have been able to detect the clone 40 years before diagnosis, and up to 10 years before diagnosis in faster-growing clones," Nangalia said.

Ross Levine, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, called the work "interesting and novel," although he cautioned that the age-of-onset estimates were based on modeling and not experimentally validated.

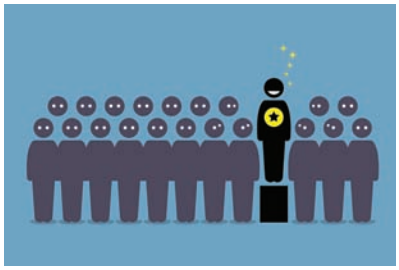
According to Paresh Vyas, PhD, of the University of Oxford in the UK, the study's modeling techniques are becoming well established, but before the knowledge gained from this work can become useful clinically, researchers need to understand what factors contribute to the trajectory of early *JAK2*-mutant clones. Knowing what cell-autonomous or non–cell-autonomous factors trigger MPN development from these clones may inform treatment decisions and prevent overtreatment.

Although the study involved a massive sequencing effort, limitations include the small patient sample size, lack of random patient selection, and retrospective nature of the work. Further research to extend and validate the findings in larger, prospective cohorts would enhance the study's impact. –*Nicole Haloupek* ■

Solving the Puzzle of Exceptional Responders

Since the NCI's 2014 launch of its Exceptional Responders Initiative, researchers have collected and examined more than 100 dramatic treatment responses. Generally, exceptional responders (ER) are not closely studied, but the team ferreted out and recently reported plausible molecular underpinnings in nearly one quarter of cases—knowledge that supports up-front, broad-based genomic testing for every patient (Cancer Cell 2020 Nov 19 [Epub ahead of print]).

Oncologists spent 3 years reviewing all submissions to verify ERs—those who achieved complete or durable responses of at least 6 months to chemotherapy or targeted drugs normally benefiting fewer than 10% of patients. The team then obtained tumor tissue from 111 ERs for comprehensive multiplatform genomic profiling. In 26 patients (23.4%), "we could identify the smoking gun for the exceptional



response," says project co-leader Louis Staudt, MD, PhD, of the NCI.

Analyzing an ER with recurrent glioblastoma who achieved a complete response to temozolomide lasting more than 10 years, the researchers determined that synthetic lethal vulnerabilities in the tumor—low MGMT expression and a rare *APEX1* translocation—impeded direct repair (DR) and base excision repair (BER), two pathways needed to fix temozolomide-induced DNA methylation. To get an ER, "we found that silencing MGMT was insufficient," notes Staudt. "You need at least a couple of parallel pathways to be compromised."

Synthetic lethality was also key in an ER with metastatic colon adenocarcinoma. The patient, whose tumor lacked MGMT but had intact BER, participated in a trial evaluating temozolomide plus TRC102, an investigational BER pathway inhibitor. A plausible mechanism for the ER's ongoing 45-month response likely involves "a triple whammy," Staudt says: Besides DR and BER pathways being crippled, the tumor harbored a rare *RAD50* mutation that stymied double-strand break (DSB) repair.

The team then reexamined results for 16 other patients with colon cancer in that trial and found only one partial response, again due to inactive MGMT; the enzyme was robustly expressed in nonresponders. Absent this information, "you might have said this drug combination is a dud," Staudt remarks. "Further enrollment in this study should focus on patients whose tumors lack MGMT."

More generally, "if a patient's genotype report shows an alteration in any of these three arms [DR, BER, DSB repair], I'd now look for a second hit—either genetic or induced pharmacologically" through drugs such as TRC102, says Charles Sawyers, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, who wasn't involved with the research. "Then you'd have therapeutic efficacy."

On the immune front, across all ERs, B cells and natural killer (NK) cells were present at higher levels compared with a control group of tumors from The Cancer Genome Atlas. "Recent reports in multiple histologies have associated tumor-infiltrating B and NK cells with favorable response, although it's not yet understood why," Staudt says. "Our data fit these observations."

To Sawyers, this finding "elevates in priority a research question: Are there therapeutic interventions to recruit B and NK cells to tumors that have few or none—and would it matter?" Bispecifics such as blinatumomab (Blincyto; Amgen) are one strategy, albeit mainly directed at engaging T cells so far, he says. However, because these biologic drugs are modular in design, "you could plug and play" with other immune cells, "and to me, this would be quite exciting to investigate."

Although researchers are no longer collecting ER cases, the data they've amassed have been deposited in the NCI's Genomic Data Commons "for others to reanalyze, or to probe the clinical puzzles we were unable to solve," Staudt says (see https://gdc.cancer.gov).

Sawyers recommends also incorporating the findings into precision oncology knowledge bases such as OncoKB, a repository that serves as "a data visualization tool with clinical utility" (see https://oncokb.org). Publishing data from new ERs would be useful, too. "When I see a dramatic response to therapy, that tells me there's real biology there," he says. "We should try to uncover the scientific basis."

In all, "that we came up with plausible mechanisms for almost 24% of cases is a testament to how much our understanding of cancer has grown," Staudt concludes. "There is real explanatory power in a patient's tumor genome." –*Alissa Poh* ■

AML Prognoses Better with Menin–MLL Inhibitor?

The investigational menin–MLL (KMT2A) complex inhibitor KO-539 (Kura Oncology) may be active in patients with acute myeloid leukemia (AML): In the phase I/IIa KOMET-001