian environment. In this article, we discuss the background to the study and its implementation, current status, and future directions.

Key Words Medical oncology, clinical trials, basket studies, precision medicine

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BACKGROUND

Cancer arises from inherited or somatic DNA alterations that lead to host cells undergoing neoplastic transformation, proliferation, invasion, and metastasis. Next-generation sequencing (NGS) can identify oncogenic driver mutations that will highlight targets for genotype-matched drug treatment, known as "precision medicine." Recently, several Ontario cancer centres integrated their targeted clinical NGS testing for specific cancer indications. However, those NGS testing initiatives have been implemented independently across various sites, using a range of technologic platforms and limited infrastructure for data-sharing between clinical laboratories. Additional challenges, such as uncertainty about the optimal size and content of the NGS gene panels being used, identification of clinically actionable genes and mutations, reimbursement for testing by the public health care system, and access to matched targeted therapy have limited the effect of NGS testing.

The IMPACT (Integrated Molecular Profiling in Advanced Cancers Trial) and COMPACT (Community Molecular Profiling in Advanced Cancer Trial) prospective genomic profiling studies were conducted at the Princess Margaret Cancer Centre (PMCC) from 2012 to 2015. Those studies used a multiplex hotspot mutation panel (23 genes, 279 variants) or a targeted NGS panel (approximately 50 genes) to provide

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molecular characterization data for patients with advanced solid tumours to help guide the clinical decision-making of their oncologists. Results from the first 1893 patients enrolled showed that only 5% of the patients profiled were subsequently treated on genotype-matched clinical trials, with a response rate higher in that selected group than in patients treated on non-genotype-matched trials[1].

Despite the growing interest in NGS testing in oncology, there are disparities between the demand for and the access to this new technology. In Ontario, the only publicly funded disease-specific indications for somatic tumour mutation testing are *ALK* and *EGFR* for non-small-cell lung cancer; *KRAS, NRAS,* and *BRAF* for colorectal cancer; *BRCA1/2* for high-grade serous ovarian cancer; and *BRAF* for malignant melanoma. Support for broader-panel NGS testing in academic institutions has been obtained largely using internal laboratory budgets, peer-reviewed grants, and philanthropic sources. In the process of generating evidence to inform decisions about reimbursement for NGS testing for broader indications, the collective experience of molecular characterization across the province has a key role to play. The goal of the Ontario-wide Cancer Targeted Nucleic Acid Evaluation (OCTANE) study is to develop a provincial registry of NGS panel-based testing results, and a repository of genomically characterized and clinically annotated tumour tissues and blood samples for future research.

Study Design

A prospective trial, OCTANE is enrolling patients with incurable solid tumours at the PMCC, the Juravinski Cancer Centre, the London Health Sciences Centre, The Ottawa Hospital Regional Cancer Centre, and the Kingston General Hospital. Eligible patients must meet these criteria:

- age 18 years or older,
- Eastern Cooperative Oncology Group performance status 0 or 1,
- adequate organ function,
- 2 or fewer prior lines of therapy for systemic disease,
- life expectancy greater than 6 months, and
- ability to provide informed consent.

The protocol was approved by the Ontario Cancer Research Ethics Board (see NCT02906943 at https://ClinicalTrials.gov/). Study participants donate tumour tissue for NGS testing and future research, provide blood samples, and grant access to medical health records and their OHIP (Ontario Health Insurance Plan) number to link to provincial health administrative databases for future research (Figure 1). Participants agree to de-identified clinical and genomic data-sharing for research.

Patient Enrolment

As of 21 January 2019, 2106 patients had been enrolled into OCTANE: 1469 at PMCC, 222 at the London Health Sciences Centre, 194 at The Ottawa Hospital Regional Cancer Centre, 101 at the Juravinski Cancer Centre, and 120 at the Kingston General Hospital. To date, 69% of the 2106 OCTANE participants are women, and the most common tumour types are cancers of the ovary (23%), uterus (12%), bowel (12%), breast (10%), and lung (5%). All clinical testing is performed at laboratories certified and licensed for targeted NGS by the Institute for Quality Management in Healthcare.

Targeted NGS testing results for genes that are either not routinely reported, or that are reported through local molecular tumour boards, are recorded in a secure Web-based research portal that can be accessed by the patient's treating physician. Blood samples (approximately 20 mL) collected from patients and formalin-fixed paraffin-embedded tissue blocks or unstained slides for research are transferred to a centralized bio-repository maintained by the Tissue Portal at the Ontario Institute for Cancer Research (OICR). For each participant, information about 11 essential clinical variables [Table I, modelled after GENIE (Project Genomics Evidence Neoplasia Information Exchange) from the American Association of Cancer Research] is collected from review of medical records[2]. Clinical data are stored using Rave EDC (Medidata, New York, NY, U.S.A.), a Web-based electronic data capture system hosted by Research Information Systems at the University Health Network.

Data Visualization

A local installation of cBioPortal[3,4], an open-source Web-based portal developed by Memorial Sloan Kettering Cancer Center, was established for OCTANE. cBioPortal was selected because the application is open source and provides an easy-to-navigate visualization platform that can

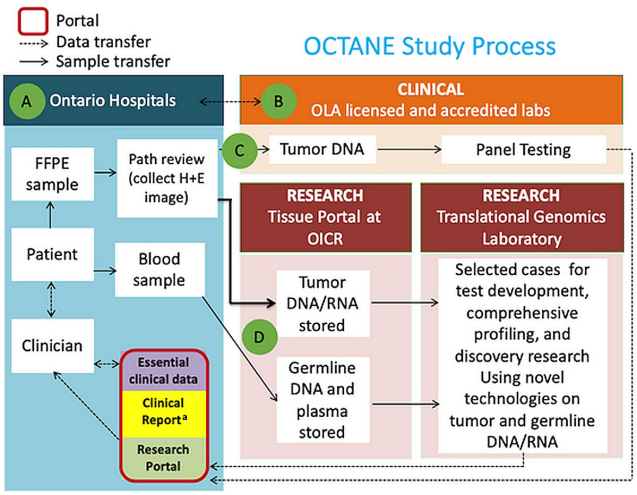

FIGURE 1 OCTANE study data and sample flow. (Item A) Within Ontario hospitals, patients are identified and consent to enrol in the study. Signing a consent permits access to archived tumour tissue. The patient also provides a blood sample for normal DNA. FFPE = formalin-fixed, paraffin-embedded; H+E = hematoxylin and eosin. [a]For patients with lung cancer, colorectal cancer, and melanoma only. (Item B) Ontario hospitals transfer de-identified clinical information to Ontario Laboratory Accreditation (OLA) laboratories. (Item C) Tumour tissue is sent to an OLA laboratory where DNA is extracted, and panel testing is performed. Results are then uploaded to cBioPortal, and a clinical report is made available to the treating clinician. OICR = Ontario Institute for Cancer Research. (Item D) Tumour DNA and RNA, and germline DNA and plasma, are transferred to the Tissue Portal where samples are stored. Cases of interest are selected for further analysis, whose results are also uploaded to the cBioPortal.

TABLE I Required clinical variables for OCTANE[2] per Project GENIE from the American Association for Cancer Research

■ Sex
■ Age
■ Ethnicity
■ Cancer type[a]
■ Date of diagnosis
■ Site of sample being profiled (primary or metastasis)
■ Date of sample collection
■ Date of sequencing results
■ Standard molecular pathology information
■ Relevant past medical history
■ Survival status

[a] Using the OncoTree code (http://oncotree.mskcc.org/).

integrate clinical and genomic data. Investigators and study personnel can visualize genomic variants linked to clinical data for queries at the cohort (Figure 2) and individual patient (Figure 3) levels. Clinical annotation for genomic variants is provided by OncoKB (https://oncokb.org/#/), a research data repository that includes 477 cancer genes[5]. For each curated variant, information about biologic effect, prevalence in a particular tumour type and across all tumours, prognostic implications, and treatment options are collected. Treatment information is classified using the levels-of-evidence system, which assigns clinical actionability to individual mutational events and enables clinical decision-making about potential treatment options[5].

Clinical Translation

Treatment options for patients with clinically actionable variants outside the approved indications are being investigated in early-phase clinical trials or the Canadian Cancer Trials Group CAPTUR study (see NCT03297606 at https://ClinicalTrials.gov/). A phase II basket trial (a type of trial that tests the effect of one drug on a single mutation in a variety of tumour types), CAPTUR aims to test the activity of commercially available targeted agents in patients who have undergone tumour profiling. Currently, 11 approved treatments from 4 pharmaceutical partners are given alone or in combination. As of March 2019, 54 patients had been enrolled across Canada, including 28 from PMCC, 12 from the London Health Sciences Centre, and 1 from The Ottawa Hospital Regional Cancer Centre. The study has been active at Kingston General Hospital since February 2019, but is not yet active at the Juravinski Cancer Centre. The CAPTUR study is one of a series of similar basket trials currently underway, including the American Society of Clinical Oncology's TAPUR [Targeted Agent and Profiling Utilization Registry (NCT02693535)] and the Netherland's DRUP [Drug Rediscovery Protocol (NCT02925234)]. Ultimately, data sharing by those trials is planned, with the objective of providing additional power to examine rare tumour genotype–drug matches.

Clinical NGS Testing

Each laboratory uses NGS panels relevant to their site and to the NGS platform available. Two panels are used at PMCC:

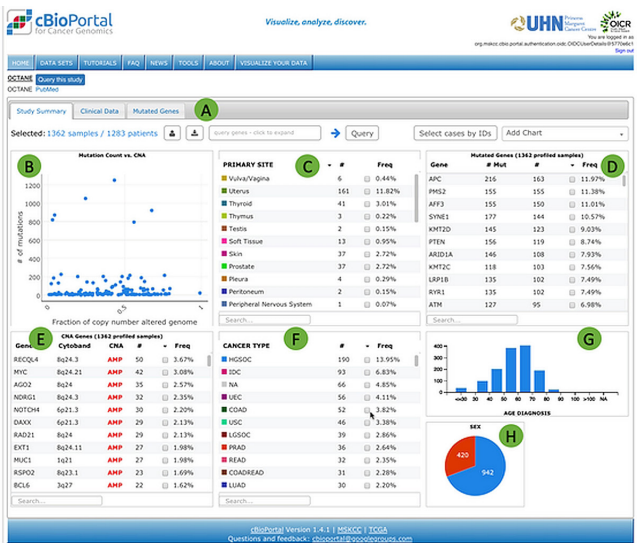

FIGURE 2 The cBioPortal dashboard for cohort-level data. (Item A) Options for reviewing the data include "Summary Overview, Clinical Data," which provides access to individual samples and "Mutated Genes," which records the genes mutated within the overall OCTANE cohort. (Item B) Graphical overview of the number of mutations compared with the fraction of the copy number–altered genome. (Item C) The primary cancer site. (D) The genes mutated and the frequency with which a gene is mutated. (Item E) Genes with copy-number alterations. (Item F) The histologic subtype of the cancer. (Item G) The distribution of age at diagnosis. (Item H) The sex of the enrolled patients. Other options for graphical representation are also available. Courtesy of cBioPortal [3,4].

a custom hybridization capture panel [SureSelect (Agilent, Santa Clara, CA, U.S.A.)] of 555 cancer-relevant genes sequenced on a NextSeq series sequencing system (Illumina, San Diego, CA, U.S.A.), and more recently, a commercial 161-gene amplicon DNA/RNA panel (Oncomine Comprehensive Assay v3: ThermoFisher Scientific, Waltham, MA, U.S.A.) sequenced on the Ion S5 XL platform (ThermoFisher Scientific). The other 4 sites are currently using the Ion AmpliSeq Cancer Hotspot Panel v2 (50 genes) on the ThermoFisher platform, and there are plans to transition those sites to larger NGS panels. To develop a robust infrastructure for clinical and genomic data-sharing across the province, 5 academic cancer centres were initially selected to participate in OCTANE. There is currently an open call to expand OCTANE to include 2–3 additional participating sites over the next year.

Additional Genomic Characterization

All blood and archival tissue samples undergo DNA/RNA co-isolation before banking. After approval by the OCTANE steering committee, selected cases undergo further analysis at the PMCC OICR Translational Genomics Laboratory (https://labs.oicr.on.ca/translational-genomics-laboratory). An ongoing research project involves whole-exome sequencing and transcriptome and methylation profiling in cases in which an oncogenic driver is not identified through targeted NGS panel testing. To date, 74 patients in that category have been profiled by the Translational Genomics Laboratory. This ongoing project will provide evidence for when more comprehensive profiling can inform clinical decision-making in selected patients with cancer.

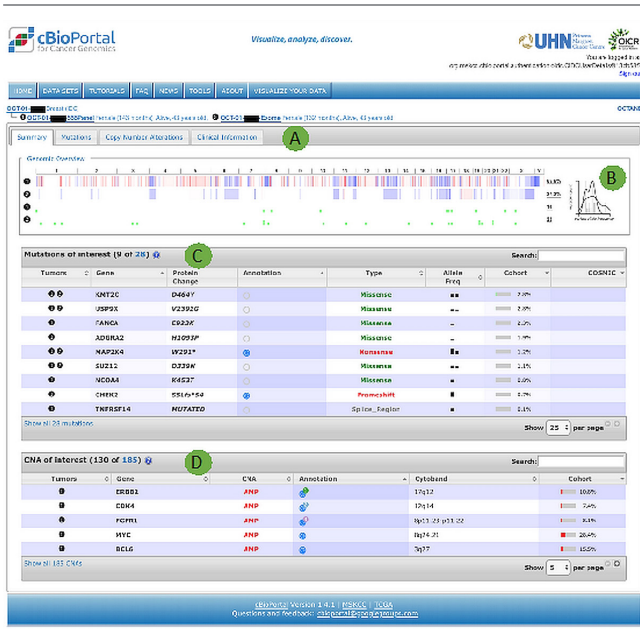

FIGURE 3 cBioPortal dashboard for patient-level data. (Item A) This image represents the summary overview for a patient. Other tabs provide options for displaying only mutation data, copy number alterations, and clinical information. (Item B) This section of the dashboard provides a genomic overview. (Item C) Shows all the mutations present, the genes involved, the resultant protein changes, whether the mutation has been annotated, type of mutation, allele frequency, and mutation frequency in the cohort. (Item D) Displays the copy-number alterations present, the genes involved, whether a change results in amplification or deletion, whether the mutation has been annotated, the cytoband, and the alteration frequency in the cohort. Courtesy of cBioPortal[3,4].

Collaboration Efforts and Data Sharing

The American Association of Cancer Research GENIE international data-sharing project (https://www.aacr.org/Research/Research/pages/aacr-project-genie.aspx) catalogs cancer genomic data and clinical outcomes from the cancer sequencing efforts of multiple international institutions[2]. As one of the 8 founding-member institutions of GENIE, PMCC is sharing results from the OCTANE study with GENIE. To date, the GENIE dataset includes more than 60,000 de-identified genomic records from 19 member institutions, including 756 from OCTANE. The repository will continue to grow as more patients are treated at participating institutions and as new centres join the project.

The OICR is a founding member of the International Cancer Genome Consortium's Accelerating Research in Genomic Oncology project (https://icgcargo.org/)[6]. The Consortium provides a forum for collaboration between leading cancer and genomic researchers. The Accelerating Research in Genomic Oncology project aims to analyze genomic data together with high-quality longitudinally collected clinical data from 100,000 cancer patients (lifestyle; patient history; cancer diagnostic data; treatment; and outcomes, including response to, and survival after, treatment). The OCTANE study will provide a framework for patients across the province to participate in the project, with comprehensive sequencing of their tumours and longitudinal clinical data collection.

Clinical Trial Matching

Busy practicing oncologists can consider it challenging to identify appropriate therapeutic clinical trials available for their patients with potentially actionable genomic alterations. MatchMiner (https://matchminer.org/) was developed at the Dana–Farber Cancer Institute as an open-source computational platform for matching patient-specific genomic and clinical data with structured eligibility criteria for clinical trials[7]. The platform matches patient-specific genomic variants with clinical trials and makes the results available to investigators and clinicians on a Web-based platform. The system is currently being integrated into cBioPortal at PMCC and should ease the process of matching patients to suitable trials by flagging patients with actionable matching mutations.

Liquid Biopsy

Small fragments of tumour DNA released into the bloodstream, known as circulating tumour DNA, allow for detection of tumour-specific DNA mutations in a peripheral blood sample. Characterization of circulating tumour DNA by NGS can now be used to guide tumour-specific therapy and might be particularly profitable in patients with scant archival tumour material available or lesions difficult to biopsy. A number of private vendors have developed liquid biopsy testing platforms. In the future, OCTANE or similar initiatives will have to evolve to incorporate this diagnostic technology.

Evaluate the Clinical Impact of Genomic Testing

Precision medicine—the use of results from multigene NGS panel testing to tailor treatment for patients with advanced cancers—has attracted the criticism that evidence for improved outcomes from the tailored treatment is lacking[8] (Table II). In the United States, the Centers for Medicare and Medicaid Services recently announced a national coverage determination that includes expanded coverage for NGS tests to be used as companion diagnostics for all patients with advanced cancer[16]. The initial funding proposal[17] included a Genetic Testing Registry to collect information relating to patient and cancer characteristics, outcomes data (overall survival, progression-free survival, objective response rate), and patient-reported outcomes. The subsequent policy document did not include a mandatory requirement for a registry to evaluate outcomes[18]. That decision has been criticized as a missed opportunity to collect valuable information about the clinical utility of NGS testing[16]. As a result, studies that collect information about clinical outcomes related to NGS testing, such as OCTANE, are vitally important to fill the information gap.

Evaluating Real-World Data

The linkage of OCTANE to Ontario administrative data sources through ICES provides an opportunity to assess the real-world clinical utility and cost-effectiveness of NGS in the context of Ontario's publicly funded health care system. As an independent not-for-profit research institute, ICES uses encoded, linked population-based data collected from individual patients in Ontario to provide scientific insights into the provincial health care system that could not be otherwise be generated. Real-world data—the ICES data being one example—is health care information derived

TABLE II Results of genotype-matching to clinical trials to date

Group	Patients tested	Platform	Genotype-matched trial enrolment
Memorial Sloan Kettering Cancer Center[9]	12,670	341- to 410-gene panel	527 of 5009 (11%) (>1 year of follow-up)
Dana–Farber Cancer Institute and Harvard Cancer Center[10]	3,727	275-Gene panel	16 of 50 (32%) (year 1)
Cancer Research Center of Lyon[11]	2,676	69-Gene panel and aCGH	143 of 1,944 (7%)
MD Anderson Cancer Centre[12]	2,000	11- to 50-gene panel	83 of 2,000 (4%)
Princess Margaret Cancer Centre[1]	1,640	23- to 48-gene panel	92 of 1,640 (6%)
Institut Gustave Roussy[13]	1,035	30- to 75-gene panel and aCGH	199 of 1,035 (19%)
University of Michigan[14]	556	WGS, WES, RNA-Seq	3%–11%
U.S. National Cancer Institute, Molecular Analysis for Therapy Choice[15]	5,963	141-Gene panel and IHC	688 of 5,963 (12%)

aCGH = array comparative genomic hybridization; WGS = whole-genome sequencing; WES = whole-exome sequencing; RNA-Seq = next-generation sequencing technique to reveal the presence and quantity of RNA; IHC = immunohistochemistry.

from multiple sources outside typical clinical research settings[19]. Those data are collected from electronic health records, physician claims datasets, disease registries, and other health data repositories in multiple institutions and clinics. The resulting analyses can provide information that complements traditional clinical trials. Follow-up might be longer than would be possible in some clinical trials, and completeness for key health encounters such as hospitalizations and emergency department visits can be more comprehensive[20]. Information gathered concerning subsequent therapies might also be more complete. Accordingly, real-world evidence from ICES has guided policymakers, managers, planners, researchers, and practitioners in their efforts to optimize the provincial health system.

Using linked ICES data, the proportion of OCTANE patients benefiting from NGS-informed therapy will be described, as will the effects of testing on overall survival. Health resource use, outcomes, and costs will be compared for patients enrolled in OCTANE and matched patients at institutions not enrolling patients on OCTANE. This use of the linked data will allow for the creation of a comprehensive picture of health care use and costs in the Ontario system based on use of NGS testing.

The real-world effects of NGS test results on clinical decision-making will also be assessed in OCTANE by surveying the treating oncologists to ascertain whether NGS testing data were used to inform treatment selection and to collect information about specific treatments prescribed, duration of matched treatment, and the best-response outcomes. Treating oncologists will be surveyed at regular intervals after a patient's NGS sequencing results are reported to OCTANE until that patient is known to be deceased. For a subset of patients, those data will be compared with data garnered through the ICES linkage.

SUMMARY

The primary goal of OCTANE is to build broad capacity for cancer genetic testing throughout Ontario. The process has required collaboration between physicians, scientists, informatics experts, and hospital sites across the province. Success in making further treatment options available to patients will be evaluated over time as patients, in increasing numbers, undergo sequencing and have their outcomes recorded.

The experience gained through OCTANE can provide guidance to other provinces that might be interested in undertaking a similar initiative. Several important lessons have been learned. Archival tumour samples for many patients are very limited, and so the engagement of pathologists is critical to ensure timely retrieval and review of available tissue for targeted sequencing and storage in the research repository. In routine practice, pathologists do not typically use the OncoTree ontology (http://oncotree.mskcc.org/#/home) for diagnostic reporting, and trained personnel are required to map diagnostic pathology terms to facilitate data-sharing. Although detection of variants by multiple clinical testing laboratories is highly concordant, reporting practices vary across sites. For instance, some laboratories create a formal report that that includes all variants detected on the panel; other sites report variants only in genes included on their laboratory testing licenses; and still others do not create a report—clinicians access research testing results through the OCTANE cBioPortal. A flexible approach to participant recruitment, NGS panel sequencing, and variant reporting that accounts for local differences in practice and research capacity can facilitate intraprovincial data-sharing.

The framework used for OCTANE can be translated to other provinces and could enable the delivery of precision oncology nationwide. The OCTANE collaborative model can also be applied to other (non-cancer) disease settings in Canada in which the effects of broad-based genetic data are uncertain and further data are needed to inform decisions about reimbursement within provincial health care systems.

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CONFLICT OF INTEREST DISCLOSURES

JB has acted as a consultant for Insight Genetics, BioNTech, BioTheranostics, Pfizer, RNA Diagnostics, and OncoXchange, has received research funding from Thermo Fisher Scientific, Genoptix, Agendia, NanoString Technologies, Stratifyer Molecular Pathology, and BioTheranostics, and holds gene signature–related patents PCT/CA2016/000247, PCT/CA2016/000304, and PCT/CA2016/000305; LLS has served as a consultant (compensated) for Merck, Pfizer, Celgene, AstraZeneca/Medimmune, MorphoSys, Roche, GeneSeeq Technology, Loxo Oncology, Oncorus, Symphogen, Seattle Genetics, GlaxoSmithKline, and Voronoi, and has received grant or research support (institutional clinical trials) related to Novartis, Bristol–Myers Squibb, Pfizer, Boehringer Ingelheim, GlaxoSmithKline, Roche/Genentech, Karyopharm, AstraZeneca/Medimmune, Merck, Celgene, Astellas, Bayer, AbbVie, Amgen, Symphogen, Intensity Therapeutics, Mirati Therapeutics, and Shattucksm Avid, and is a stockholder in Agios Pharmaceuticals (spouse); PLB has institutional financial interests (sponsored clinical trials) related to Bristol–Myers Squibb, Sanofi, AstraZeneca, Genentech/Roche, Servier, GlaxoSmithKline, Novartis, SignalChem, PTC Therapeutics, Nektar Therapeutics, Merck, Seattle Genetics, Mersana Therapeutics, Immunomedics, and Lilly, and has also served on advisory boards (uncompensated) for Bristol–Myers Squibb, Sanofi, Pfizer, Genentech/Roche. All remaining authors have no conflicts of interest to disclose.

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