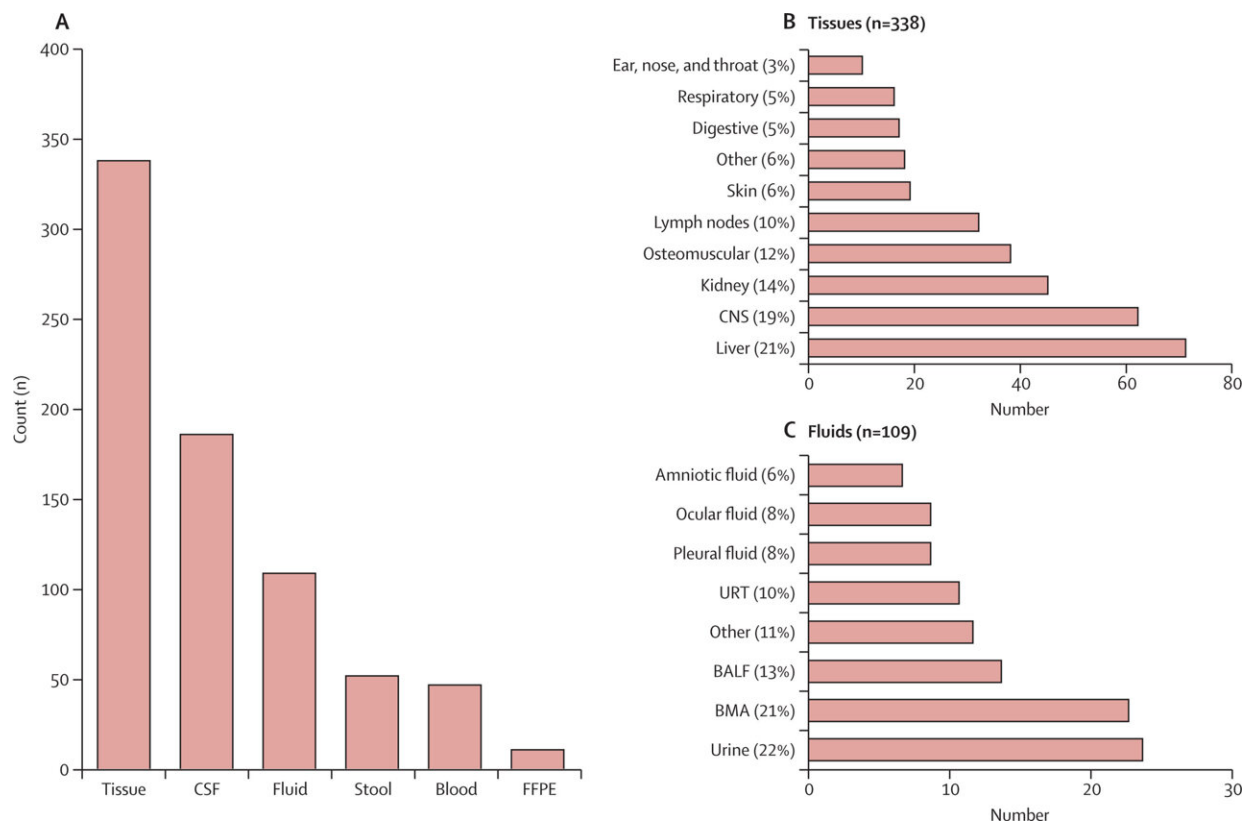


# Improving the diagnosis of infection: A prospective study clarifies the role of an innovative metagenomic tool

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Characteristics of samples analyzed by mNGS(A) Distribution of sample types among the 742 samples analyzed by mNGS in the present study. (B) Distribution of the sample origins in the tissue category. (C) Distribution of the sample origins in the fluid category. CSF=cerebrospinal fluid. FFPE=formalin-fixed paraffin-embedded. BMA=bone marrow aspiration. URT=upper respiratory tract. BALF=bronchoalveolar lavage fluid. mNGS=metagenomic next-generation sequencing. Credit: *The Lancet Microbe* (2023). DOI:

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Scientists studied the role of global genetic characterization of samples (or non-targeted metagenomics) using next-generation sequencing (mNGS) in diagnosing infections. The results of the study are published in the journal [\*Lancet Microbe\*](#).

The identification of microorganisms involved in [infection](#) is a major challenge in ensuring that patients receive optimal treatment. Recent epidemics have shown the importance of a tool capable of detecting new or unexpected pathogens and those with rapidly evolving genomes.

Currently, the search for [infectious agents](#) is mostly 'targeted' and requires prior knowledge of the possible causes of infection. In many cases, however, no microorganism is identified by first-line testing, and the cause of the infection remains unknown, leading to suboptimal treatment.

Metagenomics using next-generation sequencing (mNGS) can identify a wide range of pathogens, including rare or novel microorganisms. This study aims to improve the use of this innovative microbial identification technique, which remains complex and costly for hospital laboratories as it requires cross-disciplinary skills ranging from specific sample preparation to bioinformatics analysis of a large number of sequences.

The hospital team drew on the technical and IT skills of the Institut Pasteur's Pathogen Discovery Laboratory and worked to make mNGS available within the AP-HP and to practitioners in health care centers in mainland France and overseas.

In this study, 742 samples were collected for mNGS analysis from 523

patients between October 29, 2019, and November 7, 2022. Samples were accompanied by a mandatory prescription form completed by the physician, indicating the level of clinical suspicion of infection.

The results relate to a panel whose initial suspicion of infection was either high (63%) or low (37%). In 117 patient samples where the infection was strongly suspected—i.e., 25% of samples where the infection was strongly suspected according to the practitioners' preliminary assessment—causative or potentially causative pathogens were detected.

The diagnostic yield of mNGS was particularly high in immunocompromised patients and in patients with neurological disorders where brain biopsies were available. In fact, mNGS more easily detects a causative or potentially causative pathogenic virus in brain biopsies than in cerebrospinal fluid, which is traditionally used because it is easier to obtain.

Furthermore, the study showed that stool analyses could be used to investigate not only digestive disorders, but also hepatitis and various neurological symptoms.

In addition, the clinical performance of mNGS compares favorably to conventional microbiology. Together with future studies, the results of this prospective observational study will help to define the role of mNGS in decision making relating to diagnosis and treatment.

The team included researchers from Necker-Enfants Malades Hospital (AP-HP), the Institut Pasteur, Université Paris Cité, Inserm, Université Paris-Est Créteil and the Alfort National Veterinary School, coordinated by Professor Marc Eloit and Dr. Anne Jamet in collaboration with Dr. Jacques Fourgeaud and Beatrice Regnault.

"The Microbiology Laboratory (Prof. Leruez-Ville), in conjunction with the Department of Infectious and Tropical Diseases (Prof. Lortholary and Prof. Lecuit) and the Pediatric Immunohematology and Rheumatology Department (Prof. Quartier dit Maire and Prof. Neven) at Necker-Enfants Malades Hospital (AP-HP), has developed extensive expertise in the management of [immunocompromised patients](#) prone to infections caused by unusual microorganisms."

"The Institut Pasteur's Pathogen Discovery Laboratory, which was led by Prof. Marc Eloit at the time of the study, had already optimized the use of high-throughput sequencing for pathogen discovery by developing the technique for both sample preparation methods and bioinformatics analysis tools."

"This collaboration between Necker-Enfants Malades (AP-HP) and the Institut Pasteur was therefore well placed to identify novel causes of infection in cases where conventional techniques were missing diagnoses," explains Dr. Anne Jamet, the study's final author, who is head of mNGS at Necker-Enfants Malades Hospital (AP-HP) and a researcher at the Institut Necker-Enfants Malades (AP-HP).

"Our instincts have translated into reliable diagnoses in everyday practice as well as several noteworthy discoveries, including the identification of a new virus responsible for hepatitis," adds Dr. Jacques Fourgeaud, first author of the study and lead virologist for mNGS at Necker-Enfants Malades Hospital (AP-HP).

"This sequencing-based tool is now indispensable for diagnosing patients with a suspected infection. We are now using it earlier and earlier in severe cases, particularly those involving the brain, and in immunocompromised adults and children," says Prof. Olivier Lortholary, an infectious diseases specialist who is head of the Department of Infectious and Tropical Diseases at Necker-Enfants

Malades Hospital (AP-HP) and co-author of the study.

"We're delighted to be able to contribute to better medical care while at the same time increasing our knowledge of infectious diseases," adds Prof. Marc Eloit, co-last author of the study, who led the Pathogen Discovery Laboratory until September 2023 and is now a visiting researcher at the Institut Pasteur. The study also provides insight into the future of infection diagnostics.

"The microorganisms we identify with the Necker microbiology laboratory will enable us to develop new tools to make sequencing technology faster and more accessible for front-line microbiological analysis while enhancing its potential for the discovery of new human pathogens," says co-author Philippe Pérot, a research engineer in the Institut Pasteur's Pathogen Discovery Laboratory and lead for mNGS at the Institut Pasteur.

**More information:** Jacques Fourgeaud et al, Performance of clinical metagenomics in France: a prospective observational study, *The Lancet Microbe* (2023). [DOI: 10.1016/S2666-5247\(23\)00244-6](https://doi.org/10.1016/S2666-5247(23)00244-6)

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