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Editorial

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Next Generation Sequencing is Not Yet Ready to be Used by Itself as a Diagnostic Tool!

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Editorial

Yes, I know. If you are a pathologist I'm knocking on an open door, so you may as well stop reading this editorial and use the next five minutes of your life in a more creative way! But if you are a clinician and, especially, an oncologist, please read on…

Molecular studies, in general, and next generation sequencing (NGS), in particular, are all the rage nowadays and for good reasons. These high-tech tests contribute significantly to the diagnosis of certain cases. In addition, they also provide prognostic and, most importantly for clinicians, predictive information. Some clinicians are so enthusiastic about molecular tests that they are obsessing over them to the point of willing to open their own molecular laboratories!

But can the results of these tests be used solely by themselves without the actual clinical and pathologic context of the disease? Let's look at TET2 gene mutations as an example. TET2 alterations can be seen in normal elderly individuals [1], in patients with clonal hematopoiesis of indeterminate potential (CHIP) [2], myelodysplastic syndromes (MDS) [3], myeloproliferative neoplasms (MPN) [4], myelodysplastic/myeloproliferative neoplasms, such as chronic myelomonocytic leukemia (CMML) [5], and acute myeloid leukemia [6]. In addition, TET2 mutations can be seen with B cell [7] or T cell lymphomas [8] and even other non-malignant conditions [9]. So, can testing just for TET2, out of the clinicopathologic context, be used to make a diagnosis when abnormalities of this gene can span a range from normal individuals to highly aggressive neoplasms such as acute myeloid leukemia? The answer is a resounding no!

In the not-so-distant past, the author was interviewed for a position of medical director of a future laboratory focused on hematopathology to be owned by a group of oncologists. The site was already purchased and now they were looking for an experienced pathologist to start planning, building, and bringing all the necessary equipment for the lab to start functioning. The oncology group was relatively large, covering several sites spread across several states and the interview process required the author to drive to several geographical locations in order to speak to a number of these clinicians.

Somehow the interview process did not go too well. As moving from group to group the recurring theme of these oncologists was the opening of THE MOLECULAR laboratory! That was in contrast with what I was told from the beginning by the leadership of the group that I would be responsible for the opening of a complete laboratory that would include histology, flow cytometry, FISH, cytogenetics, and, last, but obviously not least, molecular analysis. What I found interesting, though, while talking to these doctors, was the realization that oncologists have this tunnel vision on molecular studies while everything else is a blur. Timidly at first, but as I kept moving between different locations and interviewing with different oncologists, I became more assertive in explaining that the pathological diagnostic process needs to be methodical and to follow a certain logical order. First there is a need for morphologic diagnosis supported by immunophenotyping, then, according to the specifics of the case, FISH and/or cytogenetics and only at the end, and only if needed, molecular testing. After the tests are completed, it is the role of the pathologist to integrate all these disparate elements into one overarching diagnosis that also integrates prognostic, and predictive information. The reaction to my explanation was the same across the board, a blank stare. To this day I still don't understand why I wasn't offered the job!

When in 1968 flow cytometry first appeared in the diagnostic armamentarium, the people were so enthusiastic about it that flow cytometry was deemed the death of the microscope! Fifty plus years later the microscope still is the queen of pathology while flow cytometry still plays a subservient role in the diagnostic process. Next generation sequencing, as powerful of a tool as it is in the current era of personalized medicine, like flow cytometry, it still is an ancillary testing methodology that cannot replace (not yet, at least) the entire pathologic diagnostic process that starts, yes, with this 400 years old tool called microscope!

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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