DIAGNOSTICS

CRISPR-based diagnostics

Science **360**, 436–439 (2018)
Science **360**, 439–444 (2018)
Science **360**, 444–448 (2018)

Sensitive, specific and portable diagnostics can rapidly identify viral infections.

Quick and reliable diagnosis of viral disease in the field can aid treatment and containment. The recently developed specific high-sensitivity enzymatic reporter unlocking platform (SHERLOCK) is based on the programmable RNA cutting enzyme CRISPR–Cas13 and is able to identify genetic signatures of viruses without the need for complex lab protocols.

Gootenberg et al. have developed SHERLOCK version 2, which offers four advances: quantitative detection, enhanced sensitivity, multiplex detection of up to four viruses (or other nucleic acid targets), and a visual readout. SHERLOCKv2 can also detect specific mutations even at very low frequencies, such as cancer-associated mutations found in liquid biopsies.

Myhrvold et al. were able to add a step named HUDSON to the initial SHERLOCK protocol that allows the detection of viruses directly from body fluids, creating a field-deployable diagnostic.

Doudna and colleagues showed that the enzyme Cas12a has a target-activated DNA cutting activity that can be leveraged to detect HPV in patient samples. The signal-amplifying property of Cas12a allows rapid and accurate point-of-care DNA detection.

Together these tools will help to bring portable, accurate diagnostics to the field. *HS*

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INFECTIOUS DISEASE

Zika virus shedding in semen

N. Engl. J. Med. **378**, 1377–1385 (2018)

Zika virus RNA is commonly shed in the semen of infected men, and in some of these men, this occurs beyond 6 months after the first appearance of symptoms. Shedding of infectious virus, however, appears to be limited to the month immediately after illness onset.

Zika virus is transmitted by mosquitoes and during recent outbreaks has been linked to the development of congenital microcephaly in the offspring of infected individuals. There have been reported cases of male-to-partner sexual transmission, but the duration of contagion is unknown.

Mead et al. analyzed levels of Zika virus RNA in semen samples from 184 symptomatic men (1,327 total samples) every 2 weeks over a period of 6 months. Zika virus RNA was commonly detected, and the duration of shedding was linked to ejaculatory frequency and joint pain. Detection of infectious virus in semen was less common and was rarely observed beyond the first few weeks of illness onset.

Interruption of sexual activity during the early symptomatic phase of Zika in men could be important in preventing transmission. *HS*

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NEURODEGENERATION

Training neuropathology

Nature **556**, 332–338 (2018)

The memory of previous immune stimuli peripheral to the brain is mediated by brain-resident innate immune cells called microglia and results in altered later development of neuropathologies in mice.

Previous exposure of myeloid cells to immune stimuli can result in immune training, in which subsequent immune responses are exacerbated, or immune tolerance, in which later immune responses are inhibited.

Wendeln et al. found that exposing a mouse engineered to develop Alzheimer's disease pathology to a peripheral immune stimulus that results in immune training increased Alzheimer's neuropathology, and exposing this mouse to a peripheral immune stimulus that induced tolerance decreased Alzheimer's neuropathology. These effects were mediated through epigenetic changes in the microglia. They also found that previous immune exposure modulated stoke neuropathology.

In humans, it is possible that previous exposure to infection or other inflammatory conditions in the periphery might mimic these immune memory effects on neurological disease. *HS*

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CANCER EVOLUTION

Tracing clear cell renal carcinoma evolution

Cell **173**, 595–610.e11 (2018) *Cell* **173**, 611–623.e17 (2018)
Cell **173**, 581–594.e12 (2018)

Three publications from the TRACERx consortium trace the evolution of clear cell renal carcinoma (ccRCC), providing insights that can guide therapy in this cancer.

In a whole-genome analysis of 95 biopsies from 33 patients with ccRCC, Swanton, Campbell and colleagues gain insights into the landmark early genetic mechanisms in ccRCC development.

With regards to the further evolution of these tumors, Swanton, Larkin and colleagues analyzed genetic data from 1,206 primary tumor regions from 101 patients with ccRCC. They find ccRCC evolution and outcome is determined by progressive, identifiable mutations.

Similarly, Swanton and colleagues find in an analysis of 575 primary and 335 metastatic biopsies across 100 patients with metastatic ccRCC that metastasis is largely driven by chromosomal aberrations. These create genetic drivers for either rapid progression to metastasis or attenuated progression, which in turn influences patient mortality. In the future, genetic evolutionary analysis may aid in standard-of-care decisions. *HS*

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RECOMBINANT PROTEIN THERAPY

In utero correction of a genetic disorder

N. Engl. J. Med. **378**, 1604–1610 (2018)

The genetic disorder X-linked hypohidrotic ectodermal dysplasia (XLHED) results in a lack of the protein ectodysplasin A in affected individuals, preventing the development of sweat glands, and can be corrected by amniotic delivery of the missing protein.

Individuals affected by XLHED can develop life-threatening hyperthermia after birth due to their inability to sweat. Researchers from the University of Erlangen injected the receptor-binding domain of EDA intraamniotically into two pregnant women, one with a single fetus and one with twins. These fetuses were known to be affected by XLHED from noninvasive screening and because they have affected siblings. Once born, the three infants were able to sweat normally. Importantly, the authors' mechanistic studies in mice show that the protein had to be taken up systemically by the developing offspring to be effective.

Although long-term follow-up has yet to be carried out, this study shows the effectiveness of prenatal protein therapy for this genetic disease at critical time periods in development. *HS*

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