**2.**

**Please provide a summary of your research purpose by responding to the questions below.**

**Publicly displayed**

Your responses should cover the major components of a research summary: hypothesis, methods, and anticipated findings. Therefore, please provide sufficiently detailed responses in plain language (without jargon), using as few technical terms as possible.

**2.1**

**What are the specific scientific question(s) you intend to study, and why is the question important (i.e. relevance to science or public health)?**

If you are exploring the data at this stage to formalize a specific research question, please describe the reason for exploring the data, and the scientific question you hope to be able to answer using the data.  
(Free text; 1000 character limit)

CRISPR genome editing, allowing precise targeted DNA alterations, has the potential to lead to therapies for a range of diseases ranging from cancer to genetic disorders. However, as these techniques advance into clinical use, concerns arise about "off-target" edits, where the therapy also modifies DNA at unintended locations due to sequence similarity with the target. This risk varies among individuals due to genetic differences. Current strategies aim to minimize this risk by designing CRISPR targets based on the reference genome or a small group of individuals with known DNA sequences, such as the 1000 genomes study population. However, these cohorts don't fully represent genetic variation and hence off-target risk across the population. We aim to leverage the large number of sequenced genomes in the All of Us Research Program to refine CRISPR targeting strategies, enhancing off-target safety, particularly in populations historically underrepresented in genome sequencing studies.

**2.2**

**What are the scientific approaches you plan to use for your study? Describe the datasets, research methods, and tools you will use to answer your scientific question(s).**

(Free text; 1000 character limit)

We will use genetic variation data from All of Us Participants to develop tools for assessing the extent to which genome editing off-target risk varies between individuals. If we discover that there appears to be significantly increased off-target risk in sets of individuals or populations, we will develop CRISPR target design tools that minimize risk across the entire population.

**2.3**

**What are the anticipated findings from the study? How would your findings contribute to the body of scientific knowledge in the field?**

(Free text; 1000 character limit)

Based on preliminary work, we expect that individuals from populations that have historically been underrepresented in genome studies may have an increased risk of off-target side effects using current genome editing targeting strategies. We expect that a better understanding of off-target profiles in these populations, through studies such as the one we propose here, will allow us to mitigate this risk and improve equitable access to therapies enabled by CRISPR genome editing.