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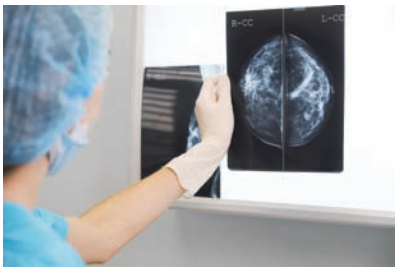

though someone took all the endoscopes overnight." Moreover, colorectal cancer diagnoses dropped by 32%, even though "we know cancer didn't stop."

Similarly, breast cancer screening largely halted. Constance Lehman, MD, PhD, of Massachusetts General Hospital (MGH) in Boston, estimates that more than 90% of mammograms were canceled in the United States due to the shutdown, including about 15,000 at MGH alone. The result: About half as many breast cancers as usual were diagnosed in April.

Skipped screenings or lengthy delays are concerning, May says, because the survival rate for stage I colorectal cancer is 90%, compared with 11% to 15% for stage IV disease. "I think, unfortunately, we'll have later stage at time of diagnosis for a while."

Lehman has already seen this play out at MGH, where more than 90% of patients diagnosed with breast cancer through screening typically have early-stage disease, a percentage that has dropped to around 65%. Also concerning, Tari King, MD, of Brigham and Women's Hospital (BWH) in Boston has patients who felt a breast lump early in the pandemic but waited 6 or 7 months to seek care, resulting in more advanced disease.

Although screening centers now have COVID-19 safety measures in place, some patients are hesitant to reschedule. To combat this, providers are educating patients about precautions they're taking, and May emphasizes that no patients screened at the UCLA endoscopy unit have contracted coronavirus. "We're trying to use a data-driven approach to help patients feel [comfortable] coming in," she says.

Eric Flenaugh, MD, of Morehouse School of Medicine and Grady Hospital in Atlanta, GA, who saw lung cancer screening drop by about 50%, has turned to public service announcements and a Facebook Live event to draw patients back.

Concerns remain, however, that that won't happen as patients juggle work and childcare—and deal with challenges such as losing health insurance. In particular, the pandemic may increase existing screening disparities for Black and Latino patients, who are disproportionately essential workers. "I'm a little bit worried that we're going to lose some of the success we've had in minimizing disparities," May says.

King agrees. "The underrepresented minority population is the group that is not rescheduling" breast cancer screening, she says.

Flenaugh largely cares for medically underserved African American patients, who are at higher risk of disease yet often resistant to lung cancer screening. His center uses automatic reminders and presses primary care physicians to recommend screening. "Every institution is going to have to assess its patient population and come up with strategies to get these patients back in," he says.

Yet there are some positive signs: May and Flenaugh are seeing screening rates for colorectal and lung cancer, respectively, rebound at their institutions. Breast cancer screening at MGH and BWH now tops 100% of the usual volume, in part due to centers opening on nights and weekends.

However, Flenaugh worries that screening may flag as coronavirus cases balloon again. "We will prioritize, we will take care of the acutely ill, we will get through this crisis," he says, "but we also need to stay preventative." *–Catherine Caruso* ■

MPN Driver Mutations May Occur *In Utero*

A lingering question regarding myeloproliferative neoplasms (MPN)—including polycythemia vera, essential thrombocythemia, and myelofibrosis—is how rapidly they develop. Many patients with MPNs present with normal blood counts just months before diagnosis, supporting a rapid-development model. However, driver mutations are present in the blood of healthy individuals with age-related clonal hematopoiesis, and these may slowly or never evolve into cancer.

"As physicians, some of the commonest questions we get asked by our patients with blood cancers are, 'How long have I had it for?' and 'How fast did it grow?'" said Jyoti Nangalia, MD, PhD, of the Wellcome Sanger Institute in Hinxton, UK, in a presentation at the 2020 American Society of Hematology Annual Meeting, held virtually December 5–8. Nangalia and her team set out to answer this question using genomic studies—generating highly provocative findings.

The group performed genomic analyses on bone marrow or peripheral blood samples collected from 10 patients diagnosed with MPNs between the ages of 20 and 76. These samples were used to grow single cell–derived hematopoietic colonies, which were subjected to whole-genome sequencing, enabling construction of phylogenetic trees for each patient's clones.

Results from three of the patients, all of whom harbored the most common driver mutation in MPNs, *JAK2*^{V617F}, are illustrative. In a patient diagnosed with essential thrombocythemia at age 20, the *JAK2*^{V617F} mutation occurred between 6.2 weeks after conception and 1.3 years of age. In a patient with polycythemia vera diagnosed at age 31, the *JAK2*^{V617F} mutation became established between 4.2 weeks postconception and 8.6 years of age. Even in the third patient, diagnosed with polycythemia vera at age 65, the mutation was entrenched between 1.8 weeks after conception to 11.4 years of age. The upshot: MPN driver mutations can occur very early in life, perhaps even *in utero*, and may take decades to progress to full-blown MPNs.

"At any one snapshot in time in our life, the mutations within individual cells represent natural barcodes that can be used to trace back the ancestry of the cells right to the start of life," Nangalia explained. Using the phylogenetic trees to depict the relative timing of driver-mutation acquisition, the absolute timing of mutation acquisition was determined using patient- and clone-specific mutation rates, revealing the age range during which the mutations likely occurred.

The rate of a clone's growth determined the time between driver mutation and diagnosis. Slower-growing clones could take 50 years to evolve into MPNs, whereas faster-growing clones could become MPNs within 10 years. "For slow-growing *JAK2*[-mutant] clones, with sensitive assays, we would

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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.

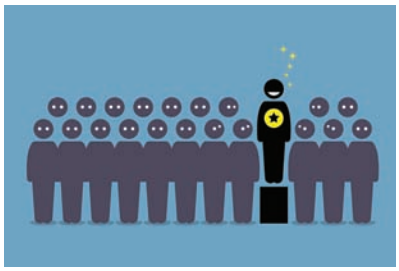
According to Paresh Vyas, PhD, of the University of Oxford in the UK, the study's modeling techniques are becoming well established, but before the knowledge gained from this work can become useful clinically, researchers need to understand what factors contribute to the trajectory of early *JAK2*-mutant 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

AACR American Association for Cancer Research

CANCER DISCOVERY

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