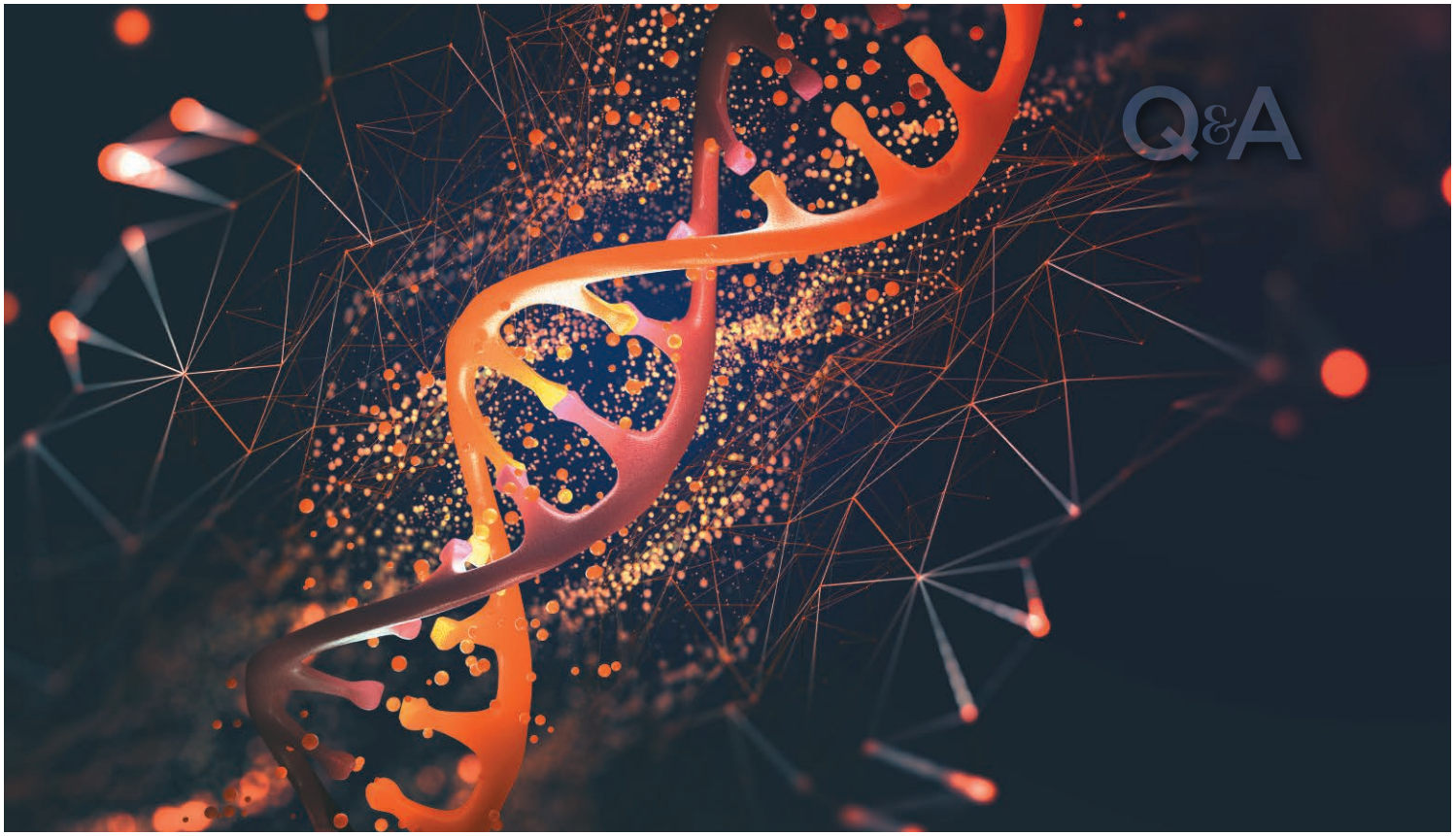

Prospective Clinicogenomic Program (PCG) at Flatiron

An interview with Ariel Bourla, MD, PhD, Medical Director II, Clinical Trials Lead at Flatiron Health

Introduction and background

Of critical importance to clinical drug development is clearly stating the questions to be addressed by the clinical team, which effectively drives the trial design. A major determining factor is deciding which is more important: to get new effective therapies to patients or to understand what treatments will have the greatest impact for which patients?

Of equal concern is how teams should weigh the cost and time of the trial relative to the long-term cost and impact of an approved drug. That is, can a team justify the greater cost to determine precision efficacy of a drug for longer-term cost saving in the face of a less-costly but more direct delivery of a drug therapy to a potentially narrower population.

Making the right choice is important since clinical trials require a significant effort and cost to plan, initiate, implement, and carry through to completion. In the competitive drug market, time to market can create an advantage for those first to market. Consider the case of the two immunooncology drugs, Nivolumab and Pembrolizumab, both of which target the PD-1/PD-L1 pathway. Pembrolizumab was marketed with an assay to identify those whose cancers were PD-L1 positive, and hence more likely to respond to the drug. Developing and validating the assay added time and expense to the process, however pembrolizumab has done well by putting a premium on precision with its companion diagnostic for PD-L1, resulting in more indications for more cancer types.

Given this background, we found the Prospective Clinicogenomic (PCG)[1] clinical study of particular interest. The investigational study is directed to identifying genetic information that may inform the question of efficient delivery to an identified responder population or to find first all the possible populations eligible for a therapy – in this case, for metastatic non-small cell lung cancer or extensive-stage small-cell lung cancer. Could such a study be a "pre-trial" model for how to decide between a directed trial for a known responder population or a trial that starts by determining subpopulations for future trials?

Three collaborators are engaged in the execution of the PCG study. We approached one of the collaborators, Flatiron Health, to ask about the trial design, its goals, the analysis plans, and the expected clinicogenomic outcomes. In particular, we focused on the Flatiron platform used to power the study, and how it might aid in improving the efficiency, speed, and ability to collect data.

Prospective Clinicogenomic Program (PCG)

The main purpose of the Prospective Clinicogenomic study is to evaluate the feasibility of a scalable, prospective research program for participants with metastatic non-small cell lung cancer (mNSCLC) or extensive-stage small-cell lung cancer (ES-SCLC) planning to start standard-of-care (SOC) systemic anti-cancer treatment. The study will also examine ctDNA status over the course of treatment as a predictor of response to therapy.

Q. What are Flatiron's goals for this study?

A. Flatiron's mission for many years has been to improve and extend lives by learning from the experience of every person with cancer. To this end, Flatiron has developed a robust data processing infrastructure to capture both structured and unstructured data from Electronic Health Records (EHRs). We turn this real-world data into de-identified and aggregated real-world evidence to help researchers understand real world outcomes.

In addition to performing retrospective observational research, we recognized that we could help fill evidence gaps with technology-enabled prospective studies run across our site network. We accomplish this through intentionally capturing additional data in the EHR that may not be documented as part of routine care.

Our primary goal for the PCG study was to establish that we could successfully recruit patients and collect the specified clinical information and biologic specimens across our network with minimal site burden by using technology according to a pre-specified protocol. We knew that, in order to do this, we would have to engage our network of research practices and the patients at these practices receiving care. This included building and deploying other clinical trial tools to make research workflows more efficient at our community oncology and academic research sites. We knew that if we did this successfully, we would be able to capture rich clinical and genomic data that could provide valuable learnings to researchers about drug responsiveness and mechanisms of resistance, ultimately benefiting patients.

Q. Can you describe the role of Flatiron Health in this collaborative clinical trial effort? What will the other two collaborators perform with respect to the Flatiron?

A. This study was a collaboration among Flatiron Health, Foundation Medicine, Inc. and Genentech, members of the Roche Group, in partnership with community and academic oncology practices. Genentech funded and sponsored this study, and Foundation Medicine processed the blood samples collected for circulating tumor DNA analysis.

Flatiron Health was responsible for bringing in the community and academic research site network, developing the study design, capturing the data straight from the EHR, and overseeing the quality and integrity of the data. Flatiron leveraged and built a number of technology features to support the PCG study such as processes and communication tools to centrally monitor the data, streamline patient identification, and centrally curate data from the EHR using a technology-assisted abstraction process, that almost entirely eliminates duplicate data entry by research sites, and the need for sites to use a separate traditional electronic data capture system. Now that we've captured a tremendous amount of data over the past two and a half years, all three companies are collaborating to analyze the data and generate scientific insights.

Q. Blood levels of circulating tumor DNA will be measured from those enrollees submitting sufficient blood samples. Are there plans to assay for other markers? For example, protein or mRNA or miRNA?[2]

A. The secondary objective of the study is to explore ctDNA status over the course of treatment as a predictor for response to therapy by evaluating the association between ctDNA levels and/or profiles and real-world clinical outcomes. Not only blood ctDNA levels, but also the particular mutational profiles, are being used for this objective.

The exploratory objective of the study is to learn more about mechanisms of resistance, surrogate markers of progression and response, and to inform drug development or assay development. Extra samples are being stored for future work which may involve, but is not limited to, next-generation sequencing, whole exome sequencing, immunohistochemistry, or gene expression analysis.

Q. Flatiron provides a link to a case study based on the trial[3] **citing a quote by Dr Emily Pauli.**[3a] **The premium here appears to focus on speed and efficiency. Can you comment on metrics used to assess these metrics?**

A. At Flatiron, we're transforming clinical research through technology that seamlessly integrates research into everyday clinical care. We believe that Flatiron's technology and operational platform for running prospective research can add value by increasing clinical trial speed, efficiency, and quality. We've had many conversations with research coordinators and physicians at our practices running PCG, and we keep hearing that the study is low-lift and easy to run. In parallel, we are working on more formal analyses, not limited to PCG, to demonstrate the time savings and data quality advantage of using our technology products. For example, we're looking at the time spent on data entry using our platform versus traditional EDC data entry, the number of queries administered, the data change rate, and more.

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Q. How is the Flatiron platform used for:

Clinical trial design, recruitment, and tracking?

A. At Flatiron, we leveraged real-world evidence to inform trial design and developed recruitment forecasting techniques that proved to be highly accurate during the conduct of PCG, even through the peak COVID-19 pandemic recruitment slowdowns across many oncology studies. We also leveraged a Flatiron software product called OncoTrials[4] and built a custom recruitment view for the PCG study, which uses EHR data to centrally curate and manage patients. The tool allows Flatiron sites to identify eligible patients easily, track them continuously, and alert the clinical team directly through the EHR so they are prompted to discuss the study opportunity at the patient's next visit.

Communication among clinical trial directors and principal investigators?

A. We know that site trial teams need to move constantly between software systems for the studies they are running, and one of our primary focuses for PCG was minimizing the burden on the team. As the sites in PCG were already active users of our OncoTrials software and were using the system to manage study recruitment, we chose to build custom features in OncoTrials as a platform for communicating study specific data questions. We also really want our study sites to let us know how we can constantly improve, so we ran a significant number of feedback sessions and roundtable discussions that have led to additional feature development and a focus on simplifying communication in future platform studies, even if they are conducted with an EDC-based system.

Data collection and oversight?

A. High quality data collection is one of the platform's strongest attributes. By intentionally collecting data from the EHR using our technology enabled abstraction process, we were able to curate almost all of the PCG study data just from routine EHR processes at each site with some lightweight requirements for things such as informed consent and confirmation of eligibility. Our routine RWE data quality processes generate data with extremely high quality and completeness; these data are then centrally reviewed by study monitors, all with minimal site interaction. As we look to the future, we see the potential for combining traditional data collection processes (e.g., traditional entry of data in EDC) with components we tested in PCG (e.g., prospective, centralized collection of data using pushes of structured data and technology enabled curation of unstructured data).

Q. How does this platform benefit patients, and does it provide them with anything?

A. A focus of ours has been to ensure that everything we build provides a positive experience for our practices and their patients.

From a patient perspective, we believe that our focus on increasing patient diversity in clinical research by engaging our community network will lead to results that are more representative of patients receiving care in this country. There is a huge benefit to all stakeholders especially by including patients who have been historically underrepresented in clinical research. More directly, our goal is to bring interesting clinical research to patients where their care is already being delivered, and to do so efficiently and seamlessly. From this study in particular, patients and their care team received genomic testing results from the ctDNA assays performed on the submitted blood samples, and this was received very positively across our sites.

What about improvement and benefit to the sites?

A. For sites, we consistently have tried to innovate with new approaches to improve their workflow and experience, and ultimately advocate for solutions that will allow them to offer trials to more patients.

Q. What improvements, updates, or extensions does Flatiron plan for this platform? For example, will this platform be extended to other therapeutic areas? Or other (multiomic) data types?

A. At Flatiron Health, we are focused on bridging the gap between care and research by reimagining the infrastructure of cancer care. We have a number of new products and concepts in development to help support this.

One recent investment we've made in this area was the acquisition of Protocol First, a software solutions provider focused on accelerating clinical research. Their software automates the direct transfer of data from EHRs into electronic data-captures (EDC), reducing the need for human transcription from one system to another, with all the time and effort and errors associated with this process. Our product suite also now provides a secure environment for remote monitoring of source documents; protocol digitization capabilities; and a nimble electronic data capture system built to handle the unique complexities of oncology but also capable of support more efficient research across other therapeutic areas – which will be an important part of the story as the role of EHRs and EDCs in clinical trials evolve over the next 5-10 years.

The PCG study included collection of blood samples and optional tissue samples for genomic assays. We have the ability to take a real integrated evidence approach, capturing different types of data including insurance claims, Patient Reported Outcomes (PROs), scans, or additional biologic samples to support discovery efforts, and link it all together into a study database.

We see all these new technologies as adding to the capabilities of this platform, making the experience more seamless and low burden for sites and patients, and more efficient for biopharma partners. While our platform for running prospective real-world studies is focused on oncology, many of our clinical research products are able to be deployed in support of phase I through IV clinical trials across any therapeutic area.

Q. Any closing comments?

A. Flatiron Health is deeply focused on reimagining the infrastructure of cancer care, so that we can come together across the ecosystem to accelerate learning in a more efficient and sustainable way. We're at an incredibly exciting time for innovation in clinical trials in which you can really see how new technologies can support all aspects of clinical research, from patient identification to trial design, to study monitoring and more. JoPM

About Flatiron Health

Flatiron Health is a healthtech company dedicated to helping cancer centers thrive and deliver better care for patients today and tomorrow. Through clinical and data science, we translate patient experiences into real-world evidence to improve treatment, inform policy, and advance research. Cancer is smart. Together, we can be smarter. Flatiron Health is an independent affiliate of the Roche Group. Flatiron.com @FlatironHealth

Ariel Bourla, MD, PhD

Dr. Ariel Bourla is a physician and clinical researcher who serves as the Medical Director II, Clinical Trials Lead at Flatiron Health. Dr. Bourla's work focuses on the development and execution of Flatiron's prospective clinical research offerings. Prior to Flatiron, Dr. Bourla was a fellow in Medical Oncology at Memorial Sloan Kettering Cancer Center. She received her BA from Yale University, and her MD and PhD degrees from the Mount Sinai School of Medicine and the National Institutes of Health. She completed her Internal Medicine residency training in the research track at Columbia University Medical Center. She has published in major peer-reviewed journals and received several honors for her research.

References

1. ClinicalTrials.gov Identifier: NCT04180176, https://clinicaltrials.gov/ct2/show/NCT04180176?term=flatiron&recrs=ad&cntry=US&draw=2&rank=4. The main purpose of this study is to evaluate the feasibility of a scalable, prospective research program for participants with metastatic non-small cell lung cancer (mNSCLC) or extensive-stage small-cell lung cancer (ES-SCLC) planning to start standard-of-care (SOC) systemic anti-cancer treatment. The study will also examine ctDNA status over the course of treatment as a predictor of response to therapy.
2. Targeted Therapies and Biomarkers in Small Cell Lung Cancer, Hirokazu Taniguchi, Triparna Sen, and Charles M. Rudin, Front. Oncol., 20 May 2020 I https://doi.org/10.3389/fonc.2020.00741
3. Case Study Report on Prospective Clinico-Genomic Study, https://flatiron.com/case-study-prospective-clinicogenomic/;
   a. On the site in Reference 3, Emily Pauli is quoted as saying: "The PCG study represents the next paradigm in clinical studies by eliminating an electronic data capture step, the potential for transcription errors, and additional staffing for data entry. By utilizing the [same] Flatiron platforms our practice uses for routine care, PCG monitors reviewing subject data in OncoEMR® and issues queries directly in OncoTrials® to streamline the study process and maximize efficiencies."
4. OncoTrials, https://flatiron.com/oncology/clinical-trials/