Congress Boosts NIH, NCI Funding

After nearly 6 months of uncertainty, appropriations for the NIH and NCI have been finalized for the 2022 fiscal year (FY) thanks to the passage of an omnibus appropriations bill signed by President Joe Biden on March 15. The bill provides funding increases for NIH and NCI and furnishes start-up money for a new effort that researchers hope will channel the same kind of visionary thinking that led to the Internet and self-driving cars.

The NIH budget of nearly $45 billion represents a net increase of $2.1 billion, or 4.7%, while the NCI's $6.9 billion budget is a 5.3% bump over FY21. The NCI's $353 million increase was more than twice the $173 million that the Biden administration had requested. Of that amount, Congress directed $150 million toward upping the NCI's grant application success rate, currently at 12%.

Congress also appropriated the money authorized for the original Cancer Moonshot, the initiative approved in 2016 to make 10 years of progress in cancer research in half that time. In the next-to-last year of funding for that effort, the NIH and NCI will receive $496 million and $194 million, respectively.

In addition, the bill provides $3.3 billion in discretionary funding for the FDA, an increase of $102 million, and $8.5 billion for the Centers for Disease Control and Prevention, an increase of $582 million, of which $4 million more than in FY21 will be dedicated to cancer programs.

Childhood cancer programs fared well—the STAR Act and the Childhood Cancer Data Initiative were fully funded at $30 million and $50 million, respectively.

In his State of the Union address on March 1, Biden called for the creation of the Advanced Research Projects Agency for Health (ARPA-H), the biomedical equivalent of the Defense Advanced Research Projects Agency (DARPA), which has backed high-risk, high-reward research, some of which paid off with significant breakthroughs—including self-driving cars, the Internet, and the global positioning system. A similar agency willing to "go way out on the limb" is necessary and could revolutionize aspects of cancer medicine, such as early detection, says Chi Van Dang, MD, PhD, scientific director of the Ludwig Institute for Cancer Research in New York, NY. "If we keep doing the same thing, we will probably get the same results."

The budget receives good marks from Clifford Hudis, MD, chief executive officer of the American Society of Clinical Oncology, because "it shows there is bipartisan support for yearly increases."

However, David Agus, MD, CEO of the Lawrence J. Ellison Institute for Transformative Medicine of USC in Los Angeles, is lukewarm on the final numbers. "It's an average budget. Nobody's cheering and nobody's crying," he says. "It will allow us to keep doing what we are doing. But that's not enough." The budget falls short, he says, on funding for ARPA-H, which garnered $1 billion to fund its launch. However, that sum is $5.5 billion less than the Biden administration had requested.

Dang was also disappointed by what he calls the "meager" funding for ARPA-H. "It's time to make a bet."

Congress may allocate larger sums for ARPA-H in the years ahead, but other major funding decisions loom. For instance, spending for the first Cancer Moonshot is authorized through FY23, but continuing any of the more than 240 projects started under the initiative may require more money. In addition, on February 2, Biden announced a reignited Moonshot, aimed at reducing cancer mortality by 50% over the next 25 years. However, the administration has not provided details on the cost of this program or how it would be funded.
–Mitch Leslie ■

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Illuminating Clustered Mutations in Cancer

Using artificial intelligence, researchers at the University of California, San Diego, have begun mapping the landscape of somatic mutations that aren't randomly scattered but cluster at hotspots in cancer genomes. These clusters were enriched in driver genes, and their presence or absence could potentially predict patient outcomes (Nature 2022;602:510–7).

Clustered mutations occur in various patterns, including kataegis and omikli (Greek for thunderstorm and fog). With kataegis, large streaks of mutations are close together, resembling a storm; omikli looks like small bursts of kataegis, or a "fog-like clustering," explains Erik Bergstrom, the study's first author.

Led by Ludmil Alexandrov, PhD, the team developed algorithms to detect and characterize every mutation in the sequenced genomes of 2,583 patients, encompassing 30 different cancers. They found, for instance, that omikli accounted for a large proportion (50.5%) of all clustered base substitutions, which occurred more often within oncogenes than tumor suppressors and at higher frequency in certain drivers—such as *BTG1* and *NOTCH2*—compared with others. In all, "we determined that approximately 10% of known driver mutations are clustered," Alexandrov says.

The researchers noted, intriguingly, that clustered rather than nonclustered *BRAF* mutations were associated with better overall survival. The opposite was true for *TP53* and *EGFR*, however. "All we did was separate samples based on whether or not clustered mutations were detected within known driver genes," Bergstrom remarks. "From that alone, we saw clear differences in survival, but we don't yet know why."

Diving deeper into kataegis specifically, the team reported its prevalence on extrachromosomal DNA (ecDNA), which—unlike linear DNA—passes along genetic information unevenly and fuels aggressive cancers by being a powerhouse of oncogene amplification. Playing on ecDNA's circular motif, they coined a new name for this clustered pattern, kyklonas (Greek for cyclone). In three tumor types—61 sarcomas, 280 lung cancers, and 186 esophageal cancers—widespread,

recurrent kyklonic events were seen in 45%, 28%, and 46% of samples harboring mutated ecDNA, respectively.

The main culprit causing kyklonas, an enzyme family called APOBEC3, "normally modulates innate immunity by restricting viruses, many of which have circular genomes," Bergstrom explains. "Our theory is that APOBEC3 may regard ecDNA as a similar foreign body that needs to be cut up."

"We saw repeated APOBEC3 attacks on ecDNA circles after they formed; it wasn't a one-off occurrence," Alexandrov adds. "This isn't unlike what's been seen on viral genomes in HPV [human papillomavirus]-driven cancers. That's why we think APOBEC3 is mistaking ecDNA for a virus, creating kyklonas along the way and, because ecDNA often carries oncogenes, inadvertently accelerating cancer development."

Roel Verhaak, PhD, of The Jackson Laboratory for Genomic Medicine in Farmington, CT, observes that "ecDNA has of late been revitalized as an important topic." Not involved in this study, he was most intrigued by the hypothesis as to why kyklonas occurs. "It suggests a targeted, proactive role for APOBEC3 in trying to prevent the genesis of ecDNA," he says. "I thought this was quite provocative, and I always appreciate it when authors go out on a limb in their study discussion."

"There's still much to unpack with our data," Alexandrov says, including validating kyklonas as a novel mode of cancer evolution. Meanwhile, he and Bergstrom are further exploring survival differences seen with clustered mutations and their clinical utility.

"More patients are undergoing routine genomic testing, and the information—whether or not mutations are clustered—is already in the results," Alexandrov notes. "It just hasn't been used to predict outcomes, but that's readily implementable. As well, are there particular therapies to which a patient with clustered mutations responds, and vice versa? It's another question to pursue to better understand the prognostic power of our findings." *–Alissa Poh* ■

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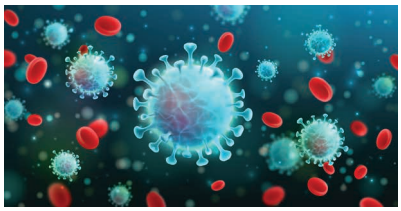
Top COVID-19 Prognostic Factors Identified



Researchers have identified more than a dozen factors that may increase COVID-19's severity. But for patients with thoracic malignancies, seven variables predict the likelihood of dying, according to a recent study that analyzed data from the international TERAVOLT registry (J Thorac Oncol 2022 Feb 1 [Epub ahead of print]). The study also demonstrates that creating real-time databases like TERAVOLT is feasible—and that they capture valuable information.

The registry, which was launched in March 2020 and now houses data from 92 centers in 19 countries, was designed to track the effect of COVID-19 on patients with thoracic malignancies. Clinicians entered patients' demographics, comorbidities, cancer treatments, and cancer lab test results. In a preliminary analysis of the first 200 patients, researchers reported a mortality rate of 33% and identified several variables that correlated with the risk of death, including age, smoking status, and comorbidities (Lancet Oncol 2020;21:914–22).

The goal of the recent study was to help clinicians determine which patients might need greater monitoring or changes in care, says coauthor Jennifer Whisenant, PhD, of Vanderbilt University Medical Center in Nashville, TN. She and her colleagues analyzed data from 1,491 patients in the TERAVOLT registry hospitalized between March 2020 and April 2021. They assessed whether any of 73 variables—such as body mass index, smoking status, age, gender, and the number and type of cancer therapies received—correlated with mortality risk during an average follow-up of 42 days. Given this short period, deaths likely resulted from COVID-19, not cancer.

At 24.2%, the overall mortality rate was lower than in the initial study. Eastern Cooperative Oncology Group (ECOG) performance status had the greatest influence on the risk of death, followed by neutrophil count, which other studies have linked to the immune overreaction that appears to kill some patients with COVID-19. The rest of the seven mortality risk factors were serum procalcitonin levels, development of pneumonia, C-reactive protein levels, tumor stage, and age.

The researchers provide a predictive nomogram that accounts for each of the seven factors.

Notably, the cutoff date for the study was April 15, 2021, before many patients were vaccinated. However, Whisenant and coauthor Alessio Cortellini, MD, of Imperial College London, UK, say that the results remain relevant because of the prevalence of vaccine hesitancy and because patients with thoracic malignancies may have weak responses to SARS-CoV-2 vaccination. They add that the TERAVOLT researchers are planning studies to examine the severity of the SARS-CoV-2 omicron strain on mortality, the effect of hospital crowding, and other factors.

"The study is addressing an important issue," says Robert Cerfolio, MD, of NYU Langone Health in New York, who wasn't connected to the research. The message, he says, is that most patients with cancer can continue their treatment.

Daniel Boffa, MD, of Yale School of Medicine in New Haven, CT, who wasn't connected to the research either, says so much has changed since the study's cutoff date—including the increased availability of vaccination, development of new viral variants, and approval of additional COVID therapies—that the findings probably won't alter treatment for most patients. However, he says, TERAVOLT is significant because it shows "a first-in-history level of connectivity among the global cancer community." TERAVOLT's rapid collection and sharing of data makes an analysis like the one the authors performed "possible in an almost real-time manner."

Similar databases could help researchers improve cancer treatment and allow rapid responses to future