


# NGS and circulating markers in the clinic at UPMC

*An interview with* **Roby Thomas, UPMC Hillman Cancer Center**

## Introduction

Over the past several years, precision medicine has moved from the research and clinical trial stage to being recognized as a viable paradigm in clinical practice. Assays developed in clinical laboratories as well as by diagnostics companies have been (are being) used to indicate *safe, effective, and personalized* treatments. The FDA has weighed in by recognizing biomarkers[1] and companion diagnostic devices[2] with their associated indications.

Along these lines, we connected with Roby Thomas, a practicing medical oncologist and hematologist at UPMC Hillman Cancer Center, to address a few questions on using precision medicine methods in his clinical work. Dr. Thomas is trained in the management of all cancers and blood disorders with a focus on genitourinary and gastrointestinal malignancies. He utilizes high technology methods in his work, including next generation sequencing (NGS), circulating tumor DNA (ctDNA) assays, and imaging. Dr. Thomas works with in-house laboratories, third-party vendors, and, of course, the staff and faculty at UPMC.

Roby's replies are informed by his experiences in the research setting, in the clinic with patients, and working with other healthcare professionals and service providers. Read on.

**Q. What types of analyses are performed on the samples in your lab? Is diagnosing a patient the primary goal, or are these samples also used for research and biomarkers?**

**A.** When we run next generation sequencing, the primary purpose is to identify any targetable mutations that might be an option for what we have for an FDA approved setting. We, at our institution, have a way of determining if certain mutations might be eligible for clinical trials, since not a lot of the mutations that we have would be for FDA approved indications. We're able to capture that information and then work closely with our pathology department and our molecular pathology department to understand the characteristics of the mutations, does it inform prognosis or potential targeted treatments through clinical trials that might be available – not just everywhere, but also what's available within our own institution, or in proximity with the patient.

That's the primary purpose. The secondary purposes are in situations where a patient may have cancer of an unknown primary origin – understanding the molecular information might be helpful in pointing toward a direction of whether it might be one malignancy or another.

Other things coming more to the forefront

include understanding how a patient's course might go while on treatment. For example, we now can look at circulating tumor DNA. Various trials have shown a benefit to detecting ctDNA and understanding what our patient's recurrence risks in the context of minimal residual disease may be for different malignancies, such as colorectal cancer.

One can see that allelic frequency may change during the course of a treatment, which might be an early sign or indication that cancer is becoming resistant or that treatment is effective.

**Q. Are clinical assays and genomic results used in combination when diagnosing a patient?**

**A.** Yes, that's why we work very closely with our pathology department who in turn also works with our molecular pathology lab to understand what exactly is going on with our patients at a molecular level, whether it's an EGFR mutant lung cancer patient or understanding microsatellite instability (MSI), not just MSI on the IHC or protein expression, but if there's a mismatch repair deficiency as well at the DNA level. Providing a full picture is certainly the best course of action for any patient, and that's why NGS is becoming an important facet of how we take care of our cancer patients.

**Q. Are you also looking at other nucleic acid species to assay? Say, mRNA, miRNA in circulation?**

**A.** We're not doing those assays at our institution as of yet. Most of this work at UPMC and elsewhere is in the research setting. We have the capabilities to run that assay, and it's certainly going to be applied more and more for research purposes.

Right now, we're able to look at whole transcriptome sequencing (WTS) results from our molecular pathology lab. When we understand how to employ WTS through our institution and the coverage that insurance will have to provide, we'll be doing more of these assays.

**Q. Can you comment on the circumstances that require a liquid biopsy and what types of cancers typically require a liquid biopsy?**

**A.** Looking at an analytics level for our institution, the most common use case that we're seeing – not only in the academic hub, but through the network – is to ascertain mutations as efficiently as possible. For lung cancer (specifically EGFR mutants), there's good data and rationale for using circulating tumor DNA assays. Various companies provide it and so usually that's a situation where we're able to get the samples to those labs.

Results come back from a lab within a short period of time, typically five to seven business days, where before it might take up to two, four, six plus weeks to receive analyses, and that includes acquisition of the biopsy for pathology for a third-party company for analysis. Of course, we have internal capabilities, which are faster, but that's the primary use case that we've seen thus far. Outside of that, I mentioned evaluating circulating tumor DNA in an adjuvant setting, specifically in colorectal cancers. It's something we're able to employ more and more outside of the clinical trial setting

Part of the challenge with that case is if you detect a positive ctDNA and there's nothing anatomically on a CT scan, what do you do with that information? Versus in a situation where you may have a patient who's on adjuvant treatment running into a lot of toxicity. If their circulating tumor DNA is negative, maybe that's an indication that you could stop your adjuvant treatment earlier.

These are things that will be employed more and more. We also see situations where a patient may require another biopsy if he/she has developed resistance due to a mutation. Obtaining additional tissue from that patient might be a challenge. In that case, we would consider withdrawing a liquid biopsy in that situation. The concordance rates have been very promising; when we do get this information, understanding the nuances of that concordance rate and what these mutations might mean are also important. In the situation of prostate cancer, for example, many patients may have had a prostatectomy a decade or even two decades ago and may now present with metastatic disease.

It's just not possible to run next generation sequencing on old tissue, or the patient has metastatic disease in the bone – that's not biopsied, or if it is biopsied, the decalcification process makes it such that you cannot run molecular analysis. That's a situation I see often. We also see many consults involving genitourinary specialists from the community sites for patients getting circulating tumor DNA analyses, and questions about what are these mutations mean, e.g., are they targetable potentially?

There are many nuances with that interpretation and whether you're capturing the right information – that's important, not only concordance, but many times you may get questions about variants of uncertain significance (VUS), whether it's ATM or CHEK2 or even BRCA (VUS). Whether that's a targetable mutation in prostate cancer remains yet to be seen.

Many times, we might see actions being taken depending on a physician's relationship with the patient and whether they feel that they might have some success with a specific action, or if they don't know when they should get placed on a PARP inhibitor, for example. Those are the big use cases for circulating tumor DNA that we see.

**Q. Can you comment on the state of linking circulating nucleic acid markers to their tumor or tissue of origin?**

**A.** I haven't mentioned any specific companies on purpose, but I think that's one of those things where we're seeing, e.g., in the colorectal space. There's a benefit to linking ctDNA to colorectal tumors, especially if you're trying to determine if there's the same circulating tumor DNA still present in patients in colorectal at stage two or three. Essentially, it's a minimal residual disease analysis, so looking for MRD positivity. That's important and, as we move forward, that's going to help in terms of healthcare utilization and tailoring a patient's care for personalized medicine point of view.

**Q. We ran a recent article in which three companies, Delphi Diagnostics, Exact Sciences, and GRAIL, discussed their respective abilities to link ctDNA to tumors through methods like the samples' methylation signatures.**[3]

**A.** I'm not familiar with those specific companies. I know Natera has commercially available tests for MRD in colorectal space. As far as the actual process is concerned, I'm not a hundred percent clear on their methodology, but they're available for physicians to order.

**Q. On to a different topic – what is the typical state of the sample that comes to your lab? Is it whole blood or biopsy tissue or what do you typically handle?**

**A.** First, let me say that I'm not a pathologist, but I have some experience with my colleagues since we've been trying to employ a standardized methodology for our entire network. The lab will receive either tumor tissue from a surgical resection that is prepared for testing (or archived) or whole blood if a liquid biopsy is necessary.

For sending samples to third-party companies: typically, an oncologist would first make a requisition and identify the archival tissue through the pathology accession number for shipping to the third-party company. In parallel, a tube of blood is drawn from the patient, paperwork is filled out, and part of the process is ensuring that there's insurance authorization prior to moving forward so that the coverage is adequate for the patient, as these tests can be thousands of dollars. That's a specific workflow; not every single patient may have a tube of blood ordered. It's position dependent on whether to do that.

Oftentimes I do take a blood sample, depending

on the company or the route you go, e.g., in the situation where there may not be enough sample tissue after being accessioned and the original analysis of IHC is performed, or whether they do microdissection, or if they're able to work with a little bit of tumor. Sometimes that's not the case so I generally will send a tube of blood just in case we don't have enough archival tissue – we may reflex to that.

**Q. What would you say to convince a clinician or physician to consider this assay who might be unaware of it or is hesitant to use it?**

**A.** If anything, I'm seeing a lot of adoption of this in the community sites, mainly because of the ease of use and the known concordance data, which is very, very promising. I think it's one of those things where physicians themselves are able to order the tests and develop that as part of their practice, as long as it's covered. If it is not an increased financial toxicity to the patient, which plays a role in how we might tailor treatments for patients, whether that's in the metastatic setting, which is the primary adoption use case originally, or in the adjuvant setting, where we're seeing some data on testing for minimal residual disease.

**Q. Does UPMC provide any clinical decision support tools for physicians about the results from NGS?**

**A.** Absolutely. UPMC is one of the forefront institutions in terms of developing a clinical decision support tool for our oncologists throughout the network. That ensures that we're getting standard care, the best care, for our patients in terms of efficacy and safety, as well as considerations for cost.

Part of that is incorporation of the next generation sequencing. Anytime there's a major update or an FDA approval, the pathways committees by disease state, disease type, will meet and update the pathways so that that information is disseminated. It's an electronic means so it's helpful in that it's a user-friendly process. Then that would link to a direct pathway order set that goes within our electronic medical record system. We've adopted these systems and methods and employ them throughout the network. This approach has been very helpful in standardizing care.

**Q. Can you comment on any of the assays, NGS or otherwise, that has had a critical impact on a patient's treatment regimen?**

**A.** NGS is the primary use case for circulating tumor DNA analyses for patients with lung cancer specifically. We know that first-line setting chemo-immunotherapy is a primary type of treatment, so patients are getting chemotherapy and immunotherapy in the first-line setting.

Typically, if they don't have a gene mutation that's targetable (oftentimes that information isn't readily available) and patients may be initiated on treatment upfront. If patients have any EGFR mutation and they're initiated on immunotherapy, sometimes there can be poor outcomes and increased risk for toxicity. That's not something that we'd like our patients to have, obviously. This is a situation in which having that information quickly can determine that patient's course. The patient should be started only on chemotherapy and then very quickly, if they had an EGFR mutation, transitioned to that, and immunotherapy should not have been part of that equation. So that's a significant number of patients with these molecular alterations that need to be captured.

**Q. Do you have any final comments or thoughts on this topic, anything to wrap up?**

**A.** Yes – as we move forward, NGS is going to be an even better technology in terms of utilizing liquid biopsies. There may come a time where hopefully we're able to identify and use this for screening purposes. We're not there yet, but I think that'll be something that we're going to see more and more in the future. My hope is that we can use these technologies in a preventative measure. An ounce of prevention is a pound of cure. This is something that we're going to see n the future.

It's also important to incorporate NGS in terms of decision support. The field is quite broad; our community partners may see many different types of diseases and we're seeing like they're a part of that decision tree. Having a means to employ that at the individual physician level and at an institutional level is extremely important. We now have a way of asking and analyzing questions like, "What are the adherence rates through the network and in my practice?" That's important for providing the best patient care! JoPM


**Roby A. Thomas, MD**

Roby A. Thomas, MD, is a medical oncologist and hematologist at UPMC Hillman Cancer Center. Dr. Thomas is trained in the management of all cancers and blood disorders with a focus in genitourinary and gastrointestinal malignancies.

Dr. Thomas is board-certified in internal medicine, medical oncology and hematology. Dr. Thomas has a background in chemical engineering from the University of Virginia in Charlottesville, followed by work as a consultant in information technology at IBM. He changed careers to medicine and received his medical degree from the American University of the Caribbean in St. Maarten. Dr. Thomas completed a residency at West Virginia University in internal medicine, followed by a fellowship at the University of Pittsburgh, serving as the chief fellow in his final year.

His research interests include precision medicine and working with researchers from Carnegie Mellon University in the development and use of machine learning and artificial intelligence to better understand cancer. He also serves as assistant director of medical information systems for UPMC Hillman Cancer Center, the electronic record medical director for oncology at UPMC and as a clinical assistant professor of medicine in the University of Pittsburgh School of Medicine. Dr. Thomas is a member of the American Medical Association, American Society of Hematology, and American Society of Clinical Oncology.



**References**

1. Table of Pharmacogenomic Biomarkers in Drug Labeling, https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
2. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools), https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools
3. See Early Detection of Cancer: Transitioning from Emerging to Established Companies and Technologies, Sam Asgarian, Nic Dracopoli, and Eric Fung, Journal of Precision Medicine, March 2021, 12-16