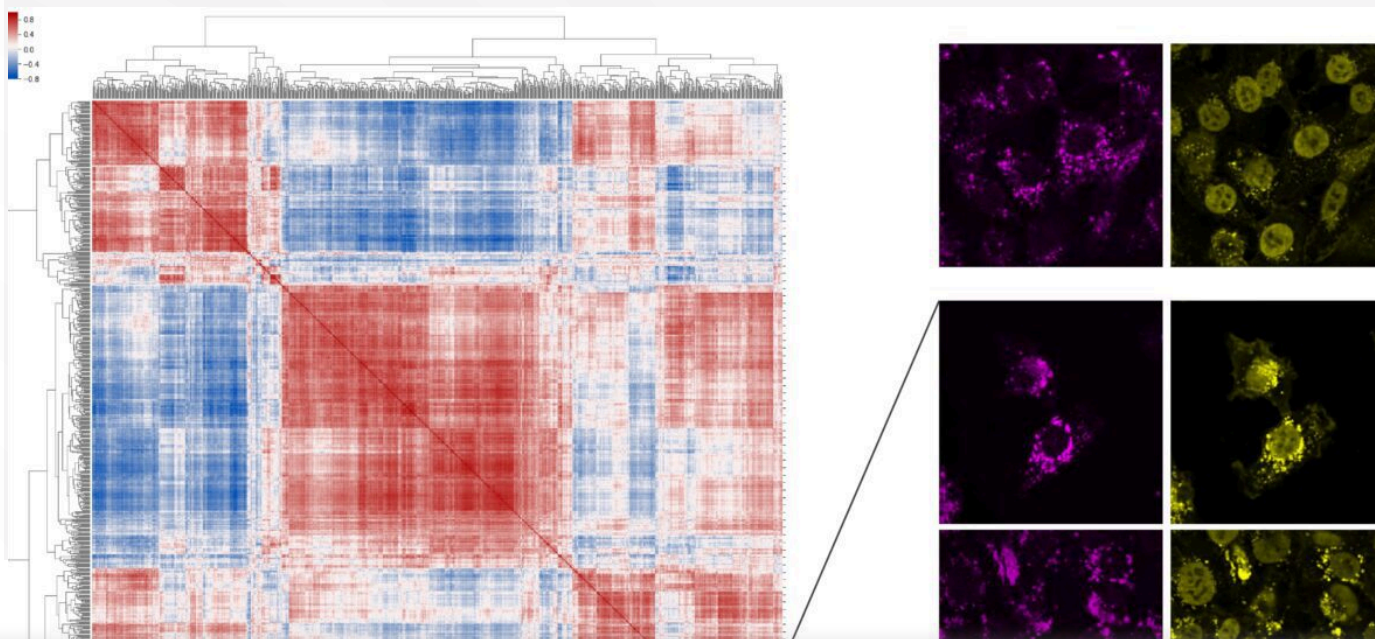


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Calico Stories

# PERISCOPE: A Powerful New Tool for Exploring Gene Function



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all this code do? A new study from scientists at Calico and the Broad Institute of MIT and Harvard published in *Nature Methods* offers a large-scale view of biological function by pairing the latest advances in cell imaging and CRISPR gene editing.

In this study, scientists used CRISPR editing to target more than 20,000 genes in more than 30 million cells — a sweeping project that would have cost far more and been much more difficult with conventional approaches. The result: a genome-wide atlas of the functional changes in cells that resulted from knocking out each gene, with morphology data to back it up. The approach is known as PERISCOPE, which brings together an image-based profiling method called Cell Painting for large-scale cellular phenotyping, optical pooled screening to edit genes and identify the specific gene edit performed, and a scalable analysis pipeline to interpret the results.

The entire approach and the atlas generated in this study have been publicly released to allow other scientists to implement the method in their own labs. "The thing that's most exciting about PERISCOPE is that it's really democratizing. The approach can be executed by most labs, with no specialized equipment required — all you need is a cell culture model of the biology you want to study," says Calvin Jan, a Principal Investigator at Calico and one of the senior authors of this publication. "We made all of the analysis packages available freely to help anyone get started with this method."

While gene expression is often studied using a technique known as RNA sequencing, a major disadvantage is that the sequencing process kills the cells. With PERISCOPE, living cells can be interrogated without harm. This allows scientists to

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sequencing at the same scale while maintaining a comparable ability to detect biological effects of genetic perturbations.

The PERISCOPE study also represents a big step toward a new way of studying the aging process. At Calico, scientists have been looking for more scalable methods to study aging, which typically has to be evaluated in animal models. The PERISCOPE project emerged from a simple question, Calvin says: "How do we study aging in a dish?" With the success of this approach, the Calico team can now turn to human cell culture models to study aging-related traits in a faster, cheaper, and larger-scale manner. Moreover, the team anticipates that PERISCOPE will be applicable to neurodegenerative disorders, such as Parkinson's disease.

*Learn more about this project in a Broad article titled, "[A genome-wide atlas of cell morphology reveals gene functions](#)" and the Nature Methods publication, "[A genome-wide atlas of cell morphology](#)."*

*This image shows a heatmap (left) grouping genes by similar morphology and highlights an uncharacterized gene, TMEM251, which PERISCOPE discovered to be similar to genes important for lysosomal function. Normal cell images (top) show standard sugar levels (yellow) and small, punctate lysosomes (purple). Cells with the TMEM251 gene knocked out (bottom), show the resulting functional changes including abnormal sugar buildup (yellow) and enlarged lysosomes (purple).*

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