

# Incorrect cell line validation and verification

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Health research is a fundamental basis to the quality of life of humans. Untold billions are invested annually in research seeking the cure to better health, and much of this research involves specific cell lines. Such cell lines have the ability to be maintained *in vitro* indefinitely, provided that they are provided with the required growth conditions. There is increasing evidence, however, that globally, a large number of cell lines have become contaminated, either as a result of poor laboratory and cell line management, or cross-contamination by other cell lines, either of the same species or another species (1), with human cervical adenocarcinoma, or HeLa cells, having the most number of contaminated lines, 106 (2).

The failure to test or authenticate cell lines for purity on a regular basis, something that can be easily achieved, and that should be done, can have negative consequences on the experimental outcome, namely failure. Incorrect cell lines will likely result in researchers investing more research dollars into trying to repeat an experiment, only to result in failure, and may be one of the large causes of the replication crisis in cancer research. This is because other researchers hoping to repeat the results of a published study that has claimed to use a certain cell line, but that has in fact used an incorrect cell line, will be attempting a repetition in vain, simply because the research material being used is wrong. As one example, Christopher Korch, a geneticist, estimated that contamination of HEP-2 and INT 407 cell lines by HeLa cells may have affected the published literature as follows: 5,789 papers in 1,182 journals and 1,336 papers in 271 journals may have used HEP-2 and INT 407 cell lines, respectively, inappropriately, thereby affecting hundreds of thousands of citations and possibly billions of US dollars in follow-up research that may be erroneously based on the wrong or cross-contaminated cell line (3). More recently, Horbach and Halfman (4) estimated that the number of

papers with misidentified cells exceeded 32,000, and that these papers were cited by half a million others, showing how potentially widely the literature using cells lines may in fact be erroneous. In China, human cell lines are widely contaminated (5). Separately, 278 popular tumor cell lines have been misidentified or are cross-contaminated (6).

The first line of defense is good laboratory practice that ensures rigorous sterile and strict cell line management. Original cell lines must be derived from a reputed cell bank and risks are introduced with “gift” lines from other colleagues. Cell line authentication can be achieved using cytogenetic or molecular methods, and is a verification step that should be conducted regularly (7,8).

Part of the lack of reproducibility in science is caused by poor quality control of reagents, and the poor description of procedures in published papers (9). Another part of the crisis in cell line reproducibility lies in the resistance of academics, editors and publishers to correct the literature, either as a result of bruised pride or fierce denial, leaving stated cell lines in a large number of published papers unclear, uncertain or incorrect. While it is likely impossible to verify the authenticity of cell lines in older papers, authors of newer papers for which doubts have been raised regarding authenticity or possible cross-contamination should have the responsibility of repeating such experiments, and in all cases, an expression of concern should be published, alerting readers that the cell lines claimed might not in fact be what they are, or that the conclusions drawn or even methods used should be interpreted cautiously. This process, monumental as it is, can only come about with a changing shift in culture, from one of resistance, to one of acceptance of error, and its correction, via retractions (10).

Cell lines, whether for basic research or for applied biomedical studies, can have an impact on the lives and health of members of society. A responsible attitude by those

that employ cell lines, beginning with strict quality control and management of the laboratory, regular authentication, and a changing perspective about the importance of post-publication peer review of erroneous literature are all complementary essential strategies to avoiding, reducing, or correcting errors related to erroneous cell lines.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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