Mutational profiling in acute myeloid leukemia

Courtney D. DiNardo

Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

E-mail: cdinardo@mdanderson.org

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TITLE	Prognostic relevance of integrated genetic profiling in acute myeloid leukemia.
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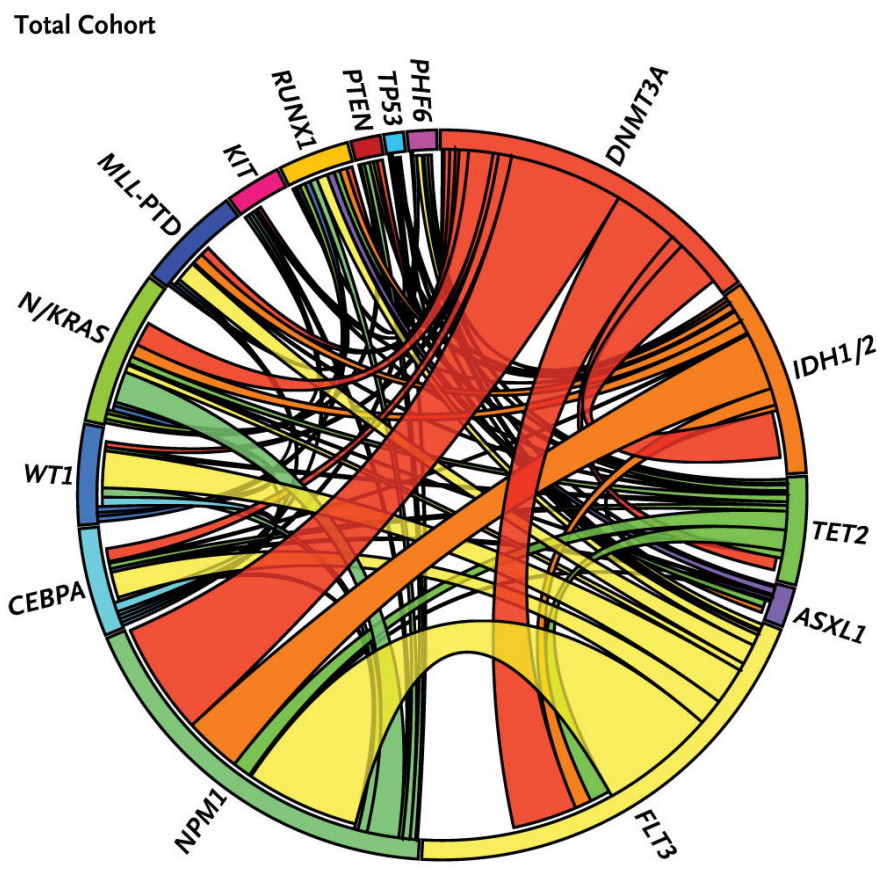
To fully appreciate how quickly molecular analysis has transformed evaluation and treatment decisions in acute myeloid leukemia (AML), we need look no further than the seminal article by JP Patel *et al*. published in 2012 in *The New England Journal of Medicine* concerning the prognostic relevance of genetic profiling in AML.[1] In this analysis, 398 younger patients with newly diagnosed AML were molecularly annotated, leading the authors to rather modestly suggest that "mutational profiling could potentially be used for risk stratification and to inform prognostic and therapeutic decisions".

Given the current scale and relevance of molecular testing, it is perhaps difficult to recall that ~15 years ago, a standard AML genetic evaluation included only karyotype analysis and testing for three mutations with prognostic importance (*FLT3, NPM1* and *CEBPA*).[2] Next-generation sequencing "myeloid panels" did not exist, and recurrent mutations in genes such as *DNMT3A, TET2* and *IDH1* were



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Figure 1. A Circos diagram depicts the relative frequency and pairwise co-occurrence of mutations in patients with newly diagnosed acute myeloid leukemia. ITD: internal tandem duplication; TKD: tyrosine kinase domain; PTD: partial tandem duplication. Figure reproduced, with permission, from Patel JP *et al*.[1]

just beginning to be recognized.[3,4] I distinctly remember pouring over the text, figures and supplements of this manuscript as a hematology/oncology fellow, amazed at this newly-appreciated molecular complexity, and feeling with certainty that an enhanced genomic understanding of AML would surely revolutionize our field and improve patient outcomes.

While our current next-generation sequencing panels now include anywhere from 50-150 genes, this pivotal manuscript examined mutations in 18 genes. Despite this now modest gene list, Patel *et al*. generated several foundational discoveries that helped pave the way to the rapid integration of mutational status into AML genetic prognostication. First, this analysis highlighted the scope of recurrent mutations in AML, detecting at least one somatic alteration in 97% of patients. To my recollection, this was also the first manuscript to acquaint the hematology world with the legendary "Circos plot", now a common method for visualizing genomic data to illustrate frequency (and mutual exclusivity) of various co-occurring genetic events.

Most importantly, this analysis verified the critical and now commonplace realization that the presence of certain mutations can "upstage" or "downstage" AML risk, helping to improve AML classification especially in the large bulk of "intermediate-risk" patients. As many therapeutic decisions center around the risk/benefit analysis of allogeneic transplant in first remission, the importance of an accurate diagnostic assessment cannot be overemphasized. And indeed, technology continues to iteratively advance our genomic understanding, with approaches such as optical genome mapping and diagnostic whole-genome sequencing now providing even further detail and opportunities for discovery.[5,6]

Finally, it is worth reflecting on the concluding message of this 2012 manuscript, which challenged the leukemia community to provide genetic information in a "timely and affordable way…and show that this information can prospectively influence treatment decisions". With the advent and approval of multiple targeted therapeutics (i.e., *FLT3, IDH1, IDH2,* menin inhibitors), the AML field has certainly established that genomic information can improve treatment decisions and clinical outcomes. However, while the turn-around time and costs of genomic testing have substantially improved, we are still a long way from offering inexpensive and point-of-care genetic results – not to mention the lack of affordability and general accessibility of targeted treatments. In this era of bioinformatics and personalized medicine, these will be essential metrics of success in the years to come.

Disclosures

No conflicts of interest to disclose.

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