

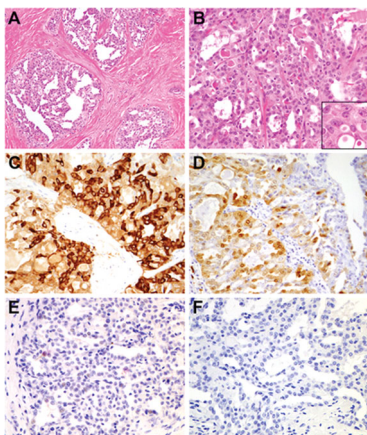
## INSIDE THE USCAP JOURNALS

<https://doi.org/10.1038/s41379-020-00694-6>

### MODERN PATHOLOGY

#### Features of *NTRK*-rearranged thyroid carcinoma

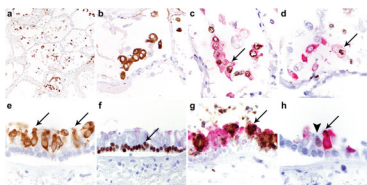
<https://doi.org/10.1038/s41379-020-0574-4>



Chu et al. investigated a rare and understudied *NTRK*-rearranged thyroid carcinoma subtype using an institutional series of 11 patients, all of whom had received a total thyroidectomy and radioactive iodine therapy. The team observed an unusual multinodular growth pattern, extensive lymphovascular invasion, and cervical lymph node metastases. Similar immunophenotypes were observed, but gene rearrangements were varied, with the most common being *ETV6-NTRK3* ( $n = 4$ ). Three of the 11 patients received *NTRK* inhibitor therapy; benefit ranged from 33% reduction in disease burden to complete resolution. While the authors acknowledge that specific features varied between the 11 patients, they developed a profile of a clinically aggressive tumor type that is highly metastatic but has a low mortality rate upon *NTRK* inhibitor therapy. They propose that the multinodular growth pattern and lymphovascular spread be considered effective histomorphologic features to prompt *NTRK* testing during differential diagnosis.

#### SARS-CoV-2 detection is dynamic over time

<https://doi.org/10.1038/s41379-020-0595-z>



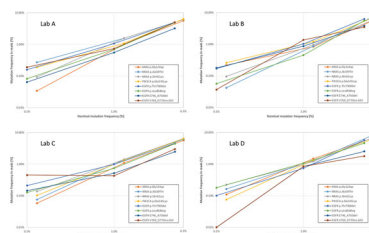
Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has led to a global public health crisis. Higher mortality rates,

frequently caused by acute respiratory distress syndrome, have been seen in the elderly and those with comorbidities. Using reverse transcriptase–polymerase chain reaction (RT-PCR) against SARS nucleocapsid protein in correlation with clinical parameters, the authors were able to determine trends. Across their seven patients, the median time to death from symptom onset was 9 days; from hospitalization, 7 days; from positive RT-PCR 7 days, and from intensive care unit admission 3 days. Chest imaging identified diffuse airspace disease in all patients that corresponded to acute and organizing diffuse alveolar damage (DAD). SARS-CoV-2 was detectable in pulmonary pneumocytes and ciliated airway cells in the patients with acute DAD but not in the lungs or airways of the two patients with organizing DAD.

### LABORATORY INVESTIGATION

#### Circulating DNA analysis comparable across platforms

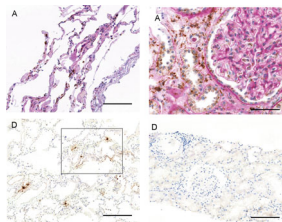
<https://doi.org/10.1038/s41374-020-0459-7>



Analysis of circulating tumor DNA (ctDNA) has applications in selection and adjustment of therapy, assessing prognosis, and predicting relapse, but it has proven technically challenging. Given the availability of commercial systems designed for ctDNA detection, Koessler et al. reported analyses from four laboratories in Switzerland that performed comparative evaluation of circulating cell-free DNA (ccfDNA) extraction and ctDNA analysis. Using six distinct methods, ccfDNA extraction and sequencing yielded very similar results. One system did have superior yield, with no impact on sensitivity, which remained linear for each method, making it possible for clinicians to safely compare results. Their conclusion was that no one system could be recommended specifically and that the focus should therefore be on good laboratory practice lab validation of extraction and sequencing protocols.

## IHC and ISH protocols for detection of SARS-CoV-2

<https://doi.org/10.1038/s41374-020-0464-x>

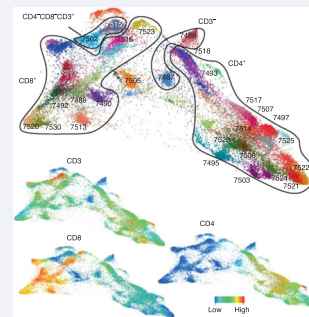


Coronavirus disease 2019 (COVID-19) is caused by the coronavirus SARS-CoV-2 and has spread around the world from its initial detection site in Wuhan, China. The symptoms of the disease are wide ranging, although it primarily affects the lower respiratory system. New diagnostic tools are crucial for better care of patients and disease prevention. Accordingly, Best Rocha et al. developed immunohistochemical (IHC) and in situ hybridization (ISH) assays for detection of the virus. Using autopsy samples from COVID-19 patients as well as individuals who had not had COVID-19, they tested a panel of commercially available antibodies and RNA probes. With both methods, whereas the lung and even placenta samples stained positive for the virus, kidney samples were negative. The group published their protocols and the list of antibodies and probes for use by other pathology and research laboratories. [nature.com/pathology](https://doi.org/10.1038/s41374-020-0464-x)

## [nature.com/pathology](https://doi.org/10.1038/s41591-020-1006-1)

### Predictive biomarkers of response to PD-1 blockade

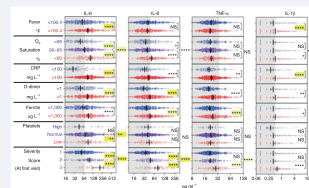
Classical Hodgkin lymphomas (cHLs) exhibit copy-number gains of *PD-1* and *PD-L1* on chromosome 9p24.1, making PD-1 blockade an effective therapy. Cader et al., using complementary T-cell-receptor (TCR) sequencing and cytometry, investigated the mechanism of action of anti-PD-1 therapy in patients with cHL. After developing a peripheral immune signature of responsiveness, the group assessed patterns that were predictive of patients likely to receive benefit from therapeutics in this family. Patients who responded to therapy—particularly those who achieved a complete response—exhibited CD4<sup>+</sup> but not CD8<sup>+</sup> TCR diversity. In addition, patients who responded had an increased abundance of activated natural killer cells and a CD3<sup>-</sup>CD68<sup>+</sup>CD4<sup>+</sup>GrB<sup>+</sup> subset. These trends can form a profile for innate effectors in the efficacy of PD-1 blockade in cHL and reveal predictive biomarkers in the identification of patients likely to benefit as well as identifying alternative therapeutic targets for individuals with cHL.



*Nature Medicine* 2020;26:1468–1479; <https://doi.org/10.1038/s41591-020-1006-1>

### IL-6 and TNF- $\alpha$ predict COVID-19 severity and survival

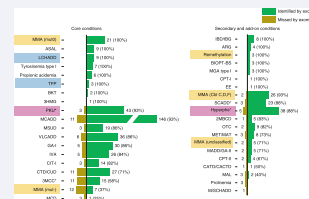
A wide range of responses to coronavirus 2 (SARS-CoV-2) infection have been noted. Del Valle et al. investigated the hyperinflammatory response induced by severe acute respiratory syndrome, using a rapid multiplex cytokine assay to measure serum interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)- $\alpha$  and IL-1 $\beta$  in hospitalized patients with COVID-19. The group showed that serum IL-6, IL-8, and TNF- $\alpha$  levels at the time of hospitalization were strong and independent predictors of patient survival. They found that after adjusting for a variety of comorbidities, hypoxia; demographics, and inflammatory markers, IL-6 and TNF- $\alpha$  remained independent and significant predictors of disease severity and death. Their data were validated by a second cohort of patients. The authors propose that serum levels of IL-6 and TNF- $\alpha$  be taken into account in the management of patients with COVID-19 to inform therapeutic options.



*Nature Medicine*, published online 24 August 2020; <https://doi.org/10.1038/s41591-020-1051-9>

### Exome sequencing in newborn screening

Public health newborn screening (NBS) for rare, treatable inborn errors of metabolism (IEMs) that require urgent intervention is performed using tandem mass spectrometry (MS/MS). The NBSseq project is the largest sequencing effort to date of an entire population of IEMs and includes an alternative method of evaluation: whole-exome sequencing (WES). Adhikari et al. used archival residual dried blood spots and data from about 1730 infants born in California between mid-2005 and 2013 as well as nearly 400 infants who tested positive by MS/MS but were found unaffected in follow-up studies. MS/MS has an established sensitivity of 99.0% and specificity of 99.8%, and WES scored 88 and 98.4% respectively, with variability between IEMs. The authors do not recommend that WES replace the existing method for initial screening, but as a secondary test it might reduce false-positive results and lead to more specific and appropriate diagnosis.



*Nature Medicine* 2020;26:1392–1397; <https://doi.org/10.1038/s41591-020-0966-5>