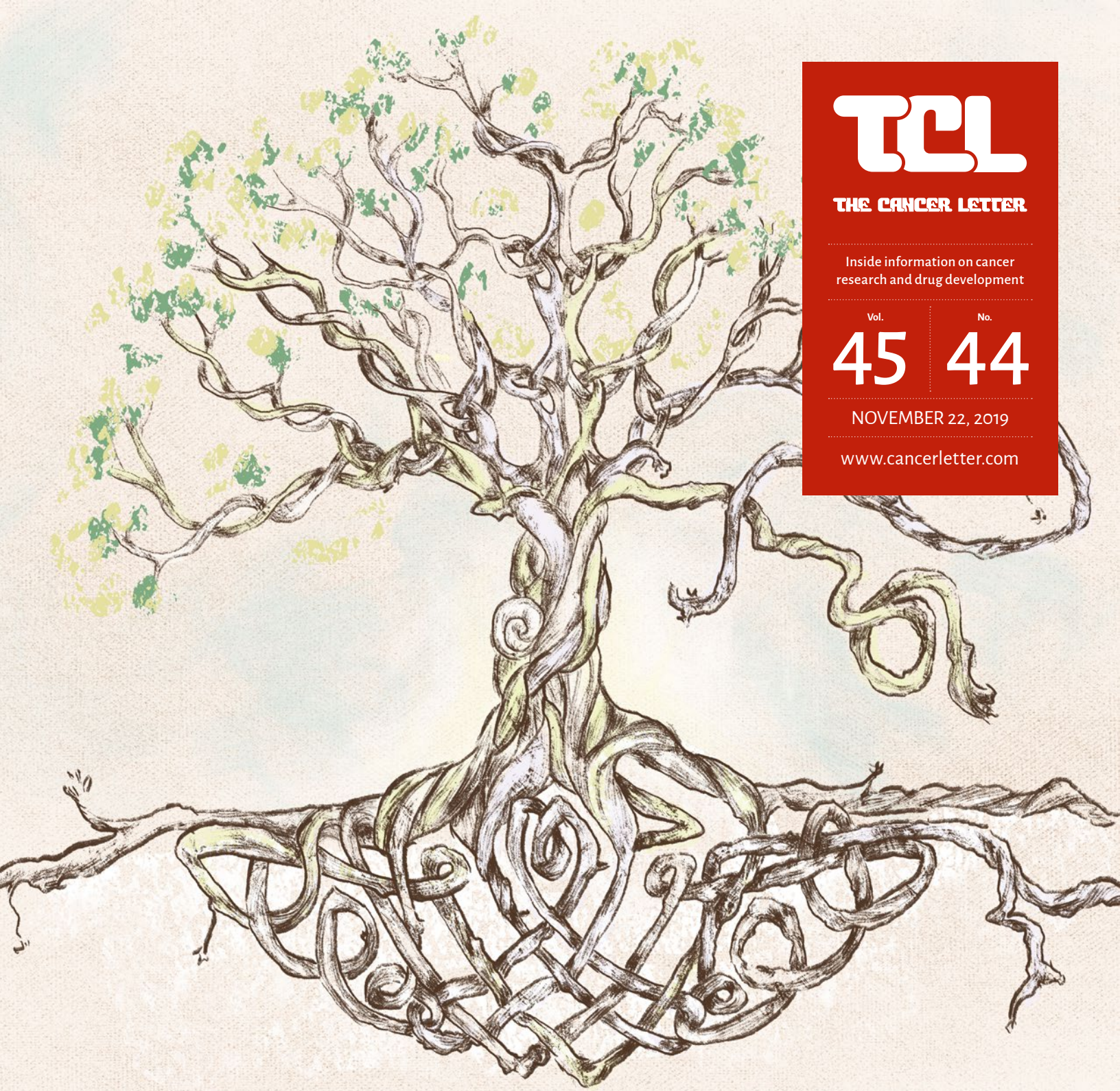

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REAL-WORLD EVIDENCE AT A GLANCE: HOW A COLLABORATION OF "FRENEMIES" PRODUCED COMMON DEFINITIONS FOR REAL-WORLD ENDPOINTS

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University of New Mexico Comprehensive Cancer Center

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REAL-WORLD EVIDENCE

REAL-WORLD EVIDENCE AT A GLANCE:

HOW A COLLABORATION OF "FRENEMIES" PRODUCED COMMON DEFINITIONS FOR REAL-WORLD ENDPOINTS

By Matthew Bin Han Ong

Ten health care research organizations, with help from FDA and NCI, have developed a set of common definitions for real-world endpoints, including overall survival, progression-free survival, and other non-traditional endpoints.

The new common definitions are published as part of a pilot study led by Friends of Cancer Research, which announced the conclusions of this phase of the project at a recent gathering in Washington, D.C.

At the Sept. 18 event, the 8th Annual Blueprint for Breakthrough Forum, a speaker nicknamed the collaboration "Frenemies of Cancer Research." The suggestion set off a wave of loud, albeit nervous laughter, because the joke was on the nose—to collaborate, many of these companies had to set aside their competitive agendas, which made for an uneasy peace.

The companies that participated in the Friends Pilot Project 2.0 are: Aetion, CancerLinQ, Concerto HealthAI, COTA, Flatiron Health, IQVIA, Kaiser Permanente, OptumLabs, McKesson Life Sciences, Syapse, and Tempus.

The Friends effort is central to realizing one of the primary mandates within the 21st Century Cures Act of 2016, which requires FDA to consider using real-world evidence to complement and supplement data generated through traditional clinical trials in drug regulation.

The project has one especially important patron. "FDA was instrumental in providing expertise throughout the entirety of the project, including its development," Jeff Allen, president and CEO of Friends, said to *The Cancer Letter.*

Most of the companies involved in the Friends effort regularly compete against each other for grants, access to health systems, and funding from pharmaceutical companies that are plotting strategy in the new RWE world.

The stakes are high:

As FDA continues to approve immunotherapies and targeted therapies that may have broad application across disease types, academic institutions, professional associations, as well as Big Data and Big Pharma, are vying to acquire patient data and put it to commercial use.

And at the heart of the business is the core lexicon—standard, agreed-upon definitions for real-world endpoints.

With FDA guiding the creation of the pilot methodologies and definitions in the Friends endeavor, data companies and research organizations that participate

gain a real advantage—by putting their thumbprints on the process, they shape the development of these endpoints and definitions, perhaps ensuring that these elements correspond with the strengths of their respective data sets.

The Cancer Letter wanted to know how the collaboration was structured in a systematic way, which problems were being solved, and what are the questions that have yet to be answered.

As they jostle for prominence, are these companies creating an RWE equivalent of the Tower of Babel, even as they claim to be finding a common tongue?

To gain a deeper understanding of how these disparate groups are working together while continuing to compete with each other, *The Cancer Letter* presented the leadership of 10 companies with the same set of questions. These include:

- What is your organization's business model, and how is your work unique?
- What are your takeaways from the Friends project?
- How did you address issues of data quality and transparency in this project?
- Will you participate in phases three and four of the project? What are the next steps?
- How would you describe your organization's RWE portfolio?
- What will you do with these endpoints should FDA accept the final definitions?
- Is it possible for you to collaborate with competitors after the Friends project is complete?

As the companies discuss the future of data sharing in cancer research and their individual projects, *The Cancer Letter* found broad consensus on the applications of the Friends framework, the necessity of collaboration in data research, and what it would take to make FDA comfortable with using real-world endpoints in regulatory decision-making.

Their responses appear on page 18.

"Ultimately, the results of [the Friends project] will be informative to oncologists and patients by filling evidence gaps about the performance of medical products used in a real-world setting, including populations that may not have been represented in clinical trials," Allen said.

"It has also helped to characterize how several metrics that are readily obtained from electronic health data (such as time-to-treatment discontinuation) correlate to more traditional clinical measures like tumor progression or survival."

A conversation with Allen appears on page 14.

Which patient populations and disease subtypes are being studied in the Friends collaboration?

The project focuses on patients with advanced non-small cell lung cancer who received immune checkpoint inhibitors.

This second phase builds on earlier work in 2018, which previously concluded that it was possible to identify a high level of shared characteristics across varying data sets—demonstrating that it is feasible to extract data about specific patient populations from disparate sources of data.

"It was amazing to see [the Friends effort] moving from Pilot 1.0 to Pilot 2.0, moving from six data partners to 10 data partners," said Amy Abernethy, principal deputy commissioner and acting chief information officer at FDA. "The idea of collaboration, on a scale like this, with the speed to which these projects got done is pretty remarkable.

"What happened is, in doing the project about endpoints, they exposed a whole bunch of other issues such as definitional issues, and differences in the source data systems, etc.," Abernethy said Sept. 18 at the Friends Breakthrough Forum. "And so, one of the things that's really important about doing this work is starting in one place exposes a whole bunch of other things that are important to work our way through."

How does the Friends project fit into FDA's priorities for building a regulatory infrastructure for RWE? How do studies based on RWE differ from traditional clinical trials?

Last December, FDA published a framework for evaluating the use of RWE, which lays out the fundamentals of the agency's approach to developing guidances for using real-world data in drug regulation.

Future guidances will focus on trial designs using real-world data as well as assessment of the reliability and relevance of real-world evidence in describing drug effectiveness (*The Cancer Letter*, Jan. 4).

"One of the first things to say about real-world evidence is that it's already here. FDA is already using RWE in certain areas," said Ned Sharpless, then FDA acting commissioner, at the Friends Breakthrough Forum. Sharpless returned to NCI as director earlier this month (*The Cancer Letter*, Nov. 8).

"The FDA, for its part, has to, in some ways, upgrade our infrastructure to be able to be a better partner for industry," Sharpless said at the Sept. 18 event, addressing the agency's Technology Modernization Action Plan (*The Cancer Letter*, Sept. 20). "FDA is going to try and upgrade its information-handling infrastructure to be a better partner for using things like real-world evidence and other kinds of data."

Unlike traditional clinical trials, in which patients are enrolled based on eligibility criteria, and information is collected according to parameters set in prospective trials designed to evaluate conventional endpoints, real-world studies use existing historical and real-time data—captured from electronic health records, claims data, and retrospective population-level data—to extract evidence that could then be evaluated in synthetic arms.

What are the objectives of the Friends study? And how are the real-world endpoints defined?

In Pilot 2.0, the Friends collaboration developed common definitions for endpoints, based on the description of advanced NSCLC patients in real-world data sets. The objectives for phase two of the study were:

1. Describe demographic and clinical characteristics of patients with advanced NSCLC receiving frontline chemotherapy doublet, PD-(L)1 monotherapy, or PD-(L)1 + doublet chemotherapy—to provide baseline understanding of the similarities and differences among the datasets to better understand the confounding factors that may need to be considered when interpreting the data.
2. Evaluate treatment effect size in frontline therapy regimens using real-world endpoints—so that researchers could agree on data source-specific definitions and measurement of endpoints assessed through real-world data in order to ensure reliability, consistency, and conservation of clinical meaning.

The Friends project concluded that the myriad data organizations were able to reach "high-level alignment" on important data elements and definitions for real-world endpoints in the context of a focused research question, despite variation in the underlying sources of data.

"This effort showed that it's possible for real-world oncology data organizations to align on considerations for identifying patients across diverse types of sources, from claims-based datasets to EHRs," Nicole Mahoney, senior director of regulatory policy at Flatiron Health, said to *The Cancer Letter*. "We were also able to align on high-level definitions for real-world endpoints, and identify important data elements that need to be collected in order to help answer a specific clinical question."

The four common definitions used—and published—by Friends are:

- **Real-world Overall Survival (rwOS):** Length of time from the index date to the date of death, or disenrollment (need to define gap in enrollment). For claims data, health plan disenrollment date is incorporated if deaths are not captured among those who leave health plan coverage.
- **Real-world Time to Next Treatment (rwTTNT):** Length of time from the index date to the date the patient received an administration of their next systemic treatment regimen or to their date of death if there is a death prior to having another systemic treatment regimen.
- **Real-world Time to Treatment Discontinuation (rwTTD):** *Data*: Length of time from the index date to the date the patient discontinues frontline treatment (i.e., the last administration or non- cancelled order of a drug contained within the same frontline regimen). Discontinuation is defined as:
  - Having a subsequent systemic therapy regimen after the frontline treatment;
  - Having a gap of more than 120 days with no systemic therapy following the last administration; or
  - Having a date of death while on the frontline regimen.
- **Real-world Progression Free Survival (rwPFS):** Length of time from the index date to the date of a real-world progression (rwP) event (i.e., distinct episode in which the treating clinician concludes that there has been growth or worsening in the aNSCLC based on review of the patient chart) at least 14 days after frontline treatment initiation, or death.

The full definitions of these real-world endpoints are available here.

Did the Friends study conclusively determine whether the survival outcomes and treatment patterns for advanced NSCLC patients—generated based on these endpoint definitions—are similar throughout real-world data sets?

At first glance, some of the Kaplan-Meier curves for these endpoints appear to be visually "tight," as if to suggest that patient survival outcomes, for instance, may be similar across data sets.

However, it's too early to derive formal conclusions regarding the performance of these treatments in real-world settings or demonstrate that real-world endpoints are accurate proxies for conventional clinical trial endpoints.

"The Friends pilot may provide an opportunity to discuss how the underlying quality of specific data elements may impact the outcomes we observe," Mahoney said. "For example, date of death is not always captured in real-world clinical settings. Given that incomplete information on death can skew overall survival analyses, data organizations have to link or supplement information with external sources.

"The impact of incomplete death data highlights the importance of benchmarking it to the gold standard, which is the National Death Index, to generate quality metrics, such as sensitivity."

Validating these endpoints will require stratification of patient populations by demographic characteristics as well as by PD-(L)1 status to compare outcomes, and additionally, subsequent benchmarking of these outcomes against clinical trials.

"We will be pursuing this and looking into other questions, like using the framework in other disease settings, and applying clinical trial inclusion/exclusion criteria to the real-world populations to validate endpoints over the coming months," Allen said. "While our goal isn't to make real-world studies mirror clinical trials, this may be an important internal validation step to increase confidence in the data quality and conclusions being drawn from a broader real-world dataset."

What role did NCI play in the study?

The Friends collaboration also includes patient information from SEER, a rigorously curated population-based data set.

"We felt like being a part of this pilot was important to understand real-world evidence and really understand how we can produce analytics on emergent therapies, obviously, the project focuses on immunotherapies," said Donna Rivera, a scientific project officer in the Surveillance Informatics Branch within the Surveillance Research Program of the Division of Cancer Control and Population Sciences at NCI.

"I think our dataset is the only population-based cancer-specific data set. SEER-Medicare is comprised of data from both SEER, which is 16 population-based cancer registries covering 34.6% of the U.S. population linked with Medicare claims data," Rivera said to *The Cancer Letter*. "Data quality studies are conducted, and, importantly, within SEER is the categorization of tumor data. So, the site, histology, laterality, grade, these categorizations of the tumor—the way we code our definition for our data is different than some of the ways the other groups are using it, because they don't have the same level of detail in their data.

"The vast amounts of data in this analysis require a lot of collaborative discussion on data elements, because the elements are coming from different places—we have claims data, but there's certainly many other companies within this pilot that also have EHR data. Some people have structured fields, unstructured fields," Rivera said. "Alignment on definitions, understanding the statistical analysis, even cohort variation, all of these things, I think, are fundamental.

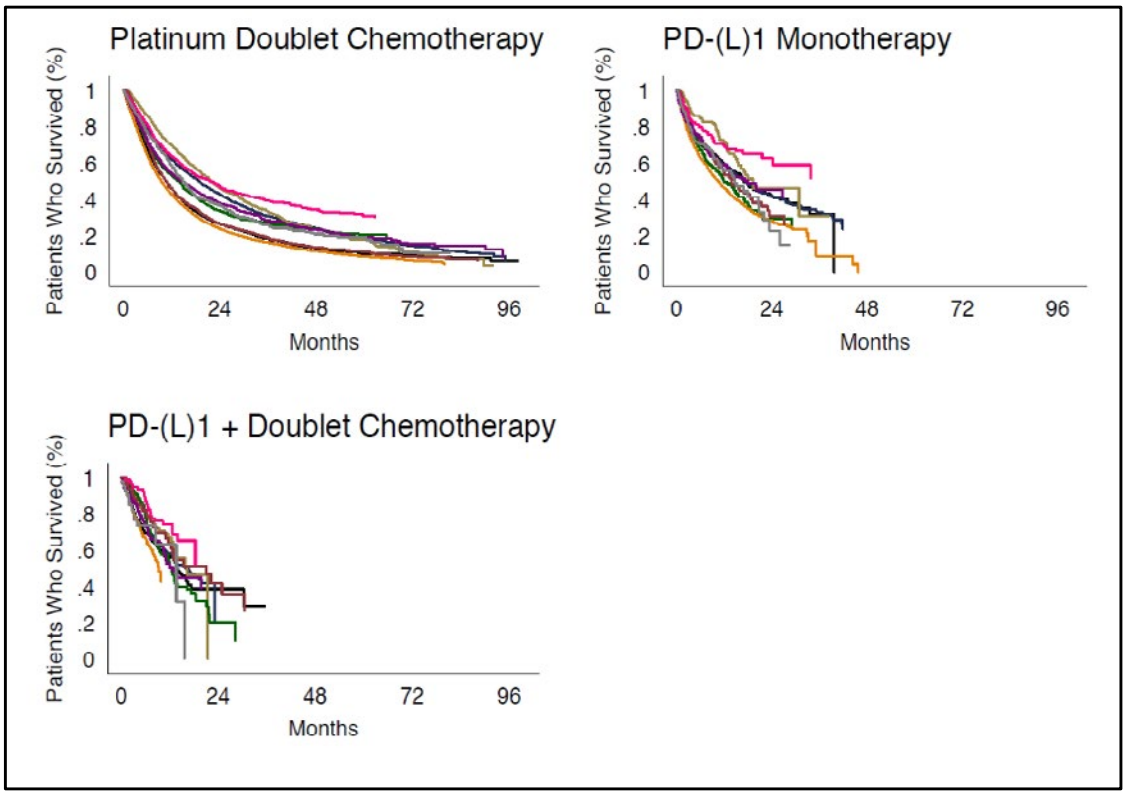
"So, differences in age, differences in stage, PD-(L)1 testing, smoking as a smoking status. Those really have to be contextually understood by each dataset when evaluating outcomes."

How is RWE used in innovative trial designs as our understanding of the genetic underpinnings for cancer continues to evolve?

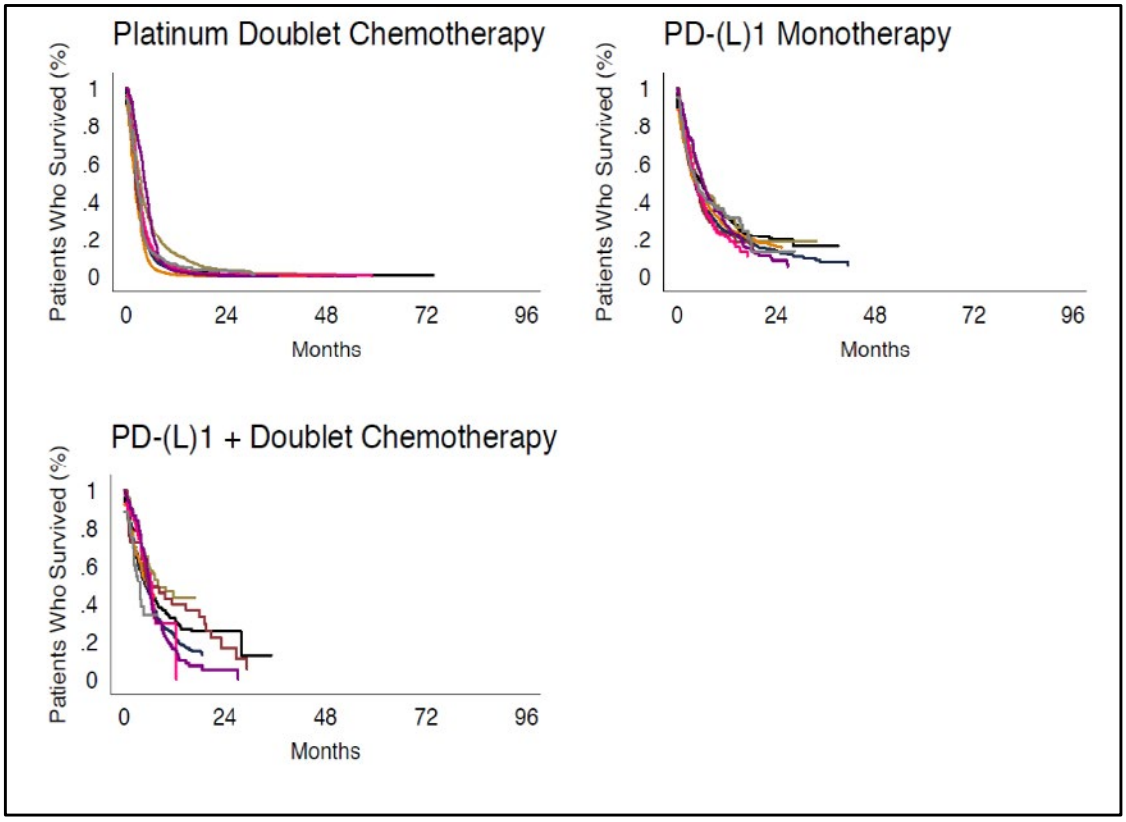
Increasingly, cancer researchers are exploring the uses of RWE in hybrid and pragmatic trial designs—and within master protocols or adaptive trial designs—to evaluate the treatment effect of immunotherapies and targeted therapies.

"Precision medicine presents a substantial challenge to the current clinical development model: as patients are categorized into smaller and smaller cohorts based on molecular and clinical criteria, it will become difficult to perform RCTs for every drug-molecular-clinical indication

Graph 14. Kaplan-Meier Curve of rwOS by Treatment Category



Graph 16. Kaplan-Meier Curve of rwTTD by Treatment Category



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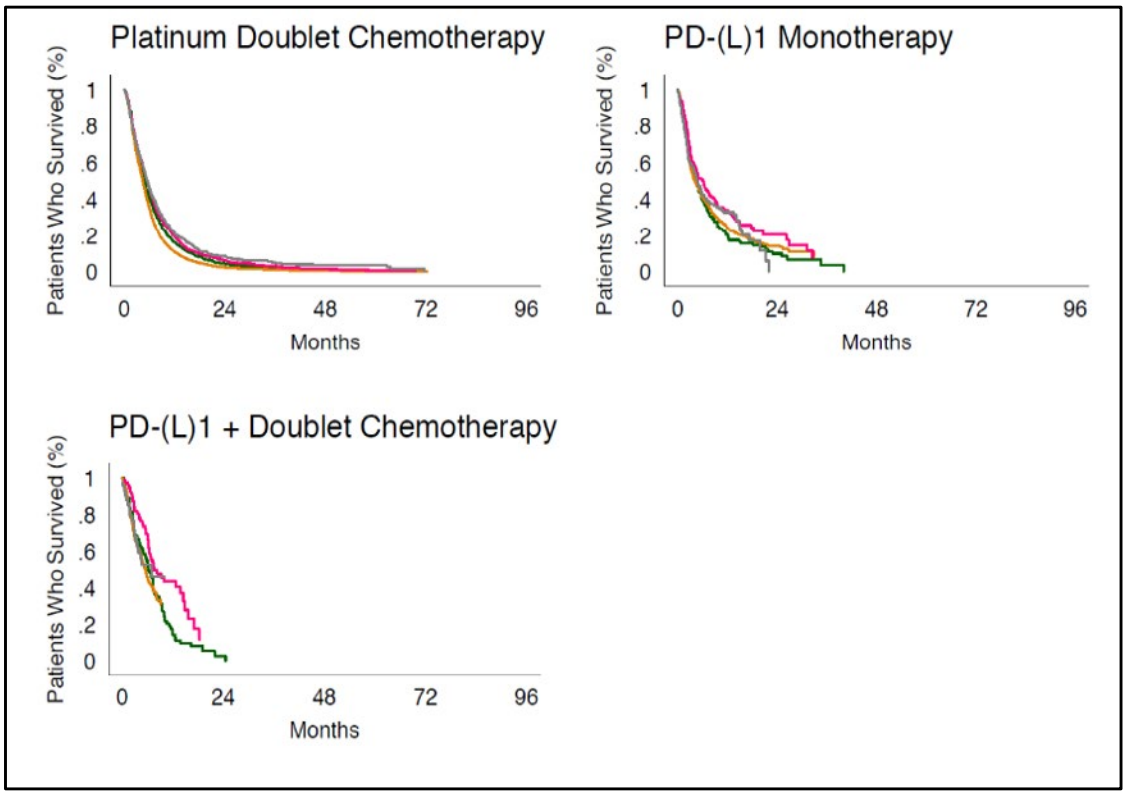
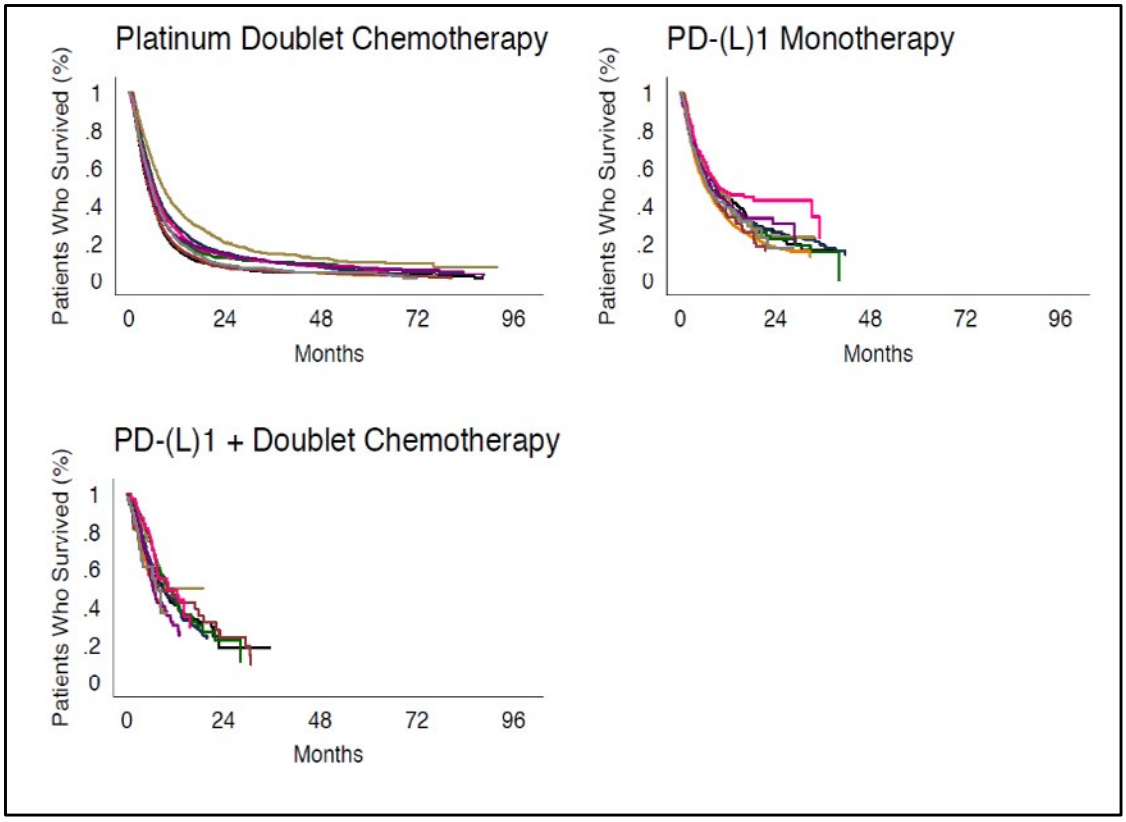
Graph 15. Kaplan-Meier Curve of rwPFS by Treatment Category



Graph 17. Kaplan-Meier Curve of rwTTNT by Treatment Category



due to lack of patient availability and high costs," Jonathan Hirsch, founder and president of Syapse, said to *The Cancer Letter*.

A scenario that is growing in importance involves the use of RWE to support granting of an expanded indication for a drug already approved in another indication on the basis of randomized clinical trial data, Andrew Norden, chief medical officer of COTA, said to *The Cancer Letter*.

"A recent example was the approval of Ibrance (palbociclib) for male breast cancer, which relied on multiple types of RWE against the backdrop of RCT data previously generated for breast cancer in women," Norden said (*The Cancer Letter*, April 19). "A related application involves the creation of an external control group from RWD. Imagine that a new drug is being developed to target a novel mutation in patients with highly refractory solid tumors.

"In this case, patients are unlikely to accept randomization to an existing standard of care—which is associated with poor outcomes—and oncologists have ethical concerns about randomization because some evidence of unusual activity has been observed during a phase I study.

"Therefore, the sponsor initiates a single arm phase II study with the blessing of the FDA. In this circumstance, the control group may be selected from a robust RWD set. Robustness is important because of the requirement to match prognostic factors between the experimental group and the RWD-derived control group as closely as possible."

In structured format, real-world data is a powerful tool that can be used to rapidly understand whether subpopulations of patients are responding to drugs that aren't indicated for their disease, whether patients with rare and potentially actionable mutations exist, and how well a drug performs in real-world patients that may be less healthy and older than those accrued to a clinical trial.

"I think that for organizations and regulatory bodies to trust real-world data more, it's not necessarily certified using 'the entirety of the dataset,' but ensuring the dataset you're using for a particular analysis is fit-for-purpose," Sarah Alwardt, vice president of data, evidence and insight operations at McKesson Life Sciences, said to *The Cancer Letter*. "So, fit-for-purpose was definitely the phrase that we heard a lot, and making sure that everything that was outlined in the FDA framework for real-world evidence around general reliability, quality, and transparency are achieved, but starting to get into, 'What does that actually mean?' and 'How is that to be defined?'"

What does it take to curate RWE that is not only fit-for-purpose, but also fit for submission to FDA and other regulatory agencies?

To mine real-world data that isn't readily structured, many data companies invest heavily in large teams of quantitative experts, data scientists, software engineers, programmers, and support staff.

The objective is to abstract information from patient records in a reliable manner without introducing errors and data artifacts as well as design programs and application interfaces that can both receive structured data and enable analyses, and ensure that the curated data is high quality and sufficiently complete for use in studies.

"In order to fully realize the potential of research and analytics in [precision and cancer], we also need to work toward better data availability to address questions in these areas—and this points to another area of data limitation currently," Lawrence Kushi, director of scientific policy in the Division of Research at Kaiser Permanente Northern California, said to *The Cancer Letter*. "One key part of this is being able to identify readily, in a structured format, people who've been tested for specific clinical genetic tests, and the results of those tests. For example, PD-(L)1 testing or EGFR testing—relevant to this specific project—are being done to guide clinical decisions.

"When these gaps in data availability are solved, then any future guidance on generating real-world evidence from the FDA would be easier to follow."

To use RWE in a consistent and meaningful way to inform regulation of cancer drugs—whether for new indications, or to confirm clinical benefit in the post-market setting—the data needs to be organized to answer specific questions rooted in standard definitions for real-world endpoints.

"Through these projects, we can develop and implement common endpoints across different real-world data sources," Robert Miller, medical director of the American Society of Clinical Oncology's CancerLinQ, said to *The Cancer Letter*. "We have demonstrated that the different sources of data can yield fairly similar results regarding patient outcomes.

"Another unique aspect is that this project is exploring non-traditional endpoints, such as time to next treatment and time to treatment discontinuation, that do show promise as potential alternate clinical endpoints to progression-free survival and others commonly used in clinical trials. TTNT and TTD may provide more clinically relevant endpoints because they are related to reasons that patients and clinicians alter clinical care, taking into account toxicity, efficacy, and other factors."

Regulatory agencies in other countries are also developing frameworks for using RWE, said Nancy Dreyer, chief scientific officer and senior vice president of

IQVIA Real-World Solutions Center for Advanced Evidence Generation.

"Once there is clarity about the evidentiary requirements for the FDA and other regulatory bodies, drug companies and medical product developers will feel more confident about using real-world evidence to supplement their regulatory applications for new indications and label expansions," Dreyer said to *The Cancer Letter*. "IQVIA is also helping regulators in Europe, Japan and China develop guidance documents. All these regulators are calling for health stakeholders to share their experiences using real-world evidence, including pilot projects that will inform the development of formal guidelines."

Researchers and companies are already able to use real-world evidence in many settings, even without specifically established guidance, said Jeremy Rassen, president and chief science officer at Aetion.

"Global regulators and value assessment bodies are increasingly incorporating RWE into their decision-making, and letting us know—in ongoing discussions and through public documents—what works and what doesn't," Rassen said to *The Cancer Letter*. "You can glean a few meta-themes from Pilot 2.0 and the related white paper: first, the importance of collaborative work among stakeholders including sponsors, data holders, analytic experts, regulatory agencies, and groups like Friends."

Is transparency in data needed? What happens once FDA finalizes the definitions for real-world endpoints?

As RWE is increasingly used to support regulatory approvals, some experts and patient advocates have called for greater transparency and a demonstration of replicability of results based on real-world data.

"Tempus agrees that transparency is critical to ensure confidence in RWE results, and the importance of investigating fit-for-purpose, quality of underlying data along with any variability in the population characteristics and/or methodological assumptions made during the analysis," Gary Palmer, chief medical officer of Tempus, said to *The Cancer Letter*.

"When the FDA issues the final guidance for RWEndpoints, collaborations between data organizations or pooling data (rather than analyses) from them become more achievable. We will still need to investigate the fit-for-purpose of each contributing data organization or dataset, as well as address the unknown level of overlap between them."

With formalization, the industry will have even more confidence and clarity as to where and how real-world data can aid pre- and post-approval decisions, said Mark Walker, chief scientific officer of outcome science and services at Concerto HealthAI.

"It further is aiding the generalizability of regulatory intent studies to the treatment decisions of community practitioners—a further goal of this move towards real-world evidence being integral to different study phases and decisions," Walker said to *The Cancer Letter*. "Different data sources can yield similar patterns of findings across endpoints—and that is what we saw with the Friends of Cancer Research project.

"The value here is that we can achieve insights into specific populations or diseases, across different data sources that are comparable—thus increasing the confidence and the utility of those different data sources alone or in combination."

There will be a need for more, not less collaboration, as the field matures, said CancerLinQ's Miller.

"The FDA framework may define regulatory endpoints for RWD, but there are still a lot of unanswered questions," Miller said. "There will continue to be conflicting interests, but based on this experience, I believe there is an opportunity to work together and collaboratively explore unanswered questions about real-world data quality, new endpoints, comparison with trials, and a host of other methodologic issues. ASCO is highly interested in continuing to be involved in this type of exploration."

Companies should be able to continue to find areas in real-world research where their interests may align, McKesson's Alwardt said.

"Of course, the easiest thing is if all data are free and freely available, and we all move forward. That is the most unlikely to happen," Alwardt said. "So, I don't think we're there yet with this, but I do believe that there is an opportunity for us to find a way forward and common ground with the data that both protects the individual value and the perception of value for the individual companies, but still be able to provide really good workable datasets for regulators and to be able to continue to make good decisions for us.

"This was definitely a first step in thinking about how different our data sets are across a number of organizations, and where we can start to find commonality to be able to use these data for the benefit of patients."

Q & A

Allen spoke with Matthew Ong, associate editor of *The Cancer Letter.*

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CONVERSATION WITH THE CANCER LETTER

Friends' Allen: Real-world endpoints can be used to fill evidence gaps about performance of medical products

"Ultimately, the results of this project will be informative to oncologists and patients by filling evidence gaps about the performance of medical products used in a real-world setting, including populations that may not have been represented in clinical trials."

Jeff Allen
President and CEO, Friends of Cancer Research

If real-world endpoints are indeed accurate proxies for clinical trial endpoints, real-world endpoints should start to look increasingly similar to the clinical trial endpoints as more stringent criteria are applied, said Jeff Allen, president and CEO of Friends of Cancer Research.

Friends has published a set of common definitions for real-world endpoints, including overall survival, progression-free survival, and other non-traditional endpoints. The project focuses on patients with advanced non-small cell lung cancer who received immune checkpoint inhibitors.

"By running these analyses in parallel with 10 different partners, we're able to identify different data characteristics, such as the histological distribution within each dataset, that can influence the outcomes measured," Allen said.

"We have also been cognizant of how disease setting, practice patterns, and specific treatment regimens would impact the meaningfulness of the real-world endpoints that we used and tried to account for those possible differences in our framework."

The pilot project is ongoing: the collaboration will focus on applying inclusion/exclusion criteria in order to isolate clinical trial "eligible" real-world patients and compare outcomes of both groups.

Allen spoke with Matthew Ong, associate editor of *The Cancer Letter.*

Matthew Ong: In a nutshell, could you describe the Friends effort—and FDA's role—in defining the utility of real-world endpoints? Also, what would this mean for oncologists and patients?

Jeff Allen: The RWE Pilot 2.0 project used our existing framework, developed during RWE Pilot 1.0, to assess several frontline treatment regimens in real-world patients with advanced non-small cell lung cancer.

Friends worked with 10 health care research organizations, FDA, and NCI to develop the pilot methodology and endpoint definitions used in Pilot 2.0. FDA was instrumental in providing expertise throughout the entirety of the project, including its development.

Ultimately, the results of this project will be informative to oncologists and patients by filling evidence gaps about the performance of medical products used in a real-world setting, including populations that may not have been represented in clinical trials.

It has also helped to characterize how several metrics that are readily obtained from electronic health data (such as time-to-treatment discontinuation) correlate to more traditional clinical measures like tumor progression or survival.

MO: What are your primary considerations in developing a real-world endpoints framework that is consistent and meaningful?

JA: Currently, a significant challenge for the field is in validating real-world endpoints that can be extracted from real-world data independent of the data source.

Sensitivity analyses, which validate real-world endpoints by testing the ability of the endpoints to detect changes within a population, are important internal controls that we are including in ongoing analysis.

We have also been cognizant of how disease setting, practice patterns, and specific treatment regimens would impact the meaningfulness of the real-world endpoints that we used and tried to account for those possible differences in our framework.

> [The collaboration] required an upfront agreement from all the participants to provide a high level of transparency regarding the type and level of detail of data they had available to align on common definitions.

That said, our future efforts will explore the use of the framework in a different disease setting to determine its broader applicability.

MO: What was the process for creating this set of common definitions for real-world endpoints?

JA: There were a lot of in-depth discussions with the groups concerning each variable to be extracted and endpoint generated.

It required an upfront agreement from all the participants to provide a high level of transparency regarding the type and level of detail of data they had available to align on common definitions.

All in all, this was a very collaborative process that demonstrates the importance of the work and commitment of the participating partners.

MO: How do you ensure that these common definitions can be used to generate evidence that might be substantially equivalent to—or that approximates—evidence created based on conventional endpoints?

JA: RWE Pilot 1.0 compared the correlation of real-world endpoints with the conventional endpoint of overall survival (OS).

In Pilot 2.0, we went back to the original pilot to identify outliers in the data and variations in how each group interpreted the endpoints to refine and standardize the real-world endpoints definitions.

MO: What have you learned, so far, using these common definitions, about the real-world outcomes for aNSCLC patients treated with frontline therapies?

JA: Although not necessarily surprising, patients treated with PD-(L)1 therapy are generally older and less healthy in real-world populations as compared to clinical trial patients.

We have also observed some interesting differences in practice patterns across the data sets that we will be exploring in the coming months with respect to distribution of drugs used across treatment groups.

By running these analyses in parallel with 10 different partners, we're able to identify different data characteristics, such as the histological distribution within each dataset, that can influence the outcomes measured.

This will be important for future applications of real-world data to consider reporting so that variations can be better understood.

MO: Within this project, what are some of the challenges with using different sources of data to provide information on treatment outcomes? What works, and what hasn't worked?

JA: In general, this is one of the biggest challenges associated with real-world data—establishing protocols and definitions that are applicable across different data sources, specifically because data sets range in the source of their data (electronic health records, claims-based, or some combination of the two) and granularity of the data that is visible within that data set.

In some cases, the alignment had to be on the intent of the definition, not the definition itself. For example, when identifying patients with complete records, this protocol looks very different, depending on whether you are looking at EHR or claims-based data.

MO: What would Pilot Project 3.0 be focusing on? Will your partners be stratifying patient cohorts to study treatment effect and outcomes at a more granular level?

JA: There was a wealth of data collected during Pilot 2.0 that can still be analyzed to provide further insights. Of specific interest to the group was the idea of stratifying patient populations by PD-(L)1 status to compare impact on outcomes.

We will be pursuing this and looking into other questions like using the framework in other disease settings, and applying clinical trial inclusion/exclusion criteria to the real-world populations to validate endpoints over the coming months.

In 2020, we hope to bring the 10 partner organizations back together to present these additional analyses for public discussion.

We've also been exploring with several additional data partners how real-world evidence and the endpoints characterized thus far may be leveraged in addition to a variety of other clinical and health care system endpoints to measure treatment effectiveness, toxicity management strategies, and acute service utilization rates (e.g. ER visit or hospitalization) to inform value assessments and quality of care.

MO: As you get closer to being able to validate real-world endpoints and benchmark them against clinical trials, what is the best-case scenario?

JA: Ongoing work with this pilot is to apply clinical trial inclusion/exclusion criteria to real-world populations in order to isolate clinical trial "eligible" real-world patients and compare outcomes of both groups.

If real-world endpoints are accurate proxies for clinical trial endpoints, we should see real-world endpoints become increasingly similar to the clinical trial endpoints as we apply increasingly stringent criteria.

While our goal isn't to make real-world studies mirror clinical trials, this may be an important internal validation step to increase confidence in the data quality and conclusions being drawn from a broader real-world dataset.

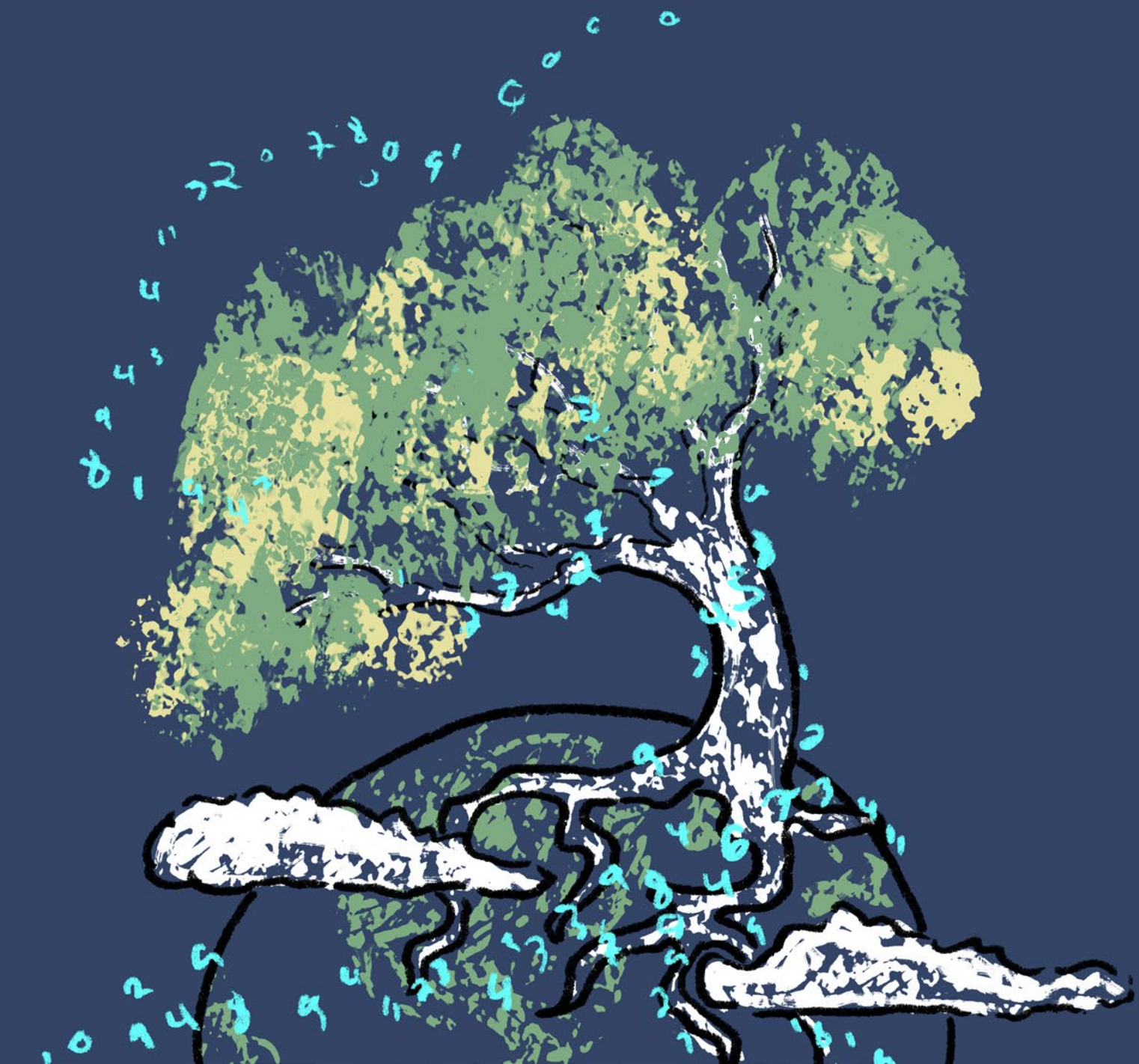
“There was a wealth of data collected during Pilot 2.0 that can still be analyzed to provide further insights. Of specific interest to the group was the idea of stratifying patient populations by PD-(L)1 status to compare impact on outcomes.”

Also, it could support the use of less strict clinical trial criteria to make clinical trial results more broadly applicable to real-world populations.

Learning to harmonize:

TEN HEALTH CARE RESEARCH ORGANIZATIONS TELL US HOW THEY FORMULATED COMMON DEFINITIONS FOR REAL-WORLD ENDPOINTS

CONVERSATION WITH THE CANCER LETTER



We asked the leadership of 10 companies to share their visions of the future of data sharing, describe their portfolios in real-world evidence, and opine on what it would take to convince FDA accept real-world endpoints in regulatory decision-making in oncology.

The new common definitions of clinical endpoints were recently published as part of a pilot study led by Friends of Cancer Research. with input from FDA and NCI.

With FDA guiding the creation of the pilot methodologies and definitions in the Friends endeavor, data companies and research organizations that participate gain a real advantage. By having a say in the process, they shape the development of these endpoints and definitions, perhaps ensuring that these elements correspond with the strengths of their respective data sets.

The Cancer Letter's questions were focused on how the collaboration was structured in a systematic way, which problems were being solved, and what are the questions that have yet to be answered.

Matthew Ong, associate editor of *The Cancer Letter*, asked all the companies the same 10 questions.

Jeremy A. Rassen

President, chief science officer, Aetion

AETION

Robert S. Miller

Medical director, CancerLinQ, American Society of Clinical Oncology

ASCO CancerLinQ
Shaping The Future Of Cancer Care

Mark S. Walker

Chief scientific officer, Outcomes Science & Services, Concerto HealthAI

Concerto HealthAI

Andrew Norden

Chief medical officer, COTA

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Lawrence H. Kushi

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Nicole Mahoney

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Jonathan Hirsch

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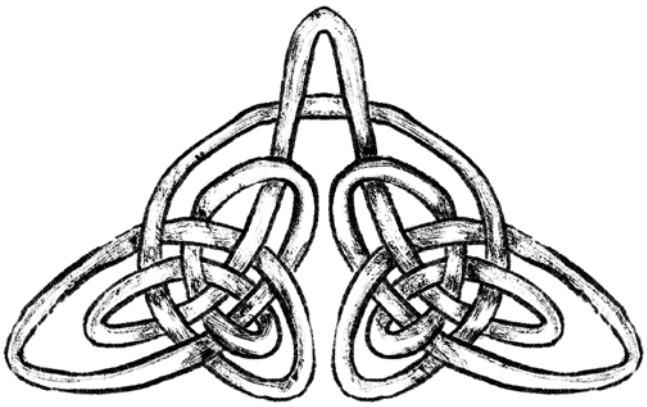
Gary Palmer

Chief medical officer, Tempus

TEMPUS



Matthew Ong: What does your organization excel at? In terms of data, what do you provide that is unique compared to your competitors and other health IT companies?

Jeremy A. Rassen, Aetion: We excel at providing transparent, reliable, and replicable real-world evidence for answering high-stakes questions. For any given question, you start with raw data, ready these data for analysis, analyze, and arrive at transparently-reported results. We bring unique expertise to data selection and transformation, to the analysis itself, and to the reporting that allows for analysis transparency and reproducibility—all guided by the principles that provide for regulatory-grade evidence.

Further, many analyses—particularly in oncology and with rare diseases—require several raw data sources to get at the answer to a given question. Working seamlessly with multiple data sets, each with its unique characteristics (such as possible data missingness), requires what we call "data fluency," a critical capability for ensuring appropriate selection and transformation of real-world data. Many companies are mono-lingual, if you will—they speak the language of their proprietary data set only, which is insufficient for many questions in oncology.

Robert S. Miller, CancerLinQ: CancerLinQ is the only physician-led, big data platform in cancer and contains comprehensive longitudinal clinical data from over 1.3 million cancer patients. This growing body of data represents a large cross section of cancer care in the U.S.—a geographically diverse mix of academic, health-system, and physician-owned practices, from 10 different EHR systems.

Mark S. Walker, Concerto: Concerto HealthAI has best-in-class expertise in creating research-ready, publications-grade data products developed from electronic medical record, genomic, claims, and patient reported outcomes data.

We refer to these products as being "use-case engineered," a novel approach where the data fields and sources are optimized to specific analyses or solutions. We complement this expertise with our AI/machine learning technologies, and study design and analytic services built on decades of experience working with real-world data.

In health data, 95% of the records are what is considered unstructured data. Consequently, our approach to working with electronic medical record data has emphasized going very 'deep' into the record, to extract information ordinarily available only in prospective data collection, and then integrating this information into structured and engineered data products and services that yield actionable information.

Concerto HealthAI understands how data and technology can be engineered together to enable insights and actions in the most devastating and rare diseases. This involves designing and delivering research ready, publications grade data products for all major solid tumors and hematological malignancies.

We are the leading company for advancing AI and machine learning methods for use with those data, allowing predictions and insights into specific patients and patient cohorts to inform new clinical study and clinical trial designs.

Andrew Norden, COTA: Using technology-enabled human abstraction techniques, COTA takes real-world patient data, hidden and fragmented within EHRs, and curates and organizes it such that clinicians can gain meaningful insights to make better decisions at the point of care—while also reducing costs.

This curated data powers COTA's CNA, a patented cohorting technology that groups clinically similar patients so a physician can understand how they respond to various treatments as well as their associated outcomes. This allows for a clearer understanding of which treatments result in the optimal outcome for a specific patient cohort.

The clinical depth of COTA's data is unmatched. With access to both academic and community-based cancer centers, COTA's EHR agnostic technology-enabled and human abstraction process makes sense of all relevant aspects of the patient journey, including data in physician notes, pathology, radiology, surgical reports, genomic testing results and referral docu-

mentation—to develop a longitudinal patient record and comprehensive picture of care.

Increasingly, COTA's regulatory-grade RWD is being used in clinical trials to develop external control arms (also known as synthetic control arms) with the goal of obviating the need for enrolling concurrent controls in certain circumstances. This has the potential to reduce the time and cost of the clinical development effort which can take as many as 10 years and cost hundreds of millions of dollars. Most importantly, it benefits patients, because no patient wants to receive a mediocre standard-of-care treatment or placebo when alternatively, there is an opportunity to receive a promising experimental agent.

Nicole Mahoney, Flatiron: Flatiron is more than a data vendor. We're bringing together clinical, statistical, analytical, and regulatory capabilities tailored to our partners' research and regulatory needs. Working closely with our partners across the health care ecosystem, we have had years of experience collaborating with our partners and the FDA, which informs our approach on data quality and analytical methodologies. In terms of our data offerings, we have access to de-identified patient level records at the source via our electronic health record and partnerships with our network of providers, which enables timely and scalable integration of clinically relevant real-world data. Furthermore, our data curation and analytical approaches are not a black box—they are transparent, with traceability of data to the source to generate evidence that is reliable.

Nancy A. Dreyer, IQVIA: IQVIA distinguishes itself in the industry by our combination of unparalleled data, advanced analytics, transformative technology and deep domain expertise. We are good at putting it all together.

We are scientific leaders who know how to generate scientific evidence about the effectiveness and safety of medical products in conditions of real-world use and how they perform in comparison to other available diagnostic or therapeutic choices. We work with regulators in major markets to create innovative ways to generate the necessary evidence to support new medicines that are safe, effective and affordable.

Our scale and depth of expertise allows us to provide fit-for-purpose research using multi-country clinical and pharmacy data to conduct clinical trials and/or prospective epidemiologic studies, including direct-to-patient research. These diverse tools and assets allow us to use randomization where needed, to collect data from clinicians following protocol-driven care and to use real-world data when it is likely to reliably capture the events of interest, as appropriate. We have an exciting portfolio of scientific tools.

Lawrence H. Kushi, Kaiser: Kaiser Permanente differs from many other organizations in that it is an integrated health care system in the full meaning of the term "integrated". That is, it is a health insurance provider, and the people who have Kaiser Permanente insurance also receive care from Kaiser Permanente providers in Kaiser Permanente facilities.

From a health care data availability, research, and analytics perspective, what this means is that, as researchers affiliated with Kaiser Permanente, we have access to the full range of clinical and administrative data, across the full spectrum of care that someone may receive. Thus, we can conduct health services research based on data across the full spectrum of cancer care, from primary prevention to end-of-life care. We can examine not just aspects of active oncology care and treatment, but also clinical encounters related to primary care, cancer screening, or comorbid conditions such as those related to cardiology or endocrinology. We can leverage electronic health records and insurance records.

This differs from most other groups that are trying to contribute in the cancer and health IT space to improve cancer care. These groups fall broadly into two categories, those that have access to health insurance claims data—OptumLabs is an example—and those that have access to detailed electronic health records documenting the cancer care experience. Flatiron Health or ASCO's CancerLinQ are examples of the latter. The former typically does not have access to the EHR data from the multiple health care systems in which they provide health insurance coverage; the latter typically does not have information about care outside the oncology experience, or does so in a relatively limited fashion, regarding time period or services covered, and may need to rely to claims data from multiple insurers to fill in these gaps in data about clinical care.

In terms of the way Kaiser Permanente is organized, I sit in one of its research groups. Each Kaiser Permanente health care region has a research group, and I'm part of the Division of Research in KP Northern California. These research groups are very similar to academic research units or departments. We're largely a soft money operation, funded primarily through grants and related mechanisms, and with minimal financial support from our parent organizations. So, we're not directly part of the health care or insurance provider side of Kaiser Permanente, although we continue to seek ways to better enhance the role of research in Kaiser's mission. But as part of Kaiser Permanente, we do have access to clinical and administrative data for research purposes. And so, that's the context in which we are participating in the Friends of Cancer Research initiative.

Just one example of how these distinctions play out in data harmonization and variable definition in the Friends of Cancer

Research effort is how we defined who was eligible to be included in a particular analysis. And so, everyone basically said, "Okay, if they've had at least two encounters within a defined time period, then we have reasonable confidence that they've been in that health care system so we can follow them for immunotherapy receipt and outcomes," whether it's the EHR-rich oncology practice group, or health insurance claims data.

In our case, we don't actually define potential data availability in that way. We can define it based on the health insurance that they have enrolled in. Because we're fully integrated, if an insured person seeks clinical care, they will do so through one of our facilities. And so, we can define eligibility for a given analysis based on enrollment periods

A rich data source like Optum could, in theory, do that, except the care that people receive could be at multiple different institutions or health care systems. And so, they only have the claims-level data from multiple different health care providers that aren't linked, except through their claims.

Note that we did align our eligibility definition with the other participating groups, based on number of visits, and it aligns well with both our enrollment approach and what the other groups ended up doing.

Sarah Alwardt, McKesson: I think one of McKesson's strongest advantages is that our iKnowMed oncology practice EHR system was not only built for oncology, but it's continually improved by practicing oncologists.

So, when we think about the data that are structured and the data that are captured through the hard work and the clicks of the oncologists, we know a number of very important clinical features that are captured for us to be able to extract and readily analyze—stage performance status, physician-documented line of therapy, and even diagnosis-naming. So, without having to either curate or algorithmically derive, there's a large breadth of information that we can get directly from oncologists.

We work with 10 of the 10 top biopharma companies and 18 out of the top 20 biopharma companies, because two of those aren't really in oncology. We also work with smaller biopharma companies. McKesson's data, evidence and insights business is an entirely externally-focused organization working with biopharma.

Jonathan Hirsch, Syapse: Syapse excels at making sense of messy real-world data in a health system environment, and enabling our health system and life sciences partners to use that RWE to improve care for patients. From a data standpoint, we believe these are the things that set us apart.

Comprehensiveness: Since we work with large integrated health systems, we are able to capture much more of the patient's longitudinal care journey, including their direct cancer care and their non-cancer care (e.g. their cardiac care). We believe this is critical to developing a full understanding of patient outcomes.

Representativeness: We work with providers across the U.S. and South Korea in many settings of care, including traditionally underserved and underrepresented communities. This provides a fuller and more representative picture of the cancer population.

Molecular: Syapse pioneered an interoperability solution for molecular data, allowing us to work directly with testing labs to structure and normalize molecular results at scale. The integration of molecular and clinical data is critical to realizing the vision of precision medicine in oncology.

Gary Palmer, Tempus: Real-world data is comprised of various types of data from a diverse set of sources including electronic health records, claims data, prescription data, and patient registries. The differences in health care systems, national guidelines, and clinical practice have driven different content.

Tempus not only has deep competency in combining these disparate datasets, but also pairing clinical data with molecular data from tumor/normal matched DNA sequencing, whole-transcriptome RNA sequencing, and immunological biomarker measurements to discover unique insights that can inform treatment decisions.

MO: What are your main takeaways from the Friends of Cancer Research pilot projects?

Rassen, Aetion: The recently-released Friends white paper covers a ton of important ground regarding the use of external control arms to augment single-arm studies in oncology. The paper goes all the way from basic methodology to a fully-worked out case study. It's an impressive effort on the part of Friends and all the stakeholders who participated in its creation.

In terms of analytic takeaways in the external control arm white paper, we as a group discussed and addressed a number of the challenges that come up when creating external control arms, and detailed a case study where external controls led to substantially the same result as randomized controls

Taking a step back, you can glean a few meta-themes from Pilot 2.0 and the related white paper: first, the importance of collaborative work among stakeholders including sponsors, data holders, analytic experts, regulatory agencies, and groups like Friends.

Second, we're starting to see the power of using RWE to transform how we understand the performance of new cancer therapies, by allowing us to compare against standards of care that are meaningful to regulators, payers, clinicians and patients.

Third, echoing what was said at a Friends meeting earlier this year, we're seeing that we can build upon the understanding offered by traditional RCTs to investigate non-traditional endpoints that can help all stakeholders—but most importantly, patients—to support thoughtful choices about what treatment is best for how an individual wants to approach their care.

Miller, CancerLinQ: Through these projects, we can develop and implement common endpoints across different real-world data sources. We have demonstrated that the different sources of data can yield fairly similar results regarding patient outcomes.

Another unique aspect is that this project is exploring non-traditional endpoints, such as time to next treatment (TTNT) and time to treatment discontinuation (TTD), that do show promise as potential alternate clinical endpoints to progression-free survival and others commonly used in clinical trials. TTNT and TTD may provide more clinically relevant endpoints because they are related to reasons that patients and clinicians alter clinical care, taking into account toxicity, efficacy, and other factors.

Walker, Concerto: Friends of Cancer Research is creating a unique and valuable community of expertise and assets to advance novel approaches for oncology research. It is creating its own "network effects" as different teams with different approaches can cross-reference each other thereby accelerate progress.

Different data sources can yield similar patterns of findings across endpoints—and that is what we saw with the Friends of Cancer Research project. The value here is that we can achieve insights into specific populations or diseases, across different data sources that are comparable—thus increasing the confidence and the utility of those different data sources alone or in combination.

The work also shows that variation in the underlying sources of data, the time frame covered by those data, geographic differences in the data, and the availability of unstructured medical records, all can affect the results of analyses in ways that may not always be obvious. Here too, we can see where these different sources may be comparable or optimized to specific analyses. Essentially, we're accelerating the understanding of the data sources fit for specific analyses and for many analyses.

Norden, COTA: The results of the pilot study showed alignment across different data sources and datasets even though companies were sourcing data differently—through EHRs, claims, tumor registries, and the like. This consistency helps prove the validity of real-world data across applications, spurring a need to understand the broad range of ways it can be used to support clinical research.

> "The differences likely reflect variability in characteristics of the different data sources, such as granularity of information captured or "data depth," differences in the underlying populations, or even selection criteria for how a patient is included in an EHR-derived cohort versus a claims-derived cohort."
>
> *– Nicole Mahoney, Flatiron Health*

Mahoney, Flatiron: Importantly, this effort showed that it's possible for real-world oncology data organizations to align on considerations for identifying patients across diverse types of sources, from claims-based datasets to EHRs. We were also able to align on high-level definitions for real-world endpoints, and identify important data elements that need to be collected in order to help answer a specific clinical question.

The pilot 2.0 work is important, and is still in the preliminary stages. Additional analyses are needed to help understand differences observed among cohorts derived from different datasets. The differences likely reflect variability in characteristics of the different data sources, such as granularity of information captured or "data depth," differences in the underlying populations, or even selection criteria for how a patient is included in an EHR-derived cohort

versus a claims-derived cohort. Further analyses are needed to better address the differences and understand how the data may be comparable.

Jennifer B. Christian, IQVIA: The goal of the Friends 2.0 pilot is to understand where and how RWE can be used to evaluate treatment effectiveness in lung cancer. To implement the 21st Century Cures Act, the FDA needs to better understand when real-world data can be trusted and determine the situations where real-world approaches can inform drug approvals and label expansions.

Through this work, we keep learning more about how RWE differs from traditional RCT data. The care a patient receives in an RCT is not the same as a patient receives in routine care, and the findings from RCTs are not necessarily generalizable to the real world. RWE, which is more reflective of routine clinical care, is complementary to RCTs, and the evidence derived from both sources provides a clearer picture to understand the benefits and risks of treatments.

Kushi, Kaiser: One main takeaway is that, as Dr. Ned Sharpless mentioned at the meeting in September, there is a "tsunami" of data from health care systems that are now available or becoming available. However, an associated takeaway is that the types of data differ, as demonstrated by the different organizations that are participating in this Friends of Cancer Research effort. There's undoubtedly a lot that we can learn about cancer care, how it's being delivered in the real-world setting, and determining the real-world effectiveness of care in populations that aren't necessarily in clinical trials.

Also, just learning about other aspects of health care delivery, whether it's disparities or the transition from active care to surveillance and long-term impact. Not that we've looked at any of those in this particular work with Friends of Cancer Research, but I think that all those things are possible given the types of data that are becoming much more readily available.

I think this Friends of Cancer Research effort is a good way of demonstrating the different strengths of different types of data sources and how they can, despite these differences, at least on clearly defined questions, can basically come up with results that look fairly similar.

Of course, the results do vary from setting to setting, and the next step that we have to work on is, "Okay, why do they vary?" Some of the obvious things are, for example, the populations probably differ a bit, such as in age range. So, we need to explore this in the next steps of what we're doing currently. But I think that, yes, there's a big opportunity.

I should mention that I used to run a grant, which no longer has funding, that was funded by the NCI called the Cancer Research Network. The CRN was basically a consortium of research groups, like the one I'm affiliated with, that are attached to health care systems, to support the conduct of cancer research in these settings.

And they were all integrated health care systems, at least in some core part. It included several Kaiser Permanente regions, Marshfield Clinic, Henry Ford, Geisinger, Health Partners, and a couple of others. and it was basically to support cancer research in these settings. I mention this partly because of the types of data that are available now, especially with the implementation of EHRs and how that was really pushed partly by federal legislation, but partly by advances in technology, that results in these data being available.

In the CRN context and in other data settings, people have said, "Oh, this is great. We can potentially better identify people to enroll in clinical trials." And sure, that's right. But that's only one application of these types of data. There are other health services and epidemiology, cancer-care delivery type of research that could be done.

One of the ways that I have sometimes thought about it has been, "Okay, we've got a research question related to cancer care, it might be appropriate for a clinical trial. Great. Go through the cooperative groups and do that." Or it may not be. And if not, maybe it's possible to look at it in these various settings, whether it's Kaiser Permanente or the Cancer Research Network, or Flatiron Health or OptumLabs. Let's make sure the question dictates what types of study designs and analytic approaches should be applied—not everything has to be a clinical trial—and data that are appropriate or necessary are used. So, some questions, yes, clinical trials. Let's do that. Other questions, maybe not.

And then there's the whole area that I think Friends of Cancer Research has been interested in and the FDA is interested in, which is, given that there are there are therapies that have been approved that are out there in clinical use, what's their real-world effectiveness? And of course, these data provider settings, whether they are claims data, detailed oncology data, or integrated health care systems data, that's where these questions could potentially be addressed. These are real-world data that could be examined to generate real-world evidence on real-world effectiveness.

I would say that, in the way that the FDA requires certain types of data and data elements and monitoring for clinical trials, that probably can't be done in the same way in the real world, so to speak. But there are probably ways of examining these real-world data that could really inform long term surveillance, long term health effects and whether drugs such as these immunotherapies are working, have the same types

of outcomes, or identify long-term unintended effects, in different populations.

Alwardt, McKesson: We're really excited to be part of that pilot. For one, it was nice to be in a room full of people who are thinking similarly—and, as I call myself, a "real-world data evangelist"—and understanding that real-world data will be important to not only the decisions we're making now, but even more important to the decisions that we'll be making in the future.

So, it was a good opportunity to have a rising-tide-raises-all-boats moment across the industry.

I think that it outlined a few things that we'll continue to need to work on, and that is understanding standard. I think that for organizations and regulatory bodies to trust real-world data more, it's not necessarily certified using "the entirety of the dataset," but ensuring the dataset you're using for a particular analysis is fit-for-purpose.

So, fit-for-purpose was definitely the phrase that we heard a lot, and making sure that everything that was outlined in the FDA framework for real-world evidence around general reliability, quality, and transparency are achieved, but starting to get into, "What does that actually mean?" and "How is that to be defined?"

I think we have a long way to go in that regard, but this was definitely a first step in thinking about how different our data sets are across a number of organizations and where we can start to find commonality to be able to use these data for the benefit of patients.

Hirsch, Syapse: This was an important effort to demonstrate that leading organizations in oncology real-world evidence can develop common definitions for cohorts and endpoints, conduct similar analyses, and come together to discuss results.

While this was not a formal validation study, it was a significant demonstration of how far the field has come in a few short years, and an illustration of the hard work in front of all of us to mature the use of real-world evidence in outcomes research, clinical decision-making, and regulatory decision-making.

Palmer, Tempus: The heterogeneity in the data source, the composition of data types, curation practices or provenance cascade at each partner organization could introduce variable amounts of missingness, biases, and confounders in the underlying data, and thereby variation in results, however, the pilot found more similarities between the groups than variation.

MO: The different groups agreed on common definitions, but my understanding is that the analyses were done independently. Is it important to talk not only about validation and evaluation of endpoints, but also about the quality and transparency of the data and analyses?

Rassen, Aetion: Yes. Pilot 2.0 helped to realize the vital importance of aligning on key questions upfront, such as variable definitions. As you note, we agree on the importance of processes to track and document the preparation and use of data at each stage of evidence generation. This is a central feature of our Aetion Evidence Platform, in which fully archived and auditable logs record all transactions and provide comprehensive versioning of the data, including data history, provenance, linkages, and transformations.

Miller, CancerLinQ: It was important for us to be in sync on validating and evaluating the endpoints, as well as have discussions about differences we were seeing that might relate to data type, source, population, and quality. The groups had frequent calls and emails to work through the details of the endpoint definitions.

Even after our first review of the results, we found that we needed to regroup and discuss again some details of the metrics and approaches for defining endpoints and approaches for censoring. We also asked each group to report censoring fractions per endpoint to help with understanding the completeness and quality of the data.

Walker, Concerto: As a pre-condition for the project, all participants in the Friends of Cancer Research work agreed that quality and transparency of methods were important.

All parties attempted to implement the analysis in the same way, following an agreed-upon plan, but we are also documenting any ways in which the implementation may have varied from that plan. Given the different participants and data sources, this sort of understanding is critical to have effective sharing and to advance the field with confidence.

Norden, COTA: Quality and transparency have been consistent parts of the Friends research discussion. We have had

numerous discussions about topics that include: partner rules on data suppression for small sample sizes to population distributions within research partners, differences in abstraction methods and types of data, analytical techniques and processes used by partners, and sources of data. Many of these topics and others will be discussed in upcoming manuscripts and congress discussions. The work presented in September only represented a small portion of the extensive collaborative work of the group.

COTA does believe establishing quality and transparency standards for data and analyses are an important precursor to being able to expand the utilization of different types of RWD for regulatory decisions. COTA has done extensive work to develop a three-pronged approach to ensure data quality and transparency based on our interactions and discussion with industry partners, life science partners and regulatory bodies.

Mahoney, Flatiron: Data quality and transparency are critically important factors and underpin the interpretability and reliability of RWE studies. A main objective of this project is to align on how to evaluate data quality/reliability.

Given the different types of data sources included in this project, we will need to think about what data quality and completeness mean in the context of routine care (as opposed to prospective randomized clinical trials), and how those criteria are measured using different data sources such as EHR or claims.The steps we've collectively taken so far as part of this pilot research project will set a foundation for future work on data quality.

Data reliability metrics are also a focus of the broader RWD/RWE stakeholder community and regulators who are working together to define best practices. Flatiron contributed to a collaborative effort by the Duke Margolis Center for Health Policy's RWE Collaborative to help identify a minimum set of data quality checks to evaluate whether RWD are reliable and may be fit for use. Those recommendations are described in a paper published in September.

The Friends pilot may provide an opportunity to discuss how the underlying quality of specific data elements may impact the outcomes we observe. For example, date of death is not always captured in real-world clinical settings. Given that incomplete information on death can skew overall survival analyses, data organizations have to link or supplement information with external sources. The impact of incomplete death data highlights the importance of benchmarking it to the gold standard, which is the National Death Index, to generate quality metrics, such as sensitivity.

Christian, IQVIA: Absolutely. Being transparent about the quality of data sources is very important in evaluating and validating endpoints. Transparency begins by describing the data sources, but goes further by characterizing the missingness of each variable used in the analysis.

Many organizations participating in the 2.0 pilot project were not able to capture certain clinical tests or generate endpoints such as progression free survival, because these data are either not routinely recorded in clinical practice, captured in the medical records or accessible from the medical records. Some of the findings from this project will focus on characterizing the data that is captured well in real-world sources and data not routinely recorded.

> "While this was not a formal validation study, it was a significant demonstration of how far the field has come in a few short years, and an illustration of the hard work in front of all of us to mature the use of real-world evidence in outcomes research, clinical decision-making, and regulatory decision-making."
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> *– Jonathan Hirsch, Syapse*

Kushi, Kaiser: You're right. We each did our analyses separately and then we sent the tabular results to Friends of Cancer Research, and then they put them together in tables that could be compared. We haven't actually combined or pooled those results in any way across all the different groups.

We've had some experience with actually pooling individual-level data, in research projects across the CRN health care systems, for example. And probably some of these other groups have done the same in their subsets. For example, Syapse partners with several different health care systems; I don't know if they've pooled data across them or not, but they are positioned to be able to do so.

I think that defining the variables in the same way to the extent possible, that's great. Then we can go back to our various data sources and look at the same analysis and describe the populations in the same way.

We have tried in our calls to be as open and transparent as possible about any hurdles we're running into or questions that we have about the distributions of population characteristics, operationalizing variable definitions, and things like that, but we haven't seen individual-level data from other participants, and that's partly because we're really doing this in an underfunded manner, let's put it that way. But this also serves as a benefit, not only for privacy concerns, but also as we are each replications of analyses in different health care or data settings.

So, yes, it's contributed time and not necessarily the primary focus of anything that any of us are involved in. I will say that Friends have been great, in terms of helping to guide this whole effort.

Alwardt, McKesson: Our discussion started with, "How do we even define real-world time to treatment discontinuation?", which is a good place to start, among a thousand definitions, but we have a way to go into how we perform that analysis, and some of it is due to the fact that the data sets are fundamentally really different.

The example that I tend to use is—this was non-small cell lung cancer—for the demonstration for our pilot, if you're in a claims data set, there's not an ICD-10 code for non-small cell lung cancer. So, just out of the gate, you're trying to think about, "How am I determining that this patient even fits the inclusion criteria for the study?" So, we're going to go beyond just definitions and think about more in Pilot 3.0 such as how we censor the data and data bias.

Hirsch, Syapse: The groups came together to construct shared definitions and methodologies, which was a significant and important undertaking. Each group quality checked their own data and conducted their own analyses, providing analysis results to Friends to pool. It is critical to discuss the quality of the underlying data and the analyses in order to determine the appropriateness of using real-world evidence to answer these types of questions.

We at Syapse have been and will continue to publish, in collaboration with our health systems partners, through consortium efforts such as Friends, and directly with the FDA throughout our research collaborations.

Palmer, Tempus: Analyses were completed independently to ensure data protection using pre-specified, congruent common data elements and statistical analysis plans. Tempus agrees that transparency is critical to ensure confidence in RWE results, and the importance of investigating fit-for-purpose, quality of underlying data along with any variability in the population characteristics and/or methodological assumptions made during the analysis. The partner organizations are carefully reviewing the data and conducting additional analyses to investigate this and plan to share findings and lessons as part of the Friends of Cancer Research collaboration.

MO: It seems that the project would need to focus on stratifying the patient cohort to validate endpoints, and then benchmarking real-world patient outcomes against results from equivalent traditional clinical trials. Who will be in charge of these efforts, and do you see them being done as part of the Friends collaboration?

Rassen, Aetion: We look forward to working closely with Friends on upcoming projects, which I'm sure will address a number of "next step" questions raised in the course of Pilot 2.0. Aetion will continue to enable RWD analyses across one or multiple data sets, and support thoughtful design and application of study methodologies.

Miller, CancerLinQ: Friends of Cancer Research has begun conversations about performing subgroup analyses as a follow-on phase to the initial work presented at the public meeting. Stratification is a necessary next step to understand the differences in the populations so this is a high priority for CancerLinQ. The benchmarking to clinical trial results will be completed as a separate project. ASCO and Concerto do not plan to participate in the clinical trial comparison because of other priorities.

Walker, Concerto: A secondary objective of the work will examine a subset of patients who match inclusion criteria for one of the pivotal trials that formed the basis for the real-world study. Several of the participants in the Pilot 2.0 study are engaged in this work, with ongoing support from the Friends leadership.

Norden, COTA: Collaboratively under the Friends 2.0 project we are working on exactly what you are proposing. During the Blueprint Forum in September, the second panel highlighted the approach we are taking to validate both a real-world data framework and real-world outcomes in advanced NSCLC. There is a subgroup within the larger collaboration who is working on developing a manuscript based on this work.

> “There is a ‘tsunami’ of data from health care systems that are now available or becoming available. We have tried in our calls to be as open and transparent as possible about any hurdles we’re running into or questions that we have about the distributions of population characteristics, operationalizing variable definitions.”
>
> *– Larry Kushi, Kaiser Permanente*

Additionally, we at COTA are doing some exciting work on real-world outcome validation in hematology and solid tumors that we hope to be able to disseminate in the near future. We also have recently embarked on a two-year research collaboration with the FDA where we will also be working to advance knowledge in this area.

Mahoney, Flatiron: The goal of the pilot project is not to directly compare the results from RWD studies to clinical trial results. Rather, the question we’re seeking to address is: Can real-world endpoints be used to characterize differences between available interventions? In pilot 2.0, clinical trials will serve as context for this question.

As a next step, Flatiron and some other pilot 2.0 participants intend to identify real-world cohorts that more closely resemble those from the clinical trials by applying as many I/E criteria from the clinical trials as possible, then will compare outcomes within real-world datasets to determine if real-world endpoints can detect differences across treatments. Future work may include additional analytic approaches to make the real-world cohorts more comparable in order to discern differences by interventions.

As with the other aspects of the Friends’ pilot study, we expect that pilot participants will align on common methods for analyses and conduct studies on their own data. Friends of Cancer Research is managing the project.

Christian, IQVIA: Initially, the group wants to compare the findings presented at the most recent Friends 2.0 pilot meeting across all data partners, including characterizing the study populations and comparing overall survival, time to next treatment and time to treatment discontinuation rates. IQVIA and some other data partners are also planning to conduct additional sensitivity analyses using clinical trials as benchmarks for comparison.

Friends will continue to lead this work, and we anticipate these subsequent analyses to continue through early next year. We expect to see differences between the RWD from all the data partners. It is necessary to understand the extent of these differences, the drivers responsible for these differences and whether they are artifacts of data recording or meaningful differences in benefits and risks among the populations.

Beyond the 2.0 project, there is a need to further evaluate this framework in other cancers, other therapeutic areas and in countries outside of the U.S. IQVIA, in collaboration with Friends and Health Data Insight in the U.K., plans to use Public Health England’s Cancer Analysis System to facilitate comparisons with the U.K. national registry data on lung cancer patients.

Kushi, Kaiser: Yes. Those are actually two things that we have talked about. One is benchmarking against the results of clinical trials, specifically in this particular area, these PD-(L)1 inhibitors, and advanced NSCLC.

One of the interesting things, getting back to the criteria by which you need to think about who gets into clinical trial—Friends did go through recent trials and showed us, “Okay, these are the inclusion criteria.” But some of them are not things that are captured in EHR data or claims data. These are things that you would ask someone specifically because you’re potentially enrolling them in a clinical trial and you wouldn’t necessarily ask them in a clinical context.

As a result, we can't really directly replicate the populations that were enrolled in a clinical trial. We can for key terms such as the cancer diagnosis or age, but not necessarily some of the things like, "Are you pregnant or planning on becoming pregnant?" Note that this is just a hypothetical example; I don't recall if this was an explicit exclusion criterion in these trials.

We may be able to pull up the first part if they had a child in a subsequent time period, but we certainly wouldn't know if people are planning to become pregnant. Maybe we could look at family planning or reproductive health visits or something like that, but intent to become pregnant is not something that we would routinely be able to capture. Obviously, that doesn't necessarily apply for all clinical trials in terms of inclusion criteria, but for some it might.

So, not necessarily all the groups are going to be able to contribute to a clinical trials population replication because they may be missing more critical information, but we are collectively going to contribute if possible.

So, an example, in our setting and in most claims or EHR-based settings, we don't have good capture of disease progression, a common outcome of interest in clinical trials.

It's likely documented somewhere, but it's usually in text notes or captured in varying ways depending on cancer type. In lung cancer, it's probably captured through imaging, but we couldn't necessarily say, "Okay, this is the particular imaging encounter that resulted in the recurrence or progression being identified." It's likely documented in text notes, and it might be inferred from subsequent initiation of therapy for advanced cancer. So, the information's there, but we decided, because of the level of funding and effort we could devote, that we weren't going to attempt any chart review to confirm recurrence or progression to advanced stage. But a group like Flatiron, where they're actually going through all the records on a routine basis and through relevant text fields, they could identify progression.

So, something like that, even though you would think would be a clinical endpoint of interest, is not necessarily routinely capturable in structured data. And the extent to which it is varies from cancer to cancer. And as a result, we or other groups may not be able to conduct a relevant comparison to results from a clinical trial.

Alwardt, McKesson: I do. From the experience that we had, I think that this was a safe place to do this together, as a whole that's greater than the sum of the parts.

Now, I will say that, independently, many of us are competing in the market today and continue to have our own opinions and versions and positions published as we're moving forward, and hopefully, what happens is that there's a convergence of these things to where that ultimately—if we look forward to a day where the FDA establishes the framework—that it was done looking into the totality of the universe of data and not picking a pony.

I think that that's where some of the opportunity really is for all of us. I focus on community oncology, but even the academic centers and large data partners and some of the up-and-coming new tech companies have their opportunity to share their thoughts and opinions. I think it will be great. It will be more powerful with that broader group than we can accomplish individually.

Friends has the right people to do it. I think that there are other groups that could try to do this with data that ultimately would be maybe less successful, only because of the strong leadership that Friends has, and really pushing this to remain focused on why this is important. I think that other data groups or other data consortiums can think about this, but Friends has that singular oncology focus.

Hirsch, Syapse: We agree, and this is an effort that Syapse and the FDA are undertaking as part of our research collaboration. We look forward to sharing the results of this work.

Palmer, Tempus: The collaboration does plan, if feasible and time permits, to include additional analyses of real-world patients that match clinical trial eligibility requirements in order to assess whether real-world data can more closely align with clinical trial results and conclusions. Studies are needed to establish how real-world endpoints relate to more traditional regulatory endpoints.

If not included in Pilot 2.0, subsequent pilots could be developed and convened by Friends of Cancer Research. It is also possible that the results of RWE data more closely mimic "truth", or what is really happening, than clinical trial data which by necessity has a highly selected patient population.

MO: Outside of this collaboration, how is your organization using real-world evidence? Also, who are paying for it?

Rassen, Aetion: The Aetion Evidence Platform is being used by biopharma companies, payers, and regulators to conduct real-world evidence studies that answer questions about which treatments work best for which populations. Aetion

works with 12 of the top 20 top biopharmaceutical companies, leading payers, and regulatory agencies including the FDA and EMA.

Besides the Friends collaboration, Aetion is also using RWE to help the FDA test where this kind of data can—and cannot—be used appropriately. The FDA's Framework for Real-World Evidence Program included a reference to a landmark study, RCT DUPLICATE, being led by researchers at Brigham and Women's Hospital using Aetion's platform, to demonstrate the value of real-world evidence as an accelerant to drug approval.

Researchers are seeking to replicate the results of 30 randomized clinical trials that were used for FDA approval decisions to see whether the incorporation of real-world evidence would have led to the same regulatory decision. This year, the RCT DUPLICATE study was expanded to predict the results of seven additional Phase IV clinical trials that are ongoing.

Miller, CancerLinQ: CancerLinQ generates real-world data as a secondary byproduct from the data collected from practices which is used primarily for quality improvement and clinical care. We make available real-world data sets via CancerLinQ Discovery® for academic, government, and non-profit users. These data sets are accessed in a controlled cloud-based environment and are not downloaded. Commercial customers obtain access to real-world datasets through the TEMPRO licensees.

The creation of real-world datasets is funded through CancerLinQ's operating budget. Customers of CancerLinQ Discovery pay to receive access to specific fit-for-purpose datasets after approval of their research proposal by our Research and Publications Committee. As recently announced, we will soon be making CancerLinQ Discovery datasets available to research customers through a customized version of the American Heart Association's Precision Medicine Platform.

Walker, Concerto: Concerto HealthAI focuses its research on research questions that can advance meaningful innovations to patients and which can provide confidence in the current treatment approaches bringing the greatest benefits to specific subpopulations.

Essentially, we are creating the tools—engineered real-world data and AI solutions—that are enabling precision oncology in practice. Concerto HealthAI uses real-world data to address a wide range of research questions of interest to health care providers, patients, life science companies, payers, and academic researchers. Some of this work is funded in partnership with life science companies, some is grant-funded, and other research is internally funded by Concerto HealthAI.

Many of our research projects are done through collaborations, such as those we presented at the 2019 ASCO annual meeting around the outcomes in patients with autoimmune disease, typically excluded from checkpoint inhibitor clinical trials—this being done with ASCO and FDA.

Norden, COTA: COTA has adopted a multi-pronged approach partnering with providers, life science companies, payers, the FDA, and others to bring clarity to the incredibly complex disease of cancer.

We work with major academic cancer centers to abstract and curate clinical data. COTA organizes this real-world, fragmented EHR data, transforming it to a clinically rich, longitudinal dataset. Institutions are using this data to unlock insights and transform care practices. Additionally, COTA is the exclusive partner in preparing NJ provider organizations to enter value-based oncology arrangements. We provide these organizations with clinical insights that cannot be gleaned from claims data alone.

Earlier this year, COTA signed a two-year Research Collaboration Agreement with FDA to establish a study protocol with an initial focus on breast cancer. The primary objective of the collaboration is to enhance our understanding of the real-world experience of cancer patients with an eye toward determining how best to use this experience in regulatory decision-making.

In addition to this work, COTA is supporting various life science companies in accelerating and augmenting clinical trials with RWD. In one case, the company has multiple clinical trials that received positive guidance from the FDA on the use of RWD given the rare trial populations as well as trial design. COTA is working collaboratively with the company to build the RWD inclusion/exclusion criteria, data models, and the relevant cohorts to the agreed upon data models. COTA anticipates that the RWD will be submitted to the FDA in multiple malignancies over the coming months.

Mahoney, Flatiron: In line with our mission, we believe that enabling the use of our de-identified datasets will help the entire cancer community advance research to find new, better therapies for patients. We license our real-world oncology de-identified datasets to researchers (typically for a fee) and to government agencies and non-profit organizations (at no charge) to accelerate cancer research.

Dreyer, IQVIA: IQVIA embraces opportunities to use RWE approaches to innovate drug approvals, to advance personalized medicine and to ultimately improve the lives of patients. We work with a variety of stakeholders from pharmaceutical and biotech companies to regulators, payers and clinical institu-

tions around the world to develop approaches that allow us to better understand the benefits, risks, and costs of therapies and devices.

For example, IQVIA is collaborating with the FDA on its Sentinel initiative, the agency's national electronic system, which uses electronic health care data to monitor the safety of FDA-regulated medical products.

Working with Deloitte Consulting, we are part of the Community Building and Outreach Center, which will focus on broadening awareness, access and use of Sentinel tools and data infrastructures. Moreover, IQVIA is working with other entities, such as the National Football League and the National Basketball Association, which are also interested in real-world data to monitor player health.

Kushi, Kaiser: There are a couple of things to note. One is that, in research groups such as the one I'm affiliated with, the Division of Research for Kaiser Permanente Northern California, most of our funding comes from extramural grants, projects not funded by Kaiser Permanente. The NCI, of course, is one of our primary cancer-related funders and NIH in general funds much of the Division's research projects—I think over half our funding comes from NIH grants. And then we have other Federal or State funding, foundation grants, and some some industry-related funding, as well as some directed internal Kaiser Permanente funds for specific projects

We have about 60 researchers in our group who conduct research across a broad spectrum of conditions, not just cancer. The other research groups affiliated with other Kaiser Permanente regions are a bit smaller, but similarly conduct research across many different areas. The work that we do is largely driven by the grants that we receive, most of which are investigator-initiated, although some are contracts.

When we do partner with an industry group, they might be interested in the type of question such as what we are doing with Friends—"what's the long-term effect of some pharmaceutical or device"—then, that would be pretty focused. I've actually not participated directly in any industry-funded initiatives, but for example, we did one of the validation studies for Oncotype DX and how the recurrence score is associated with survival after breast cancer. This was one of the first two main studies that were done in that arena.

As another example, the NCI gave the CRN some funds to look at cardiotoxicity after getting anthracyclines and other cancer agents that may have cardiac effects. The rates of these cardiac events were substantially higher in the older age group than you would surmise, just based on clinical trials. These were patients who were not actually in clinical trials, because they were older and outside the age eligibility range. I was not directly involved in this project, and Erin Aiello Bowles of Kaiser Permanente Washington led a manuscript on these findings that was published in JNCI. Thus, the possibility and magnitude of the side effects of treatment might be different from what you see in clinical trials.

Another example is in cancer screening. Kaiser Permanente researchers are leading and participating in some of the major research projects on cancer screening in health care systems. One of the examples I like to give in this area—again, I was not involved in this, and this work was led by Dr. Doug Corley at Kaiser Permanente Northern California—showed that there's wide variation in adenoma detection rates among gastroenterologists, which is the proportion of patients in their patient panel in which they detected at least one adenoma during colonoscopy. The ADR ranged from less than 10% to 50%.

More importantly, they then saw that ADR was also directly tied to subsequent 10-year colon cancer incidence. That is, the patients of gastroenterologists who had relatively high adenoma detection rates had colon cancer rates that was about half of those compared with patients of providers with low ADR. And there was this direct linear relationship for decreasing risk with higher adenoma detection rates.

That's obviously not evaluating something that was looked at in an oncology clinical trial and seeing how it works in the real world. Instead, it's taking data that are available in these types of health systems databases, with EHR data that documents what types of providers are seen, the procedures that are done and their results, and linking up with internal cancer registry information—all of which is available in the Kaiser Permanente setting. And in this case, discovering that, yes, this measure—the adenoma detection rate—makes a big difference on colorectal cancer rates, as big as anything in the colorectal cancer treatment space.

So, if you have a gastroenterologist, you probably want one that actually has experience finding those little adenomas that might be missed by some of their colleagues. This has led to more training of gastroenterologists, and is a direct example of real-world evidence informing a learning health care system, and of the type of analyses that can be done from data that are now available. So, it's real-world evidence that impacts cancer-related care. This was published in the New England Journal of Medicine about four years ago.

Alwardt, McKesson: My team is funded through our interactions with either grants, governmental funding bodies, biopharma and academic collaborations.

We use the data in two ways. On one side, it's important and it's one of our mandates that everything that we do is from a

real-world evidence-generating standpoint—we enter into it with intent to publish. Over the last couple of years, the team's published about 200 plus different publications in conjunction with our biopharma partners. Now, the benefit of this and where we add some uniqueness, is that every study we conduct has an actively practicing oncologist from The US Oncology Network (The Network) as a principal investigator. To give you some background, The Network brings together more than 1,200 independent physicians, forming a community of shared expertise and resources dedicated to advancing local cancer care and to delivering better patient outcomes.

So, we're ensuring that the clinical questions that we're answering are relevant and that the answer will be important to their practice. What ends up happening is as we continue to develop these papers and posters and manuscripts, that information works its way back into The Network. And so, there is a greater understanding of real-world performance in the real-world data in addition to the trial data—The US Oncology Network is, to a high degree, trialists, also.

They're very familiar with the trial side, but they also understand that with real-world data, there's going to have to be a way to do this. I was speaking with a physician recently who specializes in lung cancer, and he said, "No one wants to do a trial with the control of chemotherapy, because no one wants to put their patients on chemo in lung cancer anymore, unless they have to."

No one wants to do that. But they're still presented frequently with that's the standard, that's the control. And the thing is, we know what happens there. I mean, why do we still need to be using that as the control? We know what happens. We've got 40 years of experience knowing what happens with chemo and lung cancer. So, it's frustrating to them, and right now, there's not an option.

So, we're excited that with the FDA, we've had a success with the synthetic control arm approval for avelumab in metastatic Merkel cell carcinoma. We think that there's a continuing opportunity, it's part of our strategy, and it's something that we have a number of projects right now that will hopefully be successful. We've achieved buy-in from many physicians that this is going to be a good way to go to help feed some of these novel therapies to market.

Palmer, Tempus: We use RWE in many ways. We provide RWE insights to hundreds of researchers across the country, pharmaceutical companies, associations, government agencies, and regulatory bodies. In addition, we have a series of papers coming out in the near-term using RWE insights we have generated internally.

Hirsch, Syapse: Our primary goal is to enable providers and health systems to improve outcomes for cancer patients through precision medicine. One of the primary ways we achieve this is through the use of real-world evidence. The health systems we work with join the Syapse Learning Health Network, which allows their providers to use real-world evidence from across the network to understand optimal testing and treatment strategies.

For example, when a patient is presented at the molecular tumor board, an expert oncologist can find all clinically and molecularly similar patients from across the network, see their treatment journeys, and compare outcomes by therapy.

We are very proud of our efforts to put RWE into the hands of health systems. Additionally, we work with life sciences companies to help them leverage RWE to accelerate bringing therapies to patients. This includes outcomes research, clinical trials optimization, and regulatory uses.

MO: What do you see your organization being able to do once a real-world endpoints framework is established at FDA, and when real-world evidence is broadly ready to be used for regulatory purposes?

Rassen, Aetion: I want to amend the question slightly to what more do you see Aetion being able to do once the framework is established. I say that because we're able to do quite a bit today, even without specifically established guidance, because global regulators and value assessment bodies are increasingly incorporating RWE into their decision-making, and letting us know—in ongoing discussions and through public documents—what works and what doesn't.

We're working with our clients today to support regulatory submissions, while we partner with academic and industry

bodies to shape our collective understanding of what's possible with RWE. Collaborative projects will be a huge help in guiding the way—Friends' Pilot 2.0 is an important project, as are others Friends initiatives.

Beyond regulators, HTAs, U.S. payers and others are keen to understand the performance of medications in their decision-making, and to underpin efforts like value-based care. This is particularly important in oncology, where approaches like external control arms can greatly extend our knowledge about medications, especially in cases where randomized trials aren't feasible.

Miller, CancerLinQ: We expect that CancerLinQ Discovery datasets will be an even more valuable source of real-world cancer data by showing patterns of care, treatment outcomes, and new associations in large populations of patients being treated with standard-of-care or off-label treatments.

This may be particularly useful for understanding toxicities or generating hypotheses for new indications or new populations to be treated with approved drugs. We also expect that industry may start to include CancerLinQ data in their regulatory filings especially for label expansions.

As the use of real-world data increases more broadly, researchers and clinicians will gain a better understanding of the benefits and limitations of this type of data and how it may be able to complement traditional clinical trial data.

However, the greater legitimacy for real-world data that will likely come from the FDA's promulgation of its framework will be seen when clinicians begin incorporating real-world evidence into treatment decisions, particularly in situations where there is missing or poor-quality clinical trial data, for example for rare tumors not well-studied by trials.

Walker, Concerto: The FDA has taken a rather innovative approach during this interim period prior to a formal framework and guidance being provided—allowing alternative approaches to be advanced in a very transparent and consultative manner. This is really bringing together the best thinking, data, and methodologies.

Consequently, we are already seeing the value of EMR data—especially EMR data from sources that allow fully abstracting the unstructured elements for specific study designs and questions—and sometimes even combining these EMR data with full genomic datasets and payer claims data. All of this is to have confidence in comparability or superiority of these data as a source of external controls or as the basis for a standard-of-care comparison.

We are also seeing the benefit of AI and machine learning approaches linked to real-world data analyses—allowing insights that go beyond the existing literature, or that provide context to findings in the literature based on larger scale analyses. Already, we are seeing the benefit of studies with regulatory intent done at scale using real-world data alone. This is remarkable progress in only two years.

With formalization, the industry will have even more confidence and clarity as to where and how real-world data can aid pre- and post-approval decisions. It further is aiding the generalizability of regulatory intent studies to the treatment decisions of community practitioners—a further goal of this move towards real-world evidence integral to different study phases and decisions.

> IQVIA is also helping regulators in Europe, Japan and China develop guidance documents. All these regulators are calling for health stakeholders to share their experiences using real-world evidence, including pilot projects that will inform the development of formal guidelines.
>
> *– Nancy Dreyer, IQVIA*

Norden, COTA: A scenario that is growing in importance involves the use of RWE to support granting of an expanded indication for a drug already approved in another indication on the basis of RCT data. A recent example was the approval of Ibrance (palbociclib) for male breast cancer, which relied on multiple types of RWE against the backdrop of RCT data previously generated for breast cancer in women (The Cancer Letter, April 19).

A related application involves the creation of an external control group from RWD. Imagine that a new drug is being developed to target a novel mutation in patients with highly refractory solid tumors. In this case, patients are unlikely to accept randomization to an existing standard of care—which is associated with poor outcomes—and oncologists have eth-

ical concerns about randomization because some evidence of unusual activity has been observed during a phase 1 study.

Therefore, the sponsor initiates a single arm phase 2 study with the blessing of the FDA. In this circumstance, the control group may be selected from a robust RWD set. Robustness is important because of the requirement to match prognostic factors between the experimental group and the RWD-derived control group as closely as possible. Additionally, statistical matching approaches such as propensity score analysis must be applied to ensure that measurable prognostic factors are balanced between the two arms. A similar approach, though not yet as widely used, involves creation of an external control group that represents a hybrid of RWD and controls from prior clinical trials. We expect this to be further developed in short order.

Mahoney, Flatiron: Even today, RWE has the potential to be applied to various use cases to support regulatory submissions; for instance, RWE can provide disease context during clinical trial development, compare or provide context for a treatment arm in single-arm trial, characterize unmet need, provide evidence needed to modify an indication (e.g., dose), or even support product effectiveness.

In the future, we expect to see increased opportunities for FDA acceptance of RWE. Flatiron believes that our de-identified real-world datasets and analytical methods need to be fit for use, to support the specific regulatory decision. Given that each clinical context and use case has different considerations, Flatiron's involvement and support may range from providing RWD to generating fit-for-purpose RWE. As the FDA continues their work to finalize the RWE framework, our models will continue to evolve in line with best practices and regulatory guidance.

Dreyer, IQVIA: Once there is clarity about the evidentiary requirements for the FDA and other regulatory bodies, drug companies and medical product developers will feel more confident about using real-world evidence to supplement their regulatory applications for new indications and label expansions.

It's not just the FDA that is developing a framework for using real-world evidence. IQVIA is also helping regulators in Europe, Japan and China develop guidance documents. All these regulators are calling for health stakeholders to share their experiences using real-world evidence, including pilot projects that will inform the development of formal guidelines. We are contributing extensively to these efforts.

Kushi, Kaiser: I think that we can probably contribute to the evidence that would be generated. Kaiser has currently identified a handful of broad areas for enhancing research areas, with a focus on what can best integrate our research strengths or opportunities with improving the care we provide. Two of these, i.e. precision medicine and cancer, obviously dovetail directly with the type of work that we've been participating in with Friends of Cancer Research.

In order to fully realize the potential of research and analytics in these areas, we also need to work toward better data availability to address questions in these areas—and this points to another area of data limitation currently. One key part of this is being able to identify readily, in a structured format, people who've been tested for specific clinical genetic tests, and the results of those tests. For example, PD-L1 testing or EGFR testing—relevant to this specific project—are being done to guide clinical decisions.

Oftentimes, biospecimens are sent out to commercial labs for such testing, such as to Quest Diagnostics or to Ambry Genetics. Unfortunately, when they come back into the system for clinical care, they typically are documented in PDF files, so that information is not usable for analytic purposes from inside KP, unless one goes in and prints those PDFs or calls them up on the screen and re-enters that data into a structured database.

So, what we're doing currently is we're seeking out ways to capture that information in a more structured format. That includes approaching commercial vendors who conduct such genetic or molecular tests for Kaiser Permanente and basically saying, "Hey, can you give us the data that you have already given us in PDF format, and that you already have in structured format yourselves and give it to us in a similar structured way?" That would then enable our analysts to link those data to other EHR data to produce real-world evidence about the use of these tests, use of follow-on therapies, and their outcomes. And yes, the vendors that we've approached so far seem to be on board to do that. Or intent is to go beyond cancer and beyond these specific tests that were the focus of the Friends of Cancer Research effort.

So, we anticipate we can eventually get those data in a structured format. We had published a paper [in JCO CCI] that basically talked about this gap in availability of data, and one of the things that we had also said was that it would also be great if EHR vendors, such as Epic, Cerner, Allscripts, if they could also create a place where these tests and their results could be routinely captured, so that from a clinical or operational side, they would know where to put the data or where to find these data, and from an analytic side we would know where to go to pull these data.

That's something that, I think, can really realize the potential of precision medicine. I think being able to access those types

of data in a structured format is key. And when these gaps in data availability are solved, then any future guidance on generating real-world evidence from the FDA would be easier to follow, if we were to contribute to such efforts.

Alwardt, McKesson: I think we are uniquely positioned because McKesson also supports US Oncology Research, which is a site management organization for trials conducted within The US Oncology Network.

When I start thinking about the commercialization pathway for new drugs, it's important to be planful about how we use real-world evidence at the beginning of the trial. We need to connect with synthetic or historical controls on the front end of a trial rather than in trial rescue. We also partner with physicians in The Network who are conducting the trials as well as our site management teams. When we are planful and aligned across the company, then my team can really be innovative and see impactful results.

I think that it's ended up being a really powerful combination of forces across McKesson to accelerate approvals and accelerate the innovation. We're doing it for a reason and that by putting McKesson's pieces together, we have a good forward-looking plan to be able to achieve these goals.

I believe that the industry is doing so many things either in theories or thinking about it after, and I think that once there's a comfort level with the FDA and with biopharma—because it's going to have to be both of them—there will be a culture shift on all sides. But putting those pieces together upfront and being very planful, I think that that's going to be the most important.

We've seen there was a Genentech approval very recently that—I know the comments that came out saying that "We're approving it based on a single control, but we're going to ignore the real-world data that you put to it"—and so there was some good learning there and some of it was, it's really important to let the FDA know what you're doing, and if you're going to use real-world data, make sure you tell them. So, I think that we're kind of finding our way through some of this.

I was actually at a session that Aetion put out recently, and the former commissioner, Dr. [Scott] Gottlieb, spoke there. I asked him, "Normally, we always hear about approvals. We don't really hear about what wasn't approved. Is there a way that we can think about learning faster from the stuff that isn't approved?"

The sooner we can learn from what doesn't work, the faster we will understand what does, and so, I think that there's an opportunity for all of us to think about being able to release those types of data and respecting confidentiality.

Hirsch, Syapse: Precision medicine presents a substantial challenge to the current clinical development model: as patients are categorized into smaller and smaller cohorts based on molecular and clinical criteria, it will become difficult to perform RCTs for every drug-molecular-clinical indication due to lack of patient availability and high costs.

As the regulatory use of RWE matures, including determining the suitability of particular data sets and endpoints, we believe Syapse can have a large impact in working with both the FDA and life sciences companies to use RWE to assist in the evaluation of safety and efficacy of therapies.

Palmer, Tempus: As we have numerous projects in flight in this regard, and as we work closely with the FDA and ASCO as it relates to this topic, we are unable to comment at this time.

MO: With the recent emphasis on data-sharing, these pilot projects are a great example of companies coming together and working together. What happens after (or when) FDA issues a final guidance for RWendpoints? Is ongoing collaboration between data competitors necessary, going forward? Is that possible, since there may be conflicting interests?

Rassen, Aetion: There may be conflicting interests here or there, but the challenge of this conflict is dwarfed by the opportunity that can be created through collaboration, and I think most stakeholders see that.

The reality is that for many oncology questions, a single dataset won't capture either the quantity of patient experience needed to create sufficient regulatory evidence, nor will a single dataset capture the range of patient experience—dif-

ferent populations, different subgroups, different treatment settings—needed.

As such, many questions simply demand collaboration among multiple data providers, or if not explicit collaboration, at least peaceful coexistence within a study. We at Aetion work both with study sponsors and data holders to bring the full power and nuance of these data to bear in answering a question, and then we work to present the analysis in such a way that regulators can understand all of the steps that led to the result. This is the foundation for regulatory-grade evidence, and for instilling the requisite confidence in the evidence among all stakeholders.

This is done frequently today in other questions, such as drug safety, for which we combine analyses run in various datasets to get a bigger, more complete picture of the safety of a medication.

Miller, CancerLinQ: At the Friends 2.0 presentation, the diverse organizations came together for the common goal, even those that often compete in the same markets now. Dr. Wendy Rubinstein, who at the time was CancerLinQ deputy medical director, said "It's remarkable how 10 "frenemy" organizations, that are typically competing, came together to create common definitions to help advance the field."

There will be a need for more, not less collaboration, as the field matures. The FDA framework may define regulatory endpoints for RWD, but there are still a lot of unanswered questions. There will continue to be conflicting interests, but based on this experience, I believe there is an opportunity to work together and collaboratively explore unanswered questions about real-world data quality, new endpoints, comparison with trials, and a host of other methodologic issues. ASCO is highly interested in continuing to be involved in this type of exploration.

Walker, Concerto: There will continue to be conflicting interests on the margin, but most of the industry is focused on doing what is right for the patient.

Because many cancers are now being defined by narrow biomarker characteristics, they are in effect becoming more rare diseases. This means that assembling relevant datasets for these subpopulations is harder. Consequently, you will see more study-by-study collaborations across data sources. This is a present and growing mutual regard for the important societal benefit that can result when academic and industry leaders collaborate to solve difficult problems.

Concerto HealthAI has often worked with sometime-competitors, and we expect the Friends collaborators to continue to work together to enhance the value of real-world data, and to provide guidance and insight on how real-world data can best be used to generate real-world evidence.

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>
> *– Robert Miller, CancerLinQ*

Norden, COTA: The companies included in the pilot study and those that participated in the analysis portion are often considered to be competitors. However, through this collaboration, it became clear that we share similar challenges and there is a willingness to share expertise to expand the understanding and acceptance of RWD.

There was consensus that we have a collective responsibility to advance the use of RWE to improve patient outcomes. Participants have used the phrase "frenemies" to describe the companies involved in this research, noting the importance of putting "normal" business practices aside to advance cancer care for the benefit of patients.

Mahoney, Flatiron: We recognize the value that research and perspectives across the scientific community can provide to inform regulatory guidance. We believe that continued collaboration between real-world data organizations will help advance discussions and drive consensus to support the development and use of real-world endpoints.

In addition to the important work of the Friends pilot project, Flatiron and many others are contributing to Duke Margolis Center for Health Policy work that aims to establish frameworks and principles for development of real-world endpoints. We hope that this work will also identify pathways for validation of these endpoints.

Given this is a new and emerging area for the scientific community, including industry and the FDA, we are supportive of collaborations across the RWE providers and believe they will be critical to the acceptance and use of real-world endpoints.

Dreyer, IQVIA: It is certain that there will be an increasing demand for data holders to work together. This is a fact of the era of big data. The most successful companies will be those that figure out how to forge successful collaborations with mutual benefits and a satisfied workforce. There is plenty of work to go around, but it will be difficult to stay small and unaffiliated.

Kushi, Kaiser: That's a really interesting question. I think someone at the last meeting in September had mentioned that we're all "frenemies." From that perspective, on one level, it is pretty remarkable that we've been able to talk and work together.

In our case, we basically started from an NCI-funded grant, the Cancer Research Network. But Kaiser Permanente is also largely a not-for-profit health care provider, but then you've got these startups that have all this VC money, and oncology practice groups that have access to their data, such as COTA, who are realizing that there's something that they could do with it, and trying to figure out how to market it or use it to improve cancer care.

Then, there are groups that have basically come out of professional societies, such as ASCO's CancerLinQ, and they're also trying to somehow make data available from oncology care. There are other examples like that, which have somewhat different orientations, like AACR and their GENIE project, and the ORIEN network across cancer centers.

So, yes, you're absolutely right that there are these competing organizational interests, but I think that at least one central element of all of these different groups is that they are interested in trying to do what's best for everybody, for people with cancer. I think that's partly why this works.

And I think it also partly helps that it's Friends with Cancer Research who is the convener, coordinator of all this, rather than one of us. It's not that we don't trust each other. In fact, I think that there's a high degree of trust amongst all the groups that have been involved in these discussions. I think that we are each somewhat more colored by our particular perspectives and familiarity with our own data, which I think we all get to express those in an equal or an open way, a reasonably transparent way, than if, say, Flatiron or Kaiser Permanente were the convener and guiding the discussions.

Ultimately, if guidance from the FDA is generated, I think that what may result in terms of analyses may be collaborative—the FDA Sentinel project is a good example of that, in which data from multiple health insurers are made accessible. Or, it may be individual groups responding to specific questions of interest based on the strengths and appropriateness of the data that they have to address those questions.

Alwardt, McKesson: That's a really good question. We're watching data strategy evolve, and I think that there will be opportunity, in the same way that competitors have come together in the past, and in a model that's worked and still maintain competitive value.

> There aren't too many other groups other than Friends that I think can pull this off in a neutral, friendly environment. And so, they took on a tough job in organizing all of us, but they've done an amazing job.
>
> *– Sarah Alwardt, McKesson*

I'm lucky in that I'm nested in a Fortune 500 company. There are smaller VC companies that are driving a tremendous amount of valuation because of the value that is being placed in the data that they're collecting. So, it's going to be a tough thing to get through. And of course, the easiest thing is if all data are free and freely available, and we all move forward. That is the most unlikely to happen.

But I think where especially the FDA has been successful in the past with this is the Sentinel Initiative. And in that case, it was technically competitors from across a number of payer organizations providing their data directly to the FDA in a distributed data model. And I think that allowed everyone to be able to maintain a level of control with their data, but also provide data to the greater good.

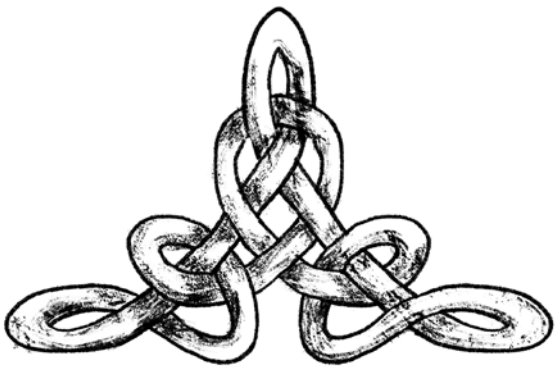
When things are framed for the greater good and for public health, that's when we can find common ground. It's going to be hard, and it'll definitely be kind of a slog to get there. But when I think about models like Sentinel, it absolutely brought together competitors in the space. In my previous role, I was the data contributor to the then-mini Sentinel, and I sat next to people against whom I would actively compete for projects. We were able to find common ground.

So, I don't think we're there yet with this, but I do believe that there is an opportunity for us to find a way forward and

common ground with the data that both protects the individual value and the perception of value for the individual companies, but still be able to provide really good workable datasets for regulators and to be able to continue to make good decisions for us.

Hirsch, Syapse: We believe it is important to work collaboratively, both with the FDA directly and as part of consortium efforts such as Friends, to inform the development of standards for RWendpoints. Syapse, alongside other RWE organizations, is well suited to do so given our daily work in the trenches of real-world data. It is in the interest of all RWE organizations and the stakeholders we serve for us to come together to advance this work.

Palmer, Tempus: Data from this pilot project intends to help inform a framework containing key data elements, RWEndpoint definitions, and algorithms. When the FDA issues the final guidance for RWEndpoints, collaborations between data organizations or pooling data (rather than analyses) from them become more achievable. We will still need to investigate the fit-for-purpose of each contributing data organization or dataset, as well as address the unknown level of overlap between them.



MO: What are the next steps at present?

Rassen, Aetion: We look forward to a continued collaboration with multiple stakeholders, led by Friends.

Miller, CancerLinQ: We are currently working on providing a more detailed report of the current Friends project for submission as abstracts to meetings and for one or more manuscripts.

Walker, Concerto: Follow-up work is underway to address various secondary questions of interest from the Pilot 2.0 engagement, and publications are in planning. Additional work is being planned to continue to advance our understanding of effectiveness endpoints drawn from real-world data, and how and under what conditions these can meaningfully be used to support regulatory decisions regarding safety and effectiveness.

Norden, COTA: The group is working on several manuscripts and congress presentations to more fully disclose the complete learnings from the current NSCLC project. There are also discussions advancing around doing more in-depth analyses to understand some of the differences identified during the project between data partners. Finally, there have been discussions regarding future collaborative work to continue to advance the use of RWD for both regulatory and non-regulatory uses to improve the care of oncology patients and to increase the speed of innovation in the market.

Mahoney, Flatiron: Flatiron plans to continue working towards the original objectives of the project. Collectively, we plan to further align as a group on definitions for important variables. Given that the results presented in September were preliminary, we also intend to apply methods that will allow us to evaluate the performance of real-world endpoints described in the objectives of the pilot project.

Kushi, Kaiser: We did an initial, reasonably well-done, look at these relationships of immunotherapies with survival, and comparison with doublet chemotherapy, etc. The immediate next step is to understand more about what we actually see in front of us. So, what are the sources of variation in the findings, to the extent that they exist, and are those things that we can reasonably easily identify, like population differences? One of the groups had a relatively younger population than most of the others, for example.

There might be some differences there, by age, race, ethnicity, and whether that's important for driving differences in observations, we don't know at this point. So, just trying to understand what we've observed better and why there may be differences amongst different groups. I think that's one thing. Part of it might also be missing data, or perhaps differing definitions of specific variables despite our upfront discussions in this area.

Another step is that clinical trials' comparison, which probably only a subset of groups may be able to participate in, but in any case, I think that's an important part because of what we're trying to do—to determine if real-world evidence aligns with or provides different information from clinical trials evidence.

What would be ideal, but of course we didn't know if this will happen, is if we can identify approximately the same population of people who would have been in a clinical trial, had they been recruited to do so, i.e., meet most key eligibility criteria. Hopefully, the results in that group would look pretty similar to what the clinical trials observed. And then, the rest of the population, results might be different, because they're older, because they have comorbid conditions, but that would be something which we're hoping to do.

And then, another step is basically laying out the procedures for how we went through all of this and documenting that in a way that other groups could potentially use it as a blueprint—perhaps not exactly a blueprint, but as points to think about as you're taking real-world data to generate real-world evidence for a focused question.

Alwardt, McKesson: We met recently to talk about Pilot 3.0. We are starting to dig into additional analyses that are happening. So, I think that we've declared our continued interest, and we will continue to be involved with the organization and the work that Friends is doing moving forward.

I'm convinced that this is a valuable platform where the "frenemies" can come together and can work towards this. So, we're excited to be part of that. I think that we're still trying to tie up pieces that didn't exactly get completely wrapped up with 2.0, before we start thinking about what really is going to be the protocol or the objective of 3.0, but we're looking forward to them.

I think it's going to be a deeper view into how we conducted the analysis. Pilot 1.0 was, "Can we even see data?" Not, can we do anything with it, or can we design anything? So, they proved that. Then, fast forward to 2.0, it's "Well, we can start to define terms, and we can start to come up with common definitions that are suitable across multiple datasets that we can start thinking about."

For 3.0, I think there's the, "Then how are we conducting these analyses so that they are similar? Are we doing that the same way? Can we start providing transparency to all of the statistical techniques or the censoring techniques, etc. that we've used to help find the population?"

For 4.0, I think it's, "How did this do compared to what we were expecting, and how did this perform compared to what the results were?" And some of that's going to be interesting discussion, because just off the bat with the real-world treatment in lung cancer, patients are about 15 years older than they were in the trial. There are some really big differences. And there's going to be some good discussion on, do we try and match the trial, and is that really what we're trying to prove?

Maybe 5.0 and 6.0 are, "Okay, so we've proven that we can match, we can measure, and we can meet all of these trial endpoints. Should we be thinking about what endpoints actually matter to the patients?"

And I think that that's a piece that Friends will be really good at helping us bring forward and, with an understanding of all the stuff that we measure and all of the analyses that we perform, are we doing things that actually matter to the patients who are being treated? And I think that will end up being some really interesting conversation.

Hirsch, Syapse: The organizations are actively working with Friends on additional analyses and publications to advance the goals of Pilot 2.0.

MO: Did we miss anything?

Rassen, Aetion: Also, of note, in the advancement of RWE for regulatory decision-making, we recently announced a partnership with McKesson which will combine the Aetion Evidence Platform with data from McKesson's iKnowMedSM oncology EHR system to power regulatory-grade RWE studies.

The solutions will first be made available to researchers at Brigham and Women's Hospital who are leading the FDA demonstration project, RCT DUPLICATE, to replicate oncology randomized controlled trials with real-world data.

Walker, Concerto: A wonderful set of questions.

Alwardt, McKesson: This is good stuff. There aren't too many other groups other than Friends that I think can pull this off in a neutral, friendly environment. And so, they took on a tough job in organizing all of us, but they've done an amazing job. So, it's been good to work with them. It'll be good to continue to work with them.

Hirsch, Syapse: Friends did an amazing job in bringing all of us together and pushing this effort to a set of achievable milestones. Their contributions to this field are immense.

Hahn pledges to be guided by "science and data" in considering vape flavor ban if confirmed at FDA

By Alex Carolan

Questions on flavored vaping products dominated the Nov. 20 Senate confirmation hearing for Stephen M. Hahn, the administration's pick for the job of FDA commissioner.

"I will use science and data to guide the decision if I'm fortunate to be confirmed, and I won't back away from that," Hahn, chief medical executive at MD Anderson and professor in the Department of Radiation Oncology, said at the Nov. 20 Senate Committee on Health Education Labor and Pensions hearing.

The question of the ban has become something of a slippery slope in today's Washington. In September, Trump said the administration was working with FDA to ban vaping flavors, which studies show appeal to youths and can lead to nicotine addiction. The plan was to enact a ban within a month.

However, earlier this week, the president said he no longer supports regulation of e-cigarette flavors. Protesters, criticism, the potential to negatively affect the economy and lose voters in battleground states resulted in the abrupt change of course, *The Washington Post* reported earlier this week.

In his Senate confirmation hearing, Hahn acknowledged that the rise in e-cigarette use among youths "is an important, urgent crisis in this country," but made no specific pledges as Democratic and Republican Senate members pressed him on whether he would resist pressure from the administration and lobbying groups.

"I understand that the compliance policy is under consideration by the administration, and I look forward to their decision," Hahn said. "I am not privy to those decision-making processes, but I very much agree and support that aggressive action needs to be taken to protect our children."

At the hearing, Hahn stressed that as a specialist in the treatment of lung cancer he is familiar with the damage tobacco causes.

"I have seen the ravages of tobacco-related cancers. It's all too real to me. I've had youngsters who were very close to me who use e-cigarette products," Hahn said at the hearing. "I'm aware of the Youth Tobacco survey data. I think this is an important, urgent crisis in this country. I do not want to see another generation of Americans addicted to tobacco and nicotine. And I believe that we need to take aggressive action to stop."

Committee Chair Lamar Alexander (R-TN) said the 23-member commit-

tee agrees on the need to take action against e-cigarettes based on two points: the upwards of 2,000 patients who have lung disease as a result of e-cigarettes recently found to be contaminated with vitamin e-acetate, and the influx of use in youths to the point where one in four high school students use e-cigarettes.

"That's one area where there should be no hesitancy about the administration moving ahead rapidly to deal with," Alexander said. "There's certainly nobody on this committee, Republican or Democrat, who doesn't want to see that problem related to e-cigarettes resolved."

Sen. Tina Smith (D-MN) asked Hahn whether he could commit to finalizing an e-cigarette flavor ban without bowing to the administration.

"I am aware of compliance policy that is being considered," Hahn said. "And I just can't pre-judge that decision at this point. I'm not involved in that decision, I don't have the data."

Data from the 2019 National Youth Tobacco Survey show more than five million youths have reported using vaping products in the past 30 days, and nearly one million reported daily use. Of the respondents, 31% said availability of "flavors such as mint, candy, fruit, or chocolate" influenced their decisions to use the devices.

"I'm always hesitant to opine on the law and regulation without having all of the facts," Hahn said when asked whether he believes he has the authority to advance or finalize the ban on e-cigarette flavors.

"I would hope that there would be some sense of urgency by the FDA under your leadership to use the authority that you already have to deal with the epidemic that we have seen with young people using e-cigarettes and of the lung diseases that are occurring that are related to e-cigarettes," Alexander said.

Senate members from both sides of the aisle addressed the threat of political pressure on the agency. Ranking Member Patty Murray (D-WA) challenged Hahn to commit to decision-making based on science and not ideology, specifically regarding pressure from the Trump administration.

"I will be looking at his commitment to putting science and data ahead of ideology," Murray said in her opening statement. "This is fundamental to the FDA's work, and when it doesn't happen, people are put in harm's way. People are unable to get care they need."

Hahn said he has not spoken with Trump about the president's decision to halt regulation on vaping flavors. "Science, data and the law will guide decisions that I would make," he pledged. "I have not had a conversation with the president."

In the past, Juul—now synonymous with the vaping epidemic—has spent millions on lobbying for friendly e-cigarette regulation. In the first half of 2019, the company spent nearly $2 million on lobbying in Washington, *Politico* reported.

The company, in which tobacco giant Altria has a 35% stake (*The Cancer Letter*, Sept. 27), has poached government officials. Vice President Mike Pence's director of media affairs, Rebeccah Propp, now serves as the company's communications director, and a former White House aide, Johnny DeStefano, is now a Juul consultant, according to Politico.

At Hahn's confirmation hearing, Sen. Mitt Romney (R-UT) said he worries about political pressure and lobbying groups exerting influence on decision-making at FDA.

"The stress that can come from politics or people who are driven by politics, or political donations, is wholly different than everything you've ever experienced in life, and I can attest to that myself," Romney said. "This issue of vaping, as it relates to this question is whether you will put science and public health ahead of politics and political contributions—and they don't come to you directly, but they come to people who will be telling you what to do."

"The decisions that we make needs to be guided by science and data and congruent with the law," Hahn responded.

The political lobbying Romney warned about are the same special interests Sen. Maggie Hassan (D-NH) said this administration has "caved to." Hassan urged Hahn to be transparent about future interactions with e-cigarette manufacturers in the FDA role.

HASSAN: "If you are confirmed, you're going to be overseeing the FDA pre-market tobacco application process for e-cigarettes. A whole lot of people are counting on the FDA to put public health first."

HAHN: "I'm not at the FDA, I don't know the rules and regulations around disclosure. But I will look into that, understand what the rules are, and follow the law."

At the hearing, Republican members stated repeatedly that Hahn's background makes him a qualified candidate, while some Democrats noted that he lacks government experience, and—as the hearing progressed—expressed frustration about what they described as Hahn's unwillingness to commit to a policy on e-cigarettes.

In his opening statement, Alexander praised Hahn's background in oncology and his experience as an executive at MD Anderson.

"Those experiences as well as your experience with the National Institutes of Health and Public Health Service Commissioned Corps have you made you well prepared and a strong choice to lead the FDA," Alexander said.

Murray, on the other hand, said Hahn lacks government experience.

"Dr. Hahn has almost no government experience, almost no public record on the policy issues related to the FDA, and no experience leading an organization anywhere near as complex as the FDA," Murray said in her opening statement.

> "I think this is an important, urgent crisis in this country. I do not want to see another generation of Americans addicted to tobacco and nicotine. And I believe that we need to take aggressive action to stop,"
>
> *– Stephen Hahn*

Sen. Doug Jones (D-AL), while noting that he was impressed with Hahn's credentials, expressed frustration with Hahn's failure to commit on vaping policy, likening the hearing to an exercise in "dodge and bob." Jones challenged Hahn to review his answers and give a personal opinion on whether the administration is right or wrong on vaping policy, and whether flavors should be banned.

"I was less than happy with many of the answers you gave to members of this committee with regard to vaping and those things," Jones said. "I just don't think that was you. I think it was prepped from handlers that kept going back to science and data.

"The question is how we go about doing [banning non-tobacco flavored e-cigarettes]—it's not a question of if we go about doing it."

The American Cancer Society earlier this week updated its position on vaping, saying that e-cigarettes shouldn't be used to quit smoking. FDA has not approved any e-cigarette product as a safe and effective cessation product.

"Recent spikes in the use of e-cigarettes, particularly among youth, and related deaths combined with the lack of regulation by the Food and Drug Administration, make it clear that more must be done to regulate the product," ACS Chief Executive Officer, Gary Reedy, wrote in an email to the society's "honorary life members, area board members, and other enterprise leadership volunteers."

Reedy's statement reads:

- No youth or young adult should begin using any tobacco product, including e-cigarettes. ACS encourages young people currently using these products to ask for help in quitting and to quit as soon as possible.
- The ACS also believes e-cigarettes should not be used to quit smoking. No e-cigarette has been approved as a safe and effective cessation product by the FDA. All tobacco products, including e-cigarettes, pose a risk to the health of the user.
- Additionally, current e-cigarette users should not also smoke cigarettes or switch to smoking cigarettes, and former smokers now using e-cigarettes should not revert to smoking. Beginning smoking or vaping or switching from e-cigarettes to smoking exposes the user to potentially devastating health effects.

Fifty-six health groups signed a consensus statement Nov. 18 supporting the proposal to remove non-tobacco-flavored e-cigarettes, including mint and menthol flavors, from the marketplace both in retail stores and online.

"The issue takes on increased urgency because there have been numerous reports about the White House's deliberations on this issue that indicate that the White House may not go forward with the original decision," the statement read.

Other groups have thrown their support behind Hahn, including Friends of Cancer Research, American Society of Clinical Oncology and American Society for Radiation Oncology. Five former FDA commissioners, among them Scott Gottlieb, who resigned in April, also publicly expressed their support.

"Dr. Hahn showed today he has a strong focus on advancing innovation, improving public health, and doing what is right by patients. We hope the Senate moves quickly on his confirmation," Ellen Sigal, chair and founder of Friends of Cancer Research, said in a statement Nov. 20.

At the hearing, a handful of protesters wearing orange t-shirts with the hashtag #DitchJuul observed the hearing from the audience. Sen. Smith asked Hahn whether there are any data that encourage flavored e-cigarette use among youths.

SMITH: "Can you imagine evidence on the other side, that these candy-flavored e-cigarettes don't contribute to youth addiction to nicotine?"

HAHN: "I am not aware of any evidence on the other side."

SMITH: "Nor am I."

The committee is expected to vote on Hahn's nomination Dec. 3.

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Robotic mastectomy surgeon sues Monmouth, alleging defamation, antitrust violations

By Paul Goldberg

Stephen A. Chagares, a New Jersey general surgeon who recently set off a national debate by using a robotic surgical device to perform mastectomies, has filed a lawsuit claiming defamation and violation of federal and state antitrust laws on the part of Monmouth Medical Center.

Earlier this year, as *The Cancer Letter* was writing a series of stories focused on robotically assisted mastectomies, Monmouth didn't respond substantively to the reporters' questions, and—the lawsuit now states—Chagares was expressly directed not to answer questions as the hospital went "radio silent" with respect to *The Cancer Letter*, the complaint filed at the Superior Court of New Jersey states.

"At all times relevant hereto, plaintiff was specifically instructed by MMC administration not to speak with any media regarding RNSM, including the publisher of *The Cancer Letter*, thereby depriving him of the ability to defend himself," the complaint states. The directive also precluded Chagares from answering basic factual questions, such as whether his study was being conducted with IRB clearance.

Monmouth, a hospital with over 500 beds, is a teaching affiliate of the Rutgers Robert Wood Johnson Medical School and a member of the RWJBarnabas Health system.

While Chagares remained silent, another individual who was privy to relevant information on the controversy triggered by robotic mastectomies, speaking on background, told *The Cancer Letter* that Chagares had performed the procedures off-protocol and without IRB approval (*The Cancer Letter*, April 5).

Subsequent to publication of the story, Chagares informed *The Cancer Letter* that the claim that he was performing a study without IRB approval was untrue. *The Cancer Letter* immediately published a correction and started an investigation to examine the manner in which this large community hospital managed research risks—and the reliability and appropriateness of guidance it had provided Chagares.

Of course, it's not nice to mislead and stonewall journalists, but in our view, the events at Monmouth presented an

opportunity to pull back the curtain on the proliferation of minimally invasive technology, such as robotically-assisted mastectomies. Robots can be impressive, but using them to perform cancer-related surgery without evidence on long-term safety and efficacy is risky business, and events that played out at Monmouth could have played out elsewhere.

The Cancer Letter's investigation turned up internal documents that, step-by-step, demonstrated that the hospital's IRB had:

- Given Chagares misguided directions on what is required to conduct a cancer-related study,
- Failed to obtain an Investigational Device Exemption from FDA in order to conduct the study, and
- Approved a surgical outcomes study that wasn't designed to provide answers on the safety and efficacy of robotic mastectomy.

As approved by the Monmouth IRB and initiated by Chagares, the study measured patient satisfaction, stating to participants incorrectly that the question of safety and efficacy had been answered in prior studies.

An FDA advisory, published following questions from *The Cancer Letter* earlier this year, urges investigators to conduct long-term studies using clinical endpoints that are more informative than patient satisfaction.

"The FDA is issuing this safety communication because it is important for health care providers and patients to understand that the safety and effectiveness of using robotically-assisted surgical devices in mastectomy procedures or in the prevention or treatment of cancer has not been established," the agency said in a statement at the time.

Device manufacturers looking to market surgical tools for use in the prevention or treatment of cancer may now be required to study long-term oncologic endpoints in surgical trials, according to FDA's advisory.

The short-lived single-arm study, approved by the Monmouth IRB and initiated with Chagares as the PI, was far from meeting this bar.

In the process of reporting the Monmouth story, *The Cancer Letter* approached all parties, at one point sending 64 questions to the hospital. Pursuant to what the complaint now describes as the policy of radio silence, *The Cancer Letter* received no answers from Monmouth.

The institution didn't acknowledge having received multiple requests for comment for this story.

According to Chagares's just-filed complaint, the surgeon was urged not to answer questions from *The Cancer Letter,* which a hospital official described as "not well read." Chagares was also told to stop follow-up on the two patients who had received robotic mastectomies while on his IRB-approved study—a woman with breast cancer, and a man with abnormal growth of breast tissue.

This directive from Monmouth's administration violates the fundamental ethical precepts of the conduct of clinical trials, ethicists say (*The Cancer Letter,* May 31).

FDA: IDE was required; patients must be followed

The Cancer Letter has learned that its earlier coverage of the Monmouth imbroglio attracted attention from FDA.

An agency official has stated in an email to Chagares that Monmouth was, indeed, required to obtain an IDE for the study, and urged the surgeon to continue to monitor the patients he treated in the course of the study.

FDA officials said no formal investigation has been conducted.

The Cancer Letter has obtained an email from the FDA official who investigated the surgical study. In the email dated June 26, Adam Donat, the agency official, writes to Chagares:

> Thank you for taking time to talk with me today. I appreciate you providing the protocol and IRB package for the closed study titled "An Observational Study Evaluating Patients' Satisfaction After Robotic Nipple-Sparing Mastectomy." As discussed, FDA's review of this documentation found that the Da Vinci Surgical System is not approved for this use, and this constitutes a new intended use for a significant risk device (21 CFR 812.3(m)). Therefore, such a study would require an IDE application to FDA.
>
> I understand that you had already closed the study and are continuing to follow up with the subjects, which is what FDA would request in this situation. In addition, we recommend working with your IRB to identify whether the informed consent document contained any incorrect language that subjects would need to be notified of.
>
> If you plan to conduct a similar study in the future, you may contact the Division of Industry and Consumer Education (DICE) by telephone at (800) 638-2041, or by email at dice@fda.hhs.gov for questions related to IDE requirements. Also, please do not hesitate to reach back out to me directly using the contact info in my signature block if I can help in any way.
>
> Sincerely,
> Adam Donat
> Deputy Director, Division of Clinical Evidence and Analysis 1

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> At the very end of the April 13, 2019, telephone conversation, defendant, Carney, offered to have a positive article published about [Chagares] in its magazine.
>
> *– Chagares's complaint against Monmouth*

Office of Clinical Evidence
and Analysis
Office of Product Evaluation
and Quality

Patients who enrolled in the Monmouth study were told—incorrectly—that the robotic procedure had been found "successful" in breast cancer:

"You are being asked to participate in this observational study because you are planning to undergo a robotic nipple-sparing mastectomy (RNSM) either for preventative or therapeutic purposes. This procedure has been tested and found successful for the treatment or prevention of breast cancer. You will not be asked to participate in any experimental procedures."

The Monmouth protocol was built on the foundation of a European randomized trial, with the control arm edited out. However, the person or persons who edited out the control arm apparently neglected to change one of the protocol's primary hypotheses: that the use of a robotic device to perform a nipple-sparing mastectomy does not worsen the oncologic outcome of patients with breast cancer or BRCA mutation.

After being dismantled and reconstituted, the Monmouth protocol simply doesn't provide the data for a hypothesis test.

As a result, Monmouth offered robotic surgery for an unapproved indication to patients without a safety and efficacy protocol, promised high-risk patients that the procedure is "successful" for use in said indication, and simultaneously enrolled patients in a data collection protocol to assess whether the procedure worsens oncologic outcomes.

As of May 2019, all cancer-related clinical trials in the RWJBarnabas Health system have been required to undergo review by the Rutgers Cancer Institute of New Jersey, said Steven K. Libutti, director of the Rutgers Cancer Institute, vice chancellor for cancer programs at Rutgers Biomedical and Health Sciences, senior vice president of oncology services at RWJBarnabas Health, and professor of surgery at Rutgers Robert Wood Johnson Medical School.

"All oncology protocols at RWJBarnabas Health will initially go through the Scientific Review Board at Rutgers Cancer Institute of New Jersey, the state's only NCI-designated Comprehensive Cancer Center, to ensure scientific quality and study design before the study can proceed," Libutti said to *The Cancer Letter.*

"We are in the process of centralizing the Institutional Review Board across the health system that will review and monitor all oncology clinical trials, keeping patient safety at the forefront of clinical research."

Chagares urged to keep silent

After directing Chagares to duck calls from *The Cancer Letter,* Eric Carney, chief operating officer at Monmouth, assured the surgeon that the problem would soon blow over, the lawsuit states.

Carney is now a defendant in the suit.

The complaint describes Carney's effort to convince Chagares to keep his mouth shut and—quid pro quo—Monmouth would publish a positive article about the surgeon in the hospital's glossy magazine:

On or about April 13, 2019, plaintiff had a telephone conversation with defendant, Carney, regarding The First Article [in *The Cancer Letter*] during which Carney admitted that The First Article "was clearly not accurate."

Carney further acknowledged that the Article did not present plaintiff in "a very good light" and that it

"smeared" his reputation. [Erroneous information provided to a reporter was immediately corrected as soon as *The Cancer Letter* became aware of inaccuracy.]

Notwithstanding, MMC made a conscious decision from a public relations and legal perspective not to attempt to correct it, that MMC would go "radio silent" about the disparaging statements about plaintiff in The First Article with the expectation that it would blow over.

Additionally, [Carney] acknowledged that *The Cancer Letter* posed an additional thirty-two questions to MMC in an effort to clarify the contents of The First Article but, MMC opted not to provide answers to those questions.

Carney defended MMC/RWJBH's decision not to attempt to correct The First Article, in part, by stating that it was an "old story" and that *The Cancer Letter* was "not a well-read, written article."

Defendant, Carney, also represented to plaintiff in that telephone conversation that MMC had a strict media policy under which employees were not permitted to speak with the media without authorization and that a violation could result in termination. [Carney] further represented that he did not have the ability to determine who at MMC made the disparaging statements about plaintiff.

At the very end of the April 13, 2019, telephone conversation, defendant, Carney, offered to have a positive article published about [Chagares] in its magazine.

Plaintiff through counsel also contacted MMC's general counsel and requested that MMC take action to correct the false and defamatory statements in The First Article. General counsel unequivocally stated that no such action would be taken by MMC/RWJBH.

"Safety concerns"

Chagares was told that his clinical study was stopped over "safety concerns." As he pressed the institution to state formally what those concerns were and to get instructions on what he should tell his patients, he was told not to collect any additional data on the subjects already enrolled, the complaint states.

To date, hospital administrators have not provided written justification for the hospital's decision to end the study—leaving surgeons, principal investigators, and patients in the dark as to what the alluded-to "safety concerns" might be.

"This is unacceptable," Arthur Caplan, the Drs. William F. and Virginia Connolly Mitty Professor of Bioethics at New York University Langone Health and the founding director of the Division of Medical Ethics, said to *The Cancer Letter* earlier this year. "When you're partnering with someone, you don't abruptly end a study without explaining why, without explaining follow-up options, what's going to happen. Are you going to track the people that were in the study, or are you just leaving them in the lurch?"

Such directives are harmful to physicians and patients, Rita Redberg, a cardiologist and professor of medicine at the University of California San Francisco, said to *The Cancer Letter* earlier this year.

"Wow. I cannot imagine that the hospital thought an Investigational Device Exemption from the FDA wasn't required. I don't understand that," Redberg said. "They weren't only throwing the surgeon under the bus, they're throwing their patients under the bus, too."

"Preferred Specialty Physician Referral List"

Chagares, who has practiced at Monmouth for 29 years, has an employment agreement to provide services as a general surgeon at the breast center. He is also a private sole practitioner at the hospital.

"At or around the time at which plaintiff complained about the termination of the RNSM study, defendants altered the MMC-BHMG Preferred Specialty Physician Referral List to take plaintiff out of alphabetical order and/or remove him completely from the list," the complaint states. "Defendants annually supplied plaintiff with a fictitious Preferred Specialty Physician Referral List."

The list is used by the hospital-owned practice to refer patients to outside specialists.

Chagares's complaint argues that the hospital's actions were "designed to exclude plaintiff from the breast surgery market, eliminate the competition that would be generated by RNSM and to capture the breast surgery market for their own financial benefit.

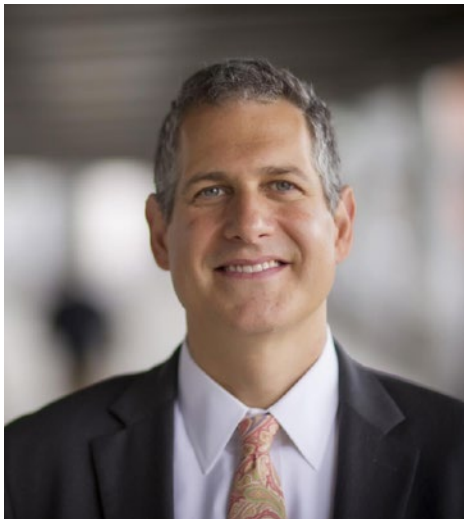
"Plaintiff had developed a national reputation for bringing RNSM to the United States and had already generated out of state patients at the time the procedure was terminated by defendants," the complaint states. "The financial impact on fees to Medicare and other health care insurers as the result of defendants' actions are substantial."

The complaint is posted here.

Matthew Bin Han Ong contributed to this story.

IN BRIEF

Ethan Basch receives ACCC Clinical Research award



Ethan Basch, director of the Cancer Outcomes Research Program and professor of hematology and oncology at UNC Lineberger Comprehensive Cancer Center, received the Association of Community Cancer Centers 2019 Clinical Research Award.

The award was presented during the ACCC National Oncology Conference in Orlando Nov. 1.

As a medical oncologist and health services researcher, Basch has focused on developing methods to bring the patient perspective into cancer clinical research and routine care delivery. For over a decade, his group has developed and implemented patient-reported outcomes tools and worked closely with public and private agencies to effect policy changes based on their findings.

Basch's goal is to conduct research that facilitates rigorous inclusion of PROs in product development, drug labels, and routine care for symptom monitoring. It is his hope that bringing the patient voice into clinical research and care delivery processes will lead to safer drug development, improved quality of care, enhanced patient-clinician communication, and better patient experiences with disease and treatment.

Basch has found that in routine care about 75% of patients are compliant with self-reported outcomes. And in some rural programs, this compliance rate has been as high as 95%.

"Integration of patient-reported symptoms into cancer care is feasible and is associated with clinical benefit," he said upon accepting the award. Basch said future efforts should focus on strategies for implementing self-reporting into clinical workflow and electronic health records.

Harmar Brereton, Dana Dornsife receive NCCS Ellen Stovall Award

Harmar Brereton and Dana Dornsife received the National Coalition for Cancer Survivorship's Ellen L. Stovall Award for Innovation in Patient-Centered Cancer Care Nov. 13.

- Brereton spent 33 years in private practice and founded the Northeast Regional Cancer Institute in Scranton, PA. He teaches at the Weill Cornell School of Medicine and is on the faculty of the Geisinger Commonwealth School of Medicine, a school he helped found. He is also a leadership team member of the International Cancer Expert Corps.

- Dornsife is chair of the Board and Founder of Lazarex Cancer Foundation, a nationwide non-profit organization she created in 2006. Lazarex's mission is to improve the outcome of cancer care—giving hope, dignity, and life to advanced stage cancer patients and the medically underserved by providing assistance with costs for FDA clini-

cal trial participation, identification of clinical trial options, community outreach and engagement.

Named for NCCS CEO, Ellen Stovall, who died in 2016 due to complications from three cancer treatments, the award highlights those who continue Ellen's work to further incorporate patients' goals, needs and values.

"This year's honorees exemplify her life's work and passion: Dr. Harmar Brereton, was her physician and friend and is a compassionate, patient-centered physician oncologist and teacher, and Dana Dornsife, has dedicated herself to ensuring that cancer patients have access to clinical trials for their treatment and to advance the science," Shelley Fuld Nasso, NCCS CEO, said in a statement.

Timothy Mullett named chair-elect of the American College of Surgeons Commission on Cancer

Cardiothoracic surgeon Timothy W. Mullett was named chair-elect of the Commission on Cancer of the American College of Surgeons during the CoC's annual meeting Oct. 27 in San Francisco. The meeting was held during the ACS Clinical Congress.

Mullett, medical director of the University of Kentucky's Markey Cancer Center, is a surgical oncologist who specializes in lung cancer. Although he began his career at the University of Kentucky as a thoracic surgeon treating heart issues, he soon shifted his professional focus to treating lung cancer, one of the state's major health problems. He is a co-leader of the Kentucky LEADS Collaborative to improve lung cancer survival.

During the coming year, Mullett will work closely with CoC leaders, including current CoC Chair, medical oncologist Lawrence Shulman. The CoC's accreditation program encourages hospitals, treatment centers and other facilities to improve their quality of patient care through various cancer-related services. The CoC maintains reporting tools to aid cancer treatment and research facilities in benchmarking and improving patient outcomes.

Also, it maintains the National Cancer Database, which tracks national trends and demographics of cancer incidence. There are more than 1,500 CoC-accredited cancer programs in the U.S. and Puerto Rico, representing 30% of all hospitals. CoC-accredited facilities diagnose and/or treat more than 70% of all newly diagnosed cancer patients each year.

Mullett will begin his two-year term as CoC Chair in October 2020 when he assumes the leadership role at the CoC's next annual meeting at the next ACS Clinical Congress in Chicago.

Roswell Park receives nearly $22M in government funding

Roswell Park received more than $21.8 million in recent competitive grants and contracts to launch new investigations or continue major research efforts. This includes funding from NCI's Cancer Moonshot program as well as renewals for high-impact projects based at Roswell Park.

The five-year, $4.1 million allocation from the NCI's Cancer Moonshot program to Kunle Odunsi, deputy director and chair of the Department of Gynecologic Oncology, and Danuta Kozbor, associate professor of immunology and microbiology at Roswell Park, supports a cooperative project with Andrea Gambotto, of the University of Pittsburgh. The team will explore ways to reprogram the cells and molecules surrounding ovarian tumors to overcome resistance mechanisms that make these cancers difficult to treat. The long-term objective of this project is to develop a new treatment option for ovarian cancer, one based on a cancer-killing or "oncolytic" virus.

Martin Morgan, professor of oncology in the Department of Biostatistics and Bioinformatics, received more than $3.6 million from the NCI to continue his leadership of the R/Bioconductor Project, a bioinformatics resource based at Roswell Park.

Roswell Park also secured the renewal of two competitive contracts totaling $3.25 million to lead and implement New York State's Advancing Tobacco-Free Communities in two regions — the Southern Tier of New York and the Genesee/Orleans/Wyoming County region. Roswell Park has led these cancer-prevention initiatives since 2014 under contract to the New York State Department of Health and led by Andrew Hyland, chair of the Department of Health Behavior.

Other highlights among projects recently awarded federal or private foundation grant funding:

- The $21.7 million in recent awards also includes two previously an-

nounced DoD grants: a multimillion-dollar Breakthrough Award to **Pawel Kalinski**, to assess a three-pronged immunotherapy strategy for treating metastatic breast cancer and a $544,360 grant to fund a multi-institutional pilot project supporting development of a detection test for ovarian cancer, an effort led by Odunsi.

- **Richard Hershberger**, chief academic officer, received a $1.6 million renewal award to continue Roswell Park's role in educating and training the next generation of cancer researchers and oncologists. This five-year grant supports summer research experiences in cancer science and oncology for more than 30 college, medical and nursing students each year.
- **John Krolewski**, professor of oncology and chair of cancer genetics and genomics, received a three-year-year, $1.05 million grant from the U.S. Department of Defense to explore how androgen deprivation therapy—the main therapy for advanced or metastatic prostate cancer—may induce an immuno-suppressive state that can promote tumor recurrence. Successful understanding of this mechanism may lead to new therapies to prevent ADT failure and prevent disease recurrence, the major cause of prostate cancer death.
- **Kevin Eng**, associate professor of oncology in the Department of Biostatistics and Bioinformatics, received a one-year, $740,298 grant from the DoD for his research exploring the role of a hereditary, X-chromosome-linked gene mutation in the risk for prostate cancer among men with daughters diagnosed with familial ovarian cancer.
- **Ethan Abel**, assistant professor of oncology in the Department of Molecular and Cellular Biology, received a two-year, $375,000 Pancreatic Cancer Action Network-AACR Pathway to Leadership Grant from AACR. His project aims to understand the role of the HNF1A protein in pancreatic cancer cells, how it contributes to tumor growth and treatment resistance, and how it might be eliminated.
- **Pamela Hershberger**, associate professor of oncology in the Department of Pharmacology and Therapeutics, received a two-year, $200,000 grant from the American Lung Association for her work in overcoming treatment resistance in EGFR-mutant lung cancers. Her team is developing a nanomedicine to deliver high-dose vitamin D directly to lung tumors to prevent resistance to EGFR tyrosine kinase inhibitors from developing.

BMS completes acquisition of Celgene

Bristol-Myers Squibb Co. has completed its acquisition of Celgene Corp. following the receipt of regulatory approval from all government authorities required by the merger agreement and, as announced on April 12, approval by Bristol-Myers Squibb and Celgene stockholders. It completed the acquisition Nov. 20.

Celgene is now a wholly owned subsidiary of BMS. On Nov. 21, 2019, newly issued Bristol-Myers Squibb shares and CVRs will commence trading on the New York Stock Exchange, with the CVRs trading under the symbol "BMYRT."

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

Care in a multidisciplinary prostate cancer clinic increases discussion of treatment options, adherence to guidelines

Men who seek treatment at a multidisciplinary prostate cancer clinic are more likely to be advised about treatment choices and to receive care that complies with evidence-based treatment guidelines, an MD Anderson Cancer Center study found.

African American men who visited the MultiD clinic also were more likely to receive definitive, or curative, therapy, compared with national trends.

The findings, published in *Cancer*, are based on the largest and longest analysis of a MultiD clinic database. The study evaluated treatment choice at MD Anderson's Multidisciplinary Prostate Cancer Clinic in comparison to U.S. national trends assessed by reviewing the SEER database.

"Men who visit a MultiD prostate clinic have the opportunity to see a radiation oncologist and a urologist in the same visit, giving them the chance to discuss treatments options and potential side effects in order to make an informed treatment decision," Chad Tang, assistant professor of Radiation Oncology and lead author, said in a statement. "Patients and their families appreciate the opportunity to hear all treatment options and receive assistance with decision-making."

The study analyzed 4,451 men with prostate cancer treated at the MultiD clinic from 2004-2016. To compare nationwide trends, 392,710 men with prostate cancer diagnosed from 2004-2015 were selected from the SEER database.

Men with low-risk disease were more likely to choose active surveillance in the MultiD clinic than the SEER group. In 2015, the rate of active surveillance among men with low-risk disease in the MultiD clinic was 74% compared with 54% in the SEER group. The tendency toward active surveillance for patients with low-risk prostate cancer is supported by NCCN guidelines and national trends.

At the high risk end of the spectrum, significantly more men were offered aggressive treatment in the MultiD clinic group as compared to SEER patients. Nearly 20% of men with high-risk disease chose non-definitive treatment in the SEER group whereas all men with high-risk disease received definitive treatment in the MultiD clinic group. NCCN guidelines recommend men with high-risk prostate cancer receive definitive treatment.

In the MultiD clinic, African American men over 70 with low-risk disease were more likely to choose active surveillance than older white men. In all other age and risk groups, African Americans were more likely to receive definitive treatment. In the SEER cohort, the opposite was found where African Americans in all risk groups were more likely to receive definitive treatment across age groups.

Previous studies have shown increased use of definitive therapy among white patients compared with African American patients. Among MultiD clinic patients an opposite trend was found for high-risk, intermediate-risk and young low-risk patients, with African American patients having higher rates of definitive therapy.

"These results suggest that when offered treatment options by a multidisciplinary team, African American men may choose a more definitive treatment choice," Tang said. "The outcomes of this study offer an important motivation to provide multidisciplinary clinical care on the national level."

MD Anderson has implemented multidisciplinary prostate cancer clinics across the MD Anderson Cancer Network.

The authors noted the study's limitations. For instance, the SEER database contains data through 2015, whereas the MultiD clinic database has information through 2016. The SEER database also lacks details regarding complete therapy and does not have data on whether patients were treated with active surveillance, watchful waiting, hormones alone or "benign neglect." Finally, there is inherent patient referral preference to this single center MultiD clinic.

This research was supported in part by the Cancer Center Support (Core) Grant NCI CA016672 to MD Anderson Cancer Center. Tang is supported in part by grants from the Cancer Prevention and Research Institute of Texas, the Radiation Oncology Institute and the Anna Fuller Foundation.

UCSD researchers focus on persistent opioid use, abuse and toxicity among cancer survivors

Within a cohort of 106,732 cancer survivors diagnosed between 2000 and 2015, researchers at the University of California San Diego determined rates of persistent post-treatment opioid use, diagnoses of opioid abuse or dependence, and admissions for opioid toxicity.

The study, "Predicting Persistent Opioid Use, Abuse and Toxicity Among Cancer Survivors," was published in the *Journal of the National Cancer Institute* Nov. 22.

The study cohort included patients diagnosed with one of the 12 most common cancers (bladder, breast, colon, esophagus, stomach, head and neck, kidney, liver, lung, pancreas, prostate, or rectal cancer), and alive without recurrence two years after treatment.

Among the patients in this study the overall incidence of persistent post-treatment opioid use was 8.3%, which varied by cancer type ranging from a low of 5.3% in prostate cancer patients to a high of 19.8% in liver cancer patients. Bladder, breast, esophagus, stomach, head and neck, liver, lung and pancreas cancer were associated with higher odds compared to prostate cancer.

The rates of persistent opioid use after treatment varied substantially by a patient's history of opioid use prior to his receiving a cancer diagnosis. The persistent post-treatment opioid use rates were lowest for patients who had never used opioids prior to their cancer diagnosis (3.5%) followed by prior intermittent users (15.0%), and prior chronic users (72.2%). The rate of post treatment diagnoses of opioid abuse or dependence was 2.9%, and opioid-related admissions occurred in 2.1% of patients.

Younger age, white race, unemployment at the time of cancer diagnosis, lower median income, increased comorbidity, and current or prior tobacco use were all associated with increased risk for persistent opioid use. Prior diagnoses of alcohol abuse, non-opioid drug abuse, opioid abuse, and depression were associated with increased odds. Prior history of chronic opioid use and prior intermittent use were associated with substantially increased odds of persistent opioid use

"Our study attempts to create an objective clinical tool that can help give providers a better understanding of a patient's risk of opioid-related toxicity," Lucas K. Vitzthum, one of the study's authors, said in a statement. "Ultimately, clinical tools such as ours could help providers identify which patients could benefit from alternative pain management strategies or referral to pain specialists."

In Opdivo + Yervoy vs. Opdivo alone in resected high-risk melanoma and PD-L1 <1% does not meet primary endpoints

A statistically significant benefit was not reached for the co-primary endpoint of recurrence-free survival in patients whose whose tumors expressed PD-L1 <1%, according to results from phase III CheckMate -915.

Bristol-Myers Squibb sponsors the study.

The study evaluated Opdivo (nivolumab) plus Yervoy (ipilimumab) versus Opdivo alone for the adjuvant treatment of patients who have had a complete surgical removal of stage IIIb/c/d or stage IV (no evidence of disease) melanoma.

The data monitoring committee at Bristol-Myers Squibb recommended that the study continue unchanged. The study remains double-blinded and will continue to assess the other co-primary endpoint of RFS in the all-comer (intent-to-treat) population.

The Cancer Letter is taking a Thanksgiving break. We will return on Dec. 6.

DRUGS & TARGETS

FDA takes second action under international collaboration, approving treatment option for CLL or SLL

As part of Project Orbis, a collaboration with the Australian Therapeutic Goods Administration and Health Canada, FDA granted supplemental approval to Calquence (acalabrutinib) for the treatment of adults with chronic lymphocytic leukemia or small lymphocytic lymphoma. This new approved indication for Calquence provides a new treatment option for patients with CLL or SLL as an initial or subsequent therapy.

The approval was announced Nov. 21. Calquence is sponsored by AstraZeneca.

"Today, as part of a U.S., Australian and Canadian collaboration known as Project Orbis, the U.S. approved a new treatment option for those living with chronic lymphocytic leukemia or small lymphocytic lymphoma. The FDA's Project Orbis provides a framework for concurrent submission and review of oncology drug applications among the FDA's international partners," Richard Pazdur, director of the FDA's Oncology Center of Excellence and acting director of the Office of Oncologic Diseases in the FDA's Center for Drug Evaluation and Research, said in a statement. "We are pleased to continue working alongside our Australian and Canadian colleagues to facilitate new treatment options for patients and the FDA looks forward to working with other countries in future application reviews."

The supplemental approval of Calquence for patients with CLL or SLL was based on two randomized clinical trials that compared Calquence to other standard treatments. The first clinical trial involved 535 patients with previously untreated CLL. Patients receiving Calquence had a longer progression-free survival compared to patients receiving other standard treatments. The second clinical trial included 310 patients with previously treated CLL. Patients receiving Calquence also had a longer progression-free survival than patients receiving other standard treatments.

In addition to the international collaboration with Australia and Canada, this review used the Real-Time Oncology Review pilot program, which can streamline the submission of data prior to the completion and submission of the entire clinical application. RTOR, and its accompanying Assessment Aid, facilitated discussions among the regulatory agencies. These applications were approved four months prior to the FDA goal date. The FDA granted this application Priority Review and Breakthrough Therapy designation.

FDA grants Q BioMed approval to manufacture non-opioid cancer palliation drug

FDA approved Q BioMed Inc.'s contract manufacturer IsoTherapeutics Group LLC Nov. 20, which it cleared to manufacture the company's FDA-approved non-opioid cancer bone pain drug Strontium-89 Chloride USP.

The approval of the facility means that this oncologic pain drug will soon be available to patients in the United States. Q BioMed is now the only FDA-approved source for this drug in the western world, the company said.

Strontium-89 is an FDA-approved non-opioid radiopharmaceutical indicated for the treatment of painful skeletal metastases caused by cancer. The product is administered intravenously once every three months as an alternative to opioid analgesics and plays a critical role in the treatment of metastatic bone pain.

The product provides relief for patients suffering from pain associated with primary cancers that have spread to the bone, including breast, prostate, lung and others.

FDA approves crizanlizumab-tmca for sickle cell disease

FDA approved Adakveo (crizanlizumab-tmca) to reduce the frequency of vaso-occlusive crises in adults and pediatric patients 16 and older with sickle cell disease.

Adakveo is sponsored by Novartis.

Rodger McEver is a physician-scientist at Oklahoma Medical Research Foundation who developed an antibody that blocks the effects of P-selectin, a protein thought to drive pain crises for sickle cell patients. To explore clinical applications, McEver helped create an Oklahoma-based biotechnology company, Selexys, which fine-tuned the antibody and created an experimental drug.

Novartis purchased Selexys and Adakveo.

The drug showed a 45% reduction in pain crises when administered intravenously every 4 weeks in a clinical trial involving 198 sickle cell patients.

"We know this drug can decrease the frequency of sickle cell pain crises in a significant and clinically meaningful way," Kenneth Ataga, who led the trial and directs the Center for Sickle Cell Disease at the University of Tennessee Health Science Center at Memphis, said in a statement.

Adakveo is the third medication now available that is based on OMRF discoveries. The others are Soliris, a treatment for patients with certain rare blood disorders, and Ceprotin, a therapy for protein C deficiency.

Efficacy was evaluated in 198 patients with sickle cell disease in SUSTAIN (NCT01895361), a 52-week, randomized, multicenter, placebo-controlled, double-blind trial. Patients were randomized (1:1:1) to crizanlizumab-tmca 5 mg/kg (N = 67), crizanlizumab-tmca 2.5 mg/kg (N = 66), or placebo (N = 65) administered intravenously over 30 minutes on week 0, 2, and every 4 weeks thereafter. Randomization was stratified by prior hydroxyurea (Y/N) and by the number of VOCs in the prior 12 months.

The primary efficacy outcome measure was the annual rate of VOCs leading to a healthcare visit, defined as an acute episode of pain with no cause other than a vaso-occlusive event requiring a medical facility visit and oral or parenteral opioids, or parenteral NSAIDs. Patients receiving crizanlizumab-tmca, 5 mg/kg, had a lower median annual rate of VOC compared to those receiving placebo (1.63 vs. 2.98, p=0.010). Reductions in the frequency of VOCs were observed among patients regardless of sickle cell disease genotype and/or hydroxyurea use. Thirty-six percent of patients treated with crizanlizumab-tmca 5 mg/kg did not experience a VOC compared to 17% in the placebo arm. The median time to first VOC from randomization was 4.1 vs. 1.4 months in the crizanlizumab-tmca 5mg/kg and placebo arm, respectively.

FDA approves givosiran for acute hepatic porphyria

FDA approved Alnylam Pharmaceuticals Inc.'s Givlaari (givosiran) for adults with acute hepatic porphyria.

Efficacy was evaluated in ENVISION (NCT03338816), a randomized, double-blind, placebo-controlled, multinational trial enrolling 94 patients with AHP. Patients were randomized (1:1) to receive once monthly subcutaneous injections of givosiran 2.5 mg/kg or placebo during a 6-month double-blind period.

The primary efficacy outcome measure was the rate of porphyria attacks requiring hospitalizations, urgent healthcare visit, or intravenous hemin administration at home. The mean rates of attacks over a 6-month time period were 1.9 (95% CI:1.3,2.8) for patients receiving givosiran and 6.5 (95% CI:4.5, 9.3) for those on placebo. On average, patients with AHP on givosiran experienced 70% (95% CI: 60%, 80%) fewer porphyria attacks compared to placebo.

European Commission approves two regimens of Keytruda for front-line metastatic, unresectable HNSCC

The European Commission has approved Merck's Keytruda as monotherapy or in combination with platinum and 5-fluorouracil chemotherapy, for the first-line treatment of patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma whose tumors express PD-L1 (combined positive score [CPS] ≥1). The drug was approved Nov. 20.

This approval is based on findings from the phase III KEYNOTE-048 trial, where Keytruda, compared with standard treatment (cetuximab with carboplatin or cisplatin plus 5-FU), demonstrated a significant improvement in overall survival as monotherapy (HR = 0.74 [95% CI, (0.61-0.90); p=0.00133] and in combination with chemotherapy (HR=0.65 [95% CI, 0.53-0.80]; p=0.00002), in patients whose tumors expressed PD-L1 (CPS ≥1).

This approval allows marketing of the Keytruda monotherapy and combination regimen in all 28 EU member states plus Iceland, Lichtenstein and Norway.

Keytruda is the First Anti-PD-1 Therapy Approved in Europe for the First-Line Treatment of Head and Neck Cancer as Monotherapy or in Combination with Chemotherapy, in Patients Whose Tumors Express PD-L1.

KEYNOTE-048 is a multi-center, randomized, open-label, active-controlled trial conducted in 882 patients with histologically confirmed metastatic or recurrent HNSCC of the oral cavity, pharynx or larynx, who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies. Randomization was stratified by tumor PD-L1 expression (Tumor Proportion Score [TPS] ≥50% or <50%), HPV status (positive or negative), and ECOG Performance Status (0 vs. 1). The dual primary endpoints were OS and progression-free survival. Patients were randomized 1:1:1 to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every three weeks;

- KEYTRUDA 200 mg intravenously every three weeks, carboplatin AUC 5 mg/mL/min intravenously every three weeks or cisplatin 100 mg/m2 intravenously every three weeks and 5-FU 1000 mg/m2/day as a continuous intravenous infusion over 96 hours every three weeks (maximum of six cycles of platinum and 5-FU);
- Cetuximab 400 mg/m2 intravenously as the initial dose then 250 mg/m2 intravenously once weekly, carboplatin AUC 5 mg/mL/min intravenously every three weeks or cisplatin 100 mg/m2 intravenously every three weeks and 5-FU 1000 mg/m2/day as a continuous intravenous infusion over 96 hours every three weeks (maximum of six cycles of platinum and 5-FU).

Treatment with Keytruda continued until RECIST v1.1-defined progression of disease as determined by the investigator, unacceptable toxicity or a maximum of 24 months.

European Commission grants marketing authorization for Darzalex + lenalidomide and dexamethasone in frontline MM

The European Commission has has granted marketing authorization for Darzalex (daratumumab) in combination with lenalidomide and dexamethasone (Rd) as treatment for adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

Genmab sponsors the drug.

The EC approval follows a positive opinion issued for Darzalex by the CHMP of the European Medicines Agency in October. In August 2012, Genmab granted Janssen Biotech, Inc. an exclusive worldwide license to develop, manufacture and commercialize daratumumab.

The approval was based on data from the phase III MAIA (MMY3008) study of daratumumab in combination with Rd as treatment for patients with newly diagnosed multiple myeloma, who are not candidates for high dose chemotherapy and ASCT. Data from this study were published in The New England Journal of Medicine and presented at the 2018 American Society of Hematology annual meeting in December 2018.

The phase III study (NCT02252172) is a randomized, open-label, multicenter study that includes 737 newly diagnosed patients with multiple myeloma who are not candidates for high dose chemotherapy and ASCT. Patients were randomized to receive either treatment with daratumumab in combination with lenalidomide (an immunomodulatory drug) and dexamethasone (a corticosteroid) or treatment with lenalidomide and dexamethasone alone.

In the daratumumab treatment arm, patients received 16 milligrams per kilogram (mg/kg) weekly for the first 8 weeks (cycles 1 and 2), every other week for 16 weeks (cycles 3 to 6) and then every 4 weeks (cycle 7 and beyond) until progression of disease or unacceptable toxicity.

Lenalidomide is administered at 25 mg orally on days 1 through 21 of each 28-day cycle, and dexamethasone is administered at 40 mg once a week for both treatment arms. Participants in both treatment arms will continue Rd until disease progression or unacceptable toxicity. The primary endpoint of the study is progression free survival.

Japan grants approval of Myriad Genetics' BRACAnalysis Diagnostic System for breast cancer patients

Japan's Ministry of Health, Labour and Welfare has approved Myriad Genetics' BRACAnalysis Diagnostic System to help physicians determine which women with breast cancer have Hereditary Breast and Ovarian Cancer syndrome and qualify for additional medical management.

BRACAnalysis is a genetic test that identifies germline mutations in the BRCA1/2 genes.

Under the MHLW decision, physicians may use BRACAnalysis to test for BRCA mutations in women with breast cancer who meet the genetic testing guidelines defined by JOHBOC. Those patients who test positive for a deleterious BRCA mutation will be eligible to receive advanced medical management, such as prophylactic surgery or targeted therapies.

Myriad has an exclusive partnership with SRL Inc., a subsidiary of Miraca Group, to commercialize the BRACAnalysis Diagnostic System in Japan.

The announcement follows two prior regulatory approvals for the BRACAnalysis Diagnostic System in Japan. In February this year, BRACAnalysis was approved as a companion diagnostic for Lynparza (olaparib) in women with ovarian cancer, and in March 2018, it was approved as a companion diagnostic for Lynparza in patients with metastatic inoperable or recurrent breast cancer.