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Jay Shendure is an Investigator of the Howard Hughes Medical Institute, Professor of Genome Sciences at the University of Washington, Director of the Allen Discovery Center for Cell Lineage Tracing, and Scientific Director of the Brotman Baty Institute for Precision Medicine. His 2005 doctoral thesis with George Church included one of the first successful reductions to practice of next generation DNA sequencing. Dr. Shendure's research group in Seattle pioneered exome sequencing and its earliest applications to gene discovery for Mendelian disorders and autism; cell-free DNA diagnostics for cancer and reproductive medicine; massively parallel reporter assays, saturation genome editing; whole organism lineage tracing, and massively parallel molecular profiling of single cells.

Dr. Shendure is the recipient of the 2012 Curt Stern Award from the American Society of Human Genetics, the 2013 FEDERAprijs, a 2013 NIH Director's Pioneer Award, the 2014 HudsonAlpha Life Sciences Prize, the 2018 Richard and Carol Hertzberg Prize for Technology Innovation, and the 2019 Richard Lounsbery Award from the National Academy of Sciences. He serves or has served as an advisor to the NIH Director, the US Precision Medicine Initiative, the National Human Genome Research Institute, the Chan-Zuckerberg Initiative and the Allen Institutes for Cell Science and Immunology. He received his MD and PhD degrees from Harvard Medical School in 2007.

Abstract: Multiplex Genome Editing for Variant Interpretation and Developmental Recording

CRISPR/Cas9 genome editing has created new opportunities for "multiplex biology". I will describe recent work from our lab in two very different areas. First, variants of uncertain significance fundamentally limit the clinical utility of genetic information. The challenge they pose is epitomized by BRCA1, a tumour suppressor gene in which germline loss-of-function variants predispose women to breast and ovarian cancer. Although BRCA1 has been sequenced in millions of women, the risk associated with most newly observed variants cannot be definitively assigned. We have used "saturation genome editing" to assay 96.5% of all possible single-nucleotide variants (SNVs) in 13 exons that encode functionally critical domains of BRCA1. We predict that these results will be immediately useful for the clinical interpretation of BRCA1 variants, and that this approach can be extended to overcome the challenge of variants of uncertain significance in additional clinically actionable genes. Second, multicellular systems develop from single cells through distinct lineages. However, current lineage-tracing approaches scale poorly to whole, complex organisms. We have used genome editing to progressively introduce and accumulate diverse mutations in a DNA barcode over multiple rounds of cell division. The barcode, an array of clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 target sites, marks cells and enables the elucidation of lineage relationships via the patterns of mutations shared between cells. We anticipate that genome editing of synthetic target arrays for lineage tracing (GESTALT) can be used to generate large-scale maps of cell lineage in multicellular systems for normal development and disease.