A call for consensus standards to ensure the quality of cell lines

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Mainstays of biomedical research, permanent lines of cloned cells, are used to study the biology of health and disease and to test prospective medical therapies. Yet, all too often, these apparent pillars of bioscience and biotechnology crumble because they are crafted from faulty starting materials: misidentified or cross-contaminated cell lines.

In their article publishing this week in the open access journal *PLOS Biology*, scientists from the U.S. National Institute of Standards and Technology (NIST) call for "community action" to assemble a "comprehensive toolkit for assuring the quality of cell lines" employed at the start of every study.

As important, they assert, more researchers and laboratories should use the tools that already exist. The NIST authors point to the American National Standard for authentication of human cell lines, which can be implemented to detect cell-line mix-ups and contamination before embarking on studies of cancer or other research using human cells. Unfortunately, the four-year-old standard has not been widely adopted, even though cell-line authentication is a growing priority among funders and publishers of research.

Cell lines are populations of clones: genetically uniform animal or plant cells that are bioengineered to proliferate indefinitely in culture. First used in the early 1950s, these immortalized cell lines, each with different properties or features, now number well into the thousands and are used as simple models for studying disease and for testing the toxicity of

compounds, producing biological drugs, and other applications.

Cell-line contamination and misidentification can undermine research results, spur additional studies of questionable value, and waste research funds—accounting for a significant portion of the estimated $28 billion of irreproducible preclinical research conducted each year in the United States alone, according to a 2015 economic analysis.

A "high level of confidence" in published research results requires valid underpinning data on methods and materials—cell lines, instrument performance and more, explain the researchers, who work in the Biosystems and Biomaterials Division of NIST's Material Measurement Laboratory. "One might argue that these control data are as important as the study data themselves."

The critical importance of authenticating cell lines is widely recognized, due, in part, to publicized reports on the costs and damaging research consequences of cell-line contamination, which could have been avoided by confirming the identity of cell lines at the outset of research projects. The National Institutes of Health, other funding agencies and organizations, and many scientific journals have established requirements for reporting on the authentication and purity of cell lines.

Still, cell line authentication is poorly reported. In 2015, the Global Biological Standards Institute reported that 52 percent of the life sciences researchers it surveyed never validate their cell lines.

The American National Standards Institute (ANSI) and American Type Culture Collection (ATCC) have developed, according to the authors, a "very thorough and helpful" standard (ASN-0002 2011) on authenticating human cell lines using short tandem repeats—a DNA "fingerprinting" method borrowed from forensics in which cells can be identified by how many times particular DNA sequences repeat within

their genome (the method in the ASN-0002 documentary standard is also freely accessible here: http://www.ncbi.nlm.nih.gov/books/NBK144066/). "Lack of awareness," the NIST authors suspect, may account for limited use of the standard, as suggested by disappointingly low levels of human cell-line authentication in studies. They recommend using the standard in training and education programs, which may get a push from authentication requirements set by funders and publishers.

Comparable authentication standards are needed for mouse, rat and other important non-human cell lines used in research and biomanufacturing. The authors advocate using inclusive, consensus standards-setting processes—like the one used for human cell-line authentication—to address these needs as well as to seize new opportunities that are arising with the commercialization of genome-sequencing technologies.

"Consensus standards that are produced in a careful, open, and official process are an integral part of the success of this endeavor," they write. "Standards help to assure that data are sharable and can be the basis of decision-making and compliance."

More information: Leonard P. Freedman et al, The Economics of Reproducibility in Preclinical Research, *PLOS Biology* (2015). DOI: 10.1371/journal.pbio.1002165

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