Blood and Lymphatic Cancer: Targets and Therapy

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COMMENTARY

# Unveiling the Mysteries of Molecular Testing in AML: A Guide for Oncologists [Podcast]

Amer M Zeidan[1,*], Sanam Loghavi[2,*]

[1]Department of Internal Medicine, Yale School of Medicine, Yale University, New Haven, CT, USA; [2]Department of Hematopathology, MD Anderson Cancer Center, Houston, TX, USA

*These authors contributed equally to this work

Correspondence: Amer M Zeidan, Yale Comprehensive Cancer Center and Smilow Cancer Hospital, 37 College Street, 1st floor, New Haven, CT, 06510, USA, Email amer.zeidan@yale.edu



**Abstract:** In the first episode of the *AML Expert Series*, titled *Unveiling the Mysteries of Molecular Testing in AML: A Guide for Oncologists*, experts from Yale Cancer Center and MD Anderson Cancer Center describe the evolving landscape of molecular diagnostics in acute myeloid leukemia (AML). The discussion traces the shift from morphology- and immunophenotype-based classification to genomics-driven stratification, catalyzed by advancements in next-generation sequencing (NGS). Discussants emphasize the clinical importance of identifying key genetic mutations—such as *FLT3, IDH1/2, TP53, NPM1, KMT2A*, and *NUP98*—to inform prognosis and guide use of targeted therapies. They review the sensitivity and applications of testing modalities including Sanger sequencing, NGS, PCR, and capillary electrophoresis, and highlight how combining DNA and RNA analyses enhances detection of both mutations and gene fusions. Practical insights are offered on assay selection, test interpretation, and turnaround times, noting that while NGS is generally adequate for most targets, single-gene PCR may be needed for urgent decision-making. The episode concludes by underscoring the need for oncologists to partner with pathologists and review test coverage data to ensure appropriate molecular profiling. These insights support the integration of precise molecular diagnostics into routine AML management, enhancing personalized therapy and improving clinical outcomes.

**Keywords:** acute myeloid leukemia, IDH inhibitors, precision medicine, cytogenetics, next generation sequencing, *IDH1*-mutation

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## Chapter 1 Introduction

**Amer Zeidan [00:40]**: Hi everyone. Welcome to our independent medical education program called, Unveiling the mysteries of molecular testing in AML: a guide for oncologists, where we will be discussing the various molecular testing methods that are available and very important in the current management of patients with acute myeloid leukemia.



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**Amer Zeidan [01:01]**: So my name is Amer Zeidan, I am the Chief of the Division of Hematologic Malignancies at Yale Cancer Center at Yale University, and I specialize in the management of acute myeloid leukemia and myelodysplastic syndromes. And it's my true pleasure to be joined today by Dr Loghavi. Sanam, do you want to introduce yourself?

**Sanam Loghavi [01:19]**: Sure. Good morning, Amer. It's a pleasure to be here with you today. My name is Sanam Loghavi. I am a hematopathologist and a molecular pathologist at MD, Anderson Cancer Center in Houston, Texas.

**Amer Zeidan [01:30]**: Thank you, Sanam. So, it's a real pleasure to be joining our audience today where we will be discussing, I think a very important subject, which is how did acute myeloid leukemia management evolve over the last 15 years? Primarily with the understanding that acute myeloid leukemia has different drivers and that targeting those drivers is important in not only in the management of patients, but it can also help in different aspects of the disease, such as understanding the prognosis and understanding the specific diagnosis.

**Amer Zeidan [02:09]**: So, it's becoming very clear that every person who manages acute myeloid leukemia should have some kind of access to molecular testing capability, either locally or as a send out because those decisions are becoming very integrated in how we recommend the best treatment for patients. And maybe, Sanam, you can take us through how did the molecular techniques evolve over the last 15 years compared to the traditional cytogenetics, which I think most people are very familiar with.

**Sanam Loghavi [02:49]**: Sure. So, let us just go back a little bit in time and start with where the classification of acute myeloid leukemia was merely based on maybe a little bit of cytogenetics for an acute leukemia like acute promyelocytic leukemia (APL) or the core binding factors.[1] And then everything else was really based on immunophenotype and morphologic differentiation. And this was largely due to the lack of technologies that would allow us to understand what the genetic drivers of disease are. And then fast forward to early two thousands is where we really started doing Sanger sequencing routinely in the labs.

**Sanam Loghavi [03:31]**: And at the time we were doing very single gene Sanger sequencing for genes like *RAS, FLT3*, later and then really, at least in our lab and maybe a little bit in the research setting, but I would say in the clinical setting you saw a revolution in the way we genomically characterize acute myeloid leukemias. And that is with the advent of NGS or next generation sequencing, that allowed us to mass parallel sequence multiple genes in one panel.

We went live with our earlier NGS panels around 2013, I think. So it's only been about 10 years where we have been doing really comprehensive NGS. And at this time, while panel testing is still the Gold standard and is mostly utilized by, I would say the majority of the clinical labs in the resource rich settings the goal and the intent is to move towards whole genome sequencing where we can characterize the entire genome of the leukemia.

**Sanam Loghavi [04:43]**: And this is largely thanks to the cost of NGS and sequencing going down. So, I think now we are at a very good point where we can sequence DNA and RNA at the same time to identify both somatic mutations and then driver fusions in acute myeloid leukemia, which I am sure we are going to talk about that are also equally as important in terms of selecting appropriate therapies for the patients.

## Chapter 2 Recommendations for Molecular Testing

**Amer Zeidan [05:07]**: No, that's a great overview, Sanam, I think a very important part in addition to having the ability to do extensive testing, even including whole exome sequencing, I think is the ability to have the right expertise for people to interpret the data. And I think this is where sometimes it can get tricky, especially for the practicing oncologist. So, what would you say the bare minimum of genes that any good practice where people see patients with acute myeloid leukemia should have access to maybe overviewing what is currently recommended in some of the guidelines such as the NCCN guidelines[2]?

**Sanam Loghavi [05:50]**: Sure. I think it really depends on the therapy and the prognostic systems that we are using. So if we are talking about the bare minimum, and this is far away from the ideal world, but if we are talking about the bare minimum and if we are talking about a resource rich setting where we have access to targeted therapies, really what's important to know is first and foremost the status of *FLT3*, of course, because we have targeted therapies for *FLT3. IDH1* and *IDH2* are important, we have targeted therapies for those. *NPM1* and *KMT2A* rearrangements now become very important as well as *NUP98* because again, we have the Menin inhibitors which are targeted therapies. p53, *TP53* is

important, not necessarily because we have targeted therapies for it unfortunately, but because we do not have any therapies really for it, and it's probably best to transplant those patients as early as you can.

## Chapter 3 Current Testing Methods and Guidelines

**Amer Zeidan [06:50]**: So, Sanam, that's great. So, you mentioned a number of genes that are very important to kind of assist for mutations. Of course, as oncologists, some people might not be very familiar with the specific technology that is used. You know, people talk about NextGen sequencing, PCR, whole exome sequencing, et cetera. So maybe you can overview some of the commonly used techniques. And are there certain techniques that are better for certain mutations, or does the oncologist kind of rely on whatever the lab recommends?

**Sanam Loghavi [07:30]**: Right. I think this is a very complicated area and thank you for asking this question. Obviously not all technologies and panels are created equally. Even the same technologies and panels in different laboratories may have different capabilities.

**Sanam Loghavi [07:46]**: But I would say, so there's two ways really to break these down. And one is by analyte, right? Are we analyzing DNA or are we analyzing RNA? So, as a general rule, if we are looking for somatic mutations or changes in the DNA, and this includes some internal tandem duplications potentially in *FLT3* or other genes, really NGS is the way to go.[3,4] *FLT3* is a little bit tricky because if the internal tandem duplications (ITDs) and what we call internal tandem duplications is just duplications of the wild type sequence that leads to the mutation. So, if we are comparing this duplicated sequence to our reference genome as sometimes for the longer ITDs, the NGS bioinformatic pipelines have difficulty determining or annotating these mutations.So, in our laboratory, we complement NGS with what is called capillary electrophoresis that essentially looks for the size of the gene. So that's your DNA. RNA is great for looking for fusion products, let us say for *BCR-ABL1*, for *KMT2A* rearrangements that lead to different fusion genes. So that's from RNA and DNA.

**Sanam Loghavi [09:10]**: The other thing is the sensitivity of the different assays. So, if we think about traditional Sanger sequencing, the sensitivity is around 20%, meaning you need one in five cells to be mutated to be able to pick up the mutation.[5]

**Sanam Loghavi [09:26]**: So if you are not seeing a mutation in a Sanger sequencing, it does not mean that the mutation's not there, it just means that it may be below 20%. Most clinical grade NGS panels have a sensitivity of about 2 to 5% if they are not error corrected. And now you know very well that we are using NGS for measurable residual disease (MRD) detection as well, particularly for *FLT3* and *NPM1*.

**Sanam Loghavi [09:53]**: And the way we are able to do that is by error correction. And what I mean by that is, so when you use NGS and when you use molecular barcodes to be able to subtract PCR error from the sequencing, then your sensitivity becomes much higher and you can go down to a sensitivity of about $10^{-6}$, which is one mutant cell in 10 million cells, right? So that's a much, much more robust technology even though we are sequencing DNA and the analyte is the same, the sensitivity is very different obviously. And then the other thing, this is just a very practical tip for the practicing oncologist is if you look at most NGS reports at the end of the report, there's going to be a long table or a long section that tells you what the coverage of this panel is, right?

**Sanam Loghavi [10:49]**: So let us say for instance, most panels right now use a combination of whole exosome, so entire exonic or hotspot regions. And this is really because everything else NGS and in NGS real estate is also important. So, you have to think about the depth of sequencing versus the coverage of sequencing because there's only a finite amount of sequencing that you can do. So if you want to achieve a reasonable depth, you are going to say, okay, let us say for *NPM1* and *IDH1* and *IDH2*, I know the mutations are hotspot. I know they recurrently occur in certain regions, so then I am going to sequence a smaller portion of that gene. But then for *TP53*, I am going to sequence the entire DNA binding domain because I know the mutations happen all over the place similarly for *TET2*.

**Sanam Loghavi [11:44]**: So if you look at that table in the bottom of the NGS report, it's going to tell you exactly what regions of those genes were sequenced, right? So I think that's a little bit of a help if you are not familiar with reading these NGS reports. And then based on that, you can decide if that assay is adequate for what you are trying to achieve or not.

## Chapter 4 Integrating Molecular Testing Into Practice

**Amer Zeidan [12:06]**: Sanam, this might be more technical question, but this, I think an issue that comes often, and I have seen that I have to say early on when the IDH inhibitors, for example, were being introduced, I actually have seen where people did not even realize there was *IDH1* and *IDH2* and the patient would've a mutation *IDH1*, and they would be given an *IDH2* inhibitor. So I think it can get quite tricky if people, of course this is, I think much less happening now these days because I think people are kind of more familiar with these drugs and differences. But how can an oncologist be assured that the test that they are sending? You mentioned the coverage and the depth, for example, IDH inhibitors are very good drugs and we want to test for *IDH1* and *IDH2* in every patient. So, is NextGen sequencing adequate or should they send the PCR or should they ask a pathologist?

**Amer Zeidan [13:07]**: I always actually have been in the opinion that you send and say, this is acute myeloid leukemia, and then the pathologist can decide all the right tests rather than ask of saying, okay, you have to do PCR for this one, and NextGen sequencing for that one.

**Sanam Loghavi [13:20]**: So at this time, actually, *IDH1* and *IDH2* are pretty easy to sequence because the mutations are single nucleotide variations typically and they are hotspot. So NGS, I would say is adequate as long as the gene is covered in the panel, which the report should clearly state the coverage of the name of the genes that are covered in the panel. And routine clinical grade NGS is adequate for IDH sequencing.

**Sanam Loghavi [13:46]**: *FLT3* is a little bit more tricky. I think some NGS panels are designed to be able to pick up *FLT3* ITDs because there's bioinformatic correction that allows to do that and some NGS panels are not. So, you really have to pay attention to that. If the report indicates that the coverage is adequate for detection of *FLT3* ITD, then the NGS assays are okay for *FLT3* ITD. If not, for laboratories that do not have a good *FLT3* NGS assay, they usually complement with capillary electrophoresis.

**Amer Zeidan [14:22]**: Perfect. So specifically for testing for *IDH1* or *IDH2*, just to recap for the audience, most of those mutations happen in specific hotspots. So the coverage for most NextGen sequencing assays that are out there is probably adequate and you do not have to get concerned too much about missing a mutation. And the level of the sensitivity goes down to around 2%, which we think is quite adequate. So I know there are PCR tests as well available for *IDH1* and *IDH2* testing as well, but I think as part of the next gen sequencing that kind of assays all the genes, I think it's probably adequate. Maybe we can talk about differences in the sensitivity and the specificity and the term around time of these. Because as you know, I think some places it can take a very long time for these results to come back and everybody's anxious. The doctor is anxious, the patient is anxious, they want to get going on treatment, especially for *IDH1*, given in all their unfit patients. We actually have a frontline approval for ivosidenib in combination with azacitidine. And one of the issues that gets commonly cited in terms of why people would use azacitdine (AZA) venetoclax is that they do not want to wait because it can take 2, 3 weeks for the *IDH1*-mutation to come back. Of course, in addition to the lower frequency of *IDH1* mutations, which is around 5%.

**Sanam Loghavi [16:00]**: Of course, I think that's a great point. And in fact, I was just about to say that, so you read my mind. I think some laboratories, you'll notice that even though their NGS panel is adequate for detecting *IDH*- mutations, they still do a single gene *IDH1* and *IDH2* PCR because of the turnaround time. So the turnaround time for NGS is variable and really depends on the volume that that laboratory is testing, their bioinformatics setup, their of course the laboratory setup and various things that go into the turnaround time, but it can range from 3 to 4 days for getting an NGS results all the way up to about 3 weeks to a month. So obviously if you are an oncologist and you are waiting to treat a newly diagnosed AML, you do not want to wait a month to get the IDH result back. So then those laboratories that have slower NGS turnaround times usually complement their NGS with a PCR assay that has the ability to detect *IDH1* and *IDH2*-mutations, similar with *FLT3* sometimes for turnaround time. So, I think that's very important.

**Sanam Loghavi [17:11]**: And then in terms of, again, sensitivity and specificity is not much of an issue if we are looking at especially high variant frequency mutations. But I think sensitivity at baseline is probably not much of an issue in a patient that's presenting for IDH particularly. That is usually a clonally dominant mutation. I think of course for *FLT3*, which can often be sub-clonal, sensitivity is very important and you want to be able to detect small clones because if

those go undetected, they can often give rise to relapse. So again, the sensitivity matters, but it depends on the context. It depends on whether we are looking for measurable residual disease versus we are characterizing the disease at baseline.

**Amer Zeidan [18:03]**: Yeah. What we started doing in my institution at Yale is we actually have a rapid gene panel, which turns around within 5 business days. And we selected a few number of genes that are very important as you mentioned, such as *NPM1, FLT3, TP53, IDH1* and *IDH2*, and some of the genes that are important to designate adverse risk leukemia such as *ASXL1, RUNX1* et cetera. And then we have a more extensive panel that is, I believe, up to 49 genes that takes longer.

**Amer Zeidan [18:38]**: Sanam, when you talk about the depth of coverage, is this the same as the limit of detection, like the 1 or 2%?

**Sanam Loghavi [18:45]**: No. So, the depth of coverage is really how many times are we sequencing, how many reads are we getting on the specific region of a gene? So the higher the depth of coverage, the lower the sensitivity, right? So let us say if, because essentially let us say I am sequencing a thousand reads in *IDH1* and there's one mutant read. So the mutation has truly an incidence of one in a thousand. So if I am sequencing a thousand reads, I have the ability perhaps to pick up that one in a thousand. But if I am only sequencing a hundred reads, if I am only looking at a hundred, then there's no way I am going to be able to pick up that one in a thousand, right? So the deeper the sequencing is, the deeper the coverage is, the better, or you may say higher sensitivity, but the number is actually a lower number, right? We are able to pick up a small, small clone in a sea of wild type cells.

**Amer Zeidan [19:57]**: For our oncologists who again might get overwhelmed a little bit when you talk about coverage and depth of coverage and sensitivity and specificity. Most of the commercially available NextGen sequencing will have adequate coverage of *IDH1* and *IDH2* mutations because most of those mutations happen in what we call hotspots specific areas of the gene, which are currently mutated, and they have enough coverage to detect clinically meaningful mutations.

**Amer Zeidan [20:30]**: So it really depends on whether you have the luxury of waiting or not. If you need to start treatment sooner, you can send the PCR because that turns around faster, which is a little bit different than the *FLT3* situation where there could be an issue of the detection of the mutation, again, depending on what is the NextGen sequencing and the other supplemental techniques that the lab uses. So I think, and this is our practice actually, we often send both PCR and NextGen sequencing for that particular situation, but I feel this is an area that always confuses people. So thank you so much for explaining all of this.

## Chapter 5 Optimizing Sample Collection

**Amer Zeidan [21:05]**: And as we come towards the end of this podcast, and maybe we can talk about some of the logistical aspects of these issues related to the sample quality. We always hear from the pathologist about the bone model or suboptimal or dilute or the sample was not good. What are some of your practical hints? Of course, we can also send from the blood when they are blasts, but what kind of practical hints and recommendations in terms of making sure you receive a good sample for analysis?

**Sanam Loghavi [21:44]**: Sure. This really goes back to the pre-analytical issues of any type of molecular testing. We need to receive an adequately representative sample. So it's not just whether or not that the sample is adequate, but it needs to be a representative of what's going on in the bone marrow that we are trying to sequence and baseline. And in an initial diagnosis of AML, most of the times, thankfully, adequacy is not an issue because we are able to get an adequate amount of blasts and neoplastic cells to sequence.

**Sanam Loghavi [22:24]**: However, there are times where you have a dry tap. If you are trying to save the patient from getting a bone marrow, you are sending a peripheral blood sample. If there are not adequate circulating blasts and we are only sequencing lymphocytes, we just will not have the ability to pick up a mutation because the lymphocytes are going to be wild type, and of course they are not part of the clone.

**Sanam Loghavi [22:46]**: The other issue is, I think it's mostly post-treatment that we deal with these adequacy issues a lot is because, so when we are doing a bone marrow aspiration, the sample gets split between several laboratories. Obviously, it goes for morphologic assessment because the pathologist wants to do a blast count. It goes for flow

cytometry. Flow cytometry labs typically want either the first or the second pool, obviously because of sensitivity issues, they do not want a hemodilute sample because then that leads to inadequate assessment.

**Sanam Loghavi [23:21]**: And so the molecular lab oftentimes ends up getting the last pool, which may be even further hemodiluted. So those are things that you want to talk about. You want to think about when you are interpreting an NGS report, it's always good to look at the corresponding bone marrow report because there's always an adequacy assessment there that says whether or not this sample was an adequate sample. I think that's very important. And again, just this is a very practical, I think, simple tip, but if something does not make sense in the context of what you are trying to clinically determine, it's always good to question at least the validity of the test results and consult with the pathologist, consult with molecular lab or whoever is interpreting that report and provide them with information that you may have that is not available to them that may help them better interpret those results. And I think this is just very important common-sense practice to practice using every piece of information that's available to you.

## Chapter 6 Overcoming Barriers to Testing

**Amer Zeidan [24:24]**: Before we conclude, just one last question, or I think important because we do not operate in a vacuum, these cost considerations and barriers to getting this testing. And this is I think one of the most challenging aspects to talk about because it varies extensively across the country. And I think there are certain hospitals or certain states where it's relatively easier to do some of this next NextGen sequencing. You probably do not deal on this side of things, but any recommendations to make sure this works smoothly that you would communicate to the oncologists who order these tests?

**Sanam Loghavi [25:04]**: Yes, I think we actually do deal with this a lot. And so I think the most practical and simple tip I would say is, please be mindful and order a test if you think it's going to alter your clinical management. Let us say for a patient that has an *NPM1* mutation doing serial *NPM1*, MRD is absolutely indicated. It will definitely alter the course of this patient's management. So those are the issues that I think we need to carefully document in the chart, why are we ordering this? How is this going to alter our management?

**Amer Zeidan [25:39]**: So thank you so much, Sanam. This was excellent discussion.

## Chapter 7 Key Takeaways and Conclusion

**Amer Zeidan [25:42]**: Maybe we can conclude by some of your main key, like take home messages for our audience.

**Sanam Loghavi [25:50]**: Sure. So, my take home message is we are very lucky. We practice in an era where we have targeted therapies available to our patients, and we have very robust, extensive technologies that allow us to identify these targets of therapy. So let us use them appropriately and be mindful of the variations that exist in these different assays to be able to provide the best therapy available to our patients.

**Amer Zeidan [26:17]**: And I echo that, and I think the availability of targeted therapies with pills such as *IDH1* and *IDH2* inhibitors, *FLT3* inhibitors, but also some of the newly evolving treatments such as MENIN inhibitors, et cetera, it's a very exciting era. And diagnostics, including molecular testing is very vital to all of this development. And with that, I like to thank you so much for joining me today and thanking our audience, and hopefully we will talk to you in the next edition of this podcast. Thank you so much.

**Sanam Loghavi [26:55]**: Thank you so much. Thank you so much for having me. This was great.

## Abbreviations

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; NGS, next generation sequencing; NextGen, next-generation; ITDs, internal tandem duplications; AZA, azacitidine; MRD, minimal residual disease.

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