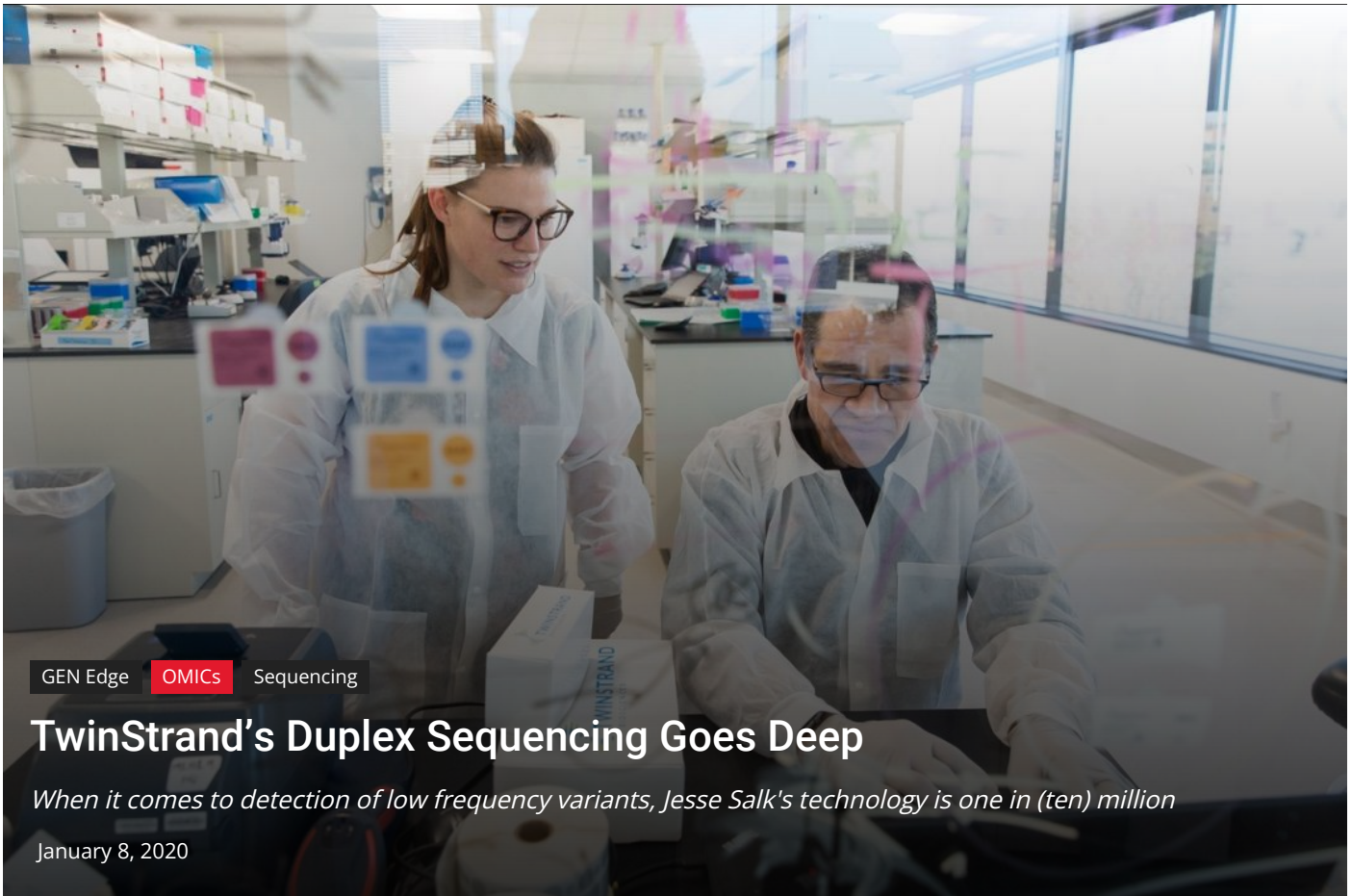




GEN Edge OMICS Sequencing

TwinStrand's Duplex Sequencing Goes Deep

When it comes to detection of low frequency variants, Jesse Salk's technology is one in (ten) million

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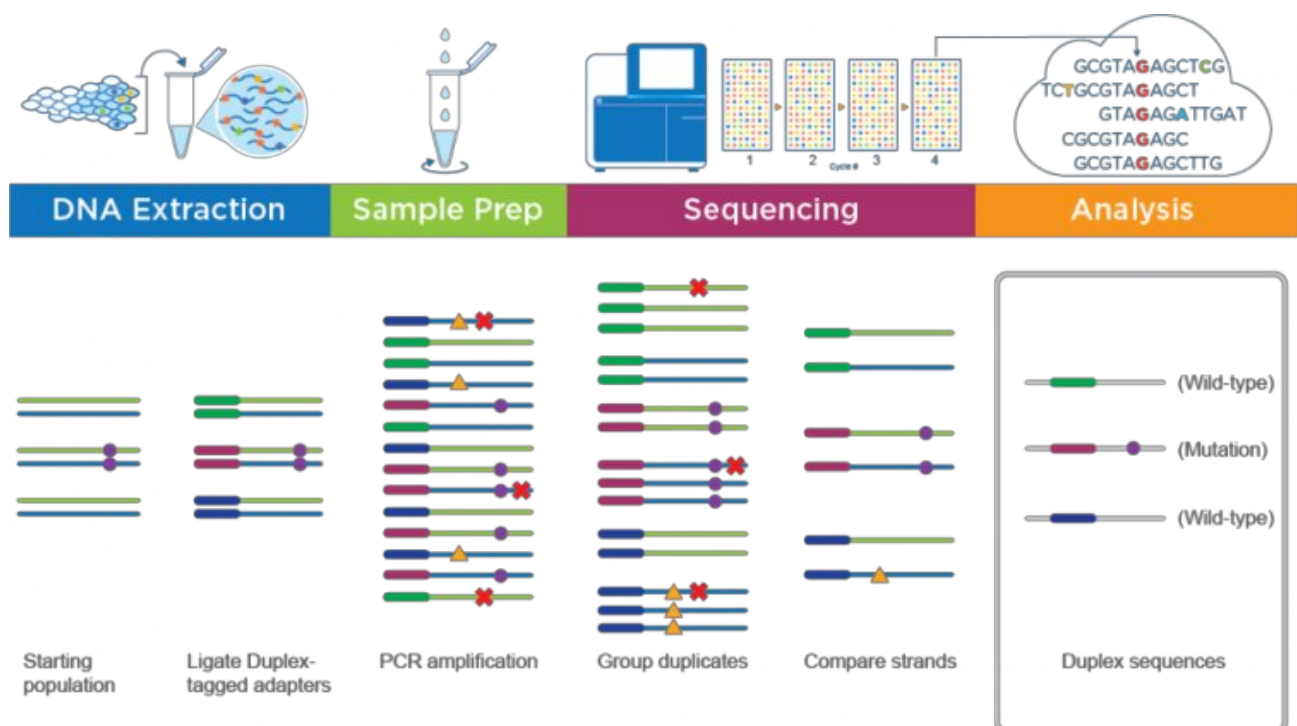


As companies strive to make their sequencing capabilities longer, more accurate, faster, and cheaper, the detection of low frequency DNA mutations remains one limitation that no one has overcome. The young start-up, TwinStrand Biosciences, a spin out of the University of Washington, is hoping to crack that nut with their duplex sequencing technology.

Duplex sequencing improves sequencing accuracy to a very high degree, making it possible to detect low frequency variants such as one cancer cell among 10,000 normal cells or ultra-rare mutations caused by carcinogens, aging, and the earliest stages of cancer.

To do this, the technique independently tracks both strands of individual DNA molecules and compares the results to identify and eliminate errors. This concept, TwinStrand notes, is borrowed from the molecular machinery used by cells throughout the natural world to replicate their genomes with high accuracy.

Duplex sequencing starts with the attachment of adaptor molecules which are ligated onto the DNA. This unique tag consisting of a randomized sequence, distinguishes each double stranded DNA molecule from others in the population. Known as a unique molecular identifier (UMI), the tag is identical between strands of DNA, making it possible to relate the strands back to each other once separated. In addition to the UMI, an asymmetric portion of the adapters—the strand defining element (SDE)—distinguishes the strands so that each can be recognized as the original reference or anti-reference strand of the duplex. Together these elements create a data structure where every single sequence can be tied back to an individual strand of an individual molecule.



Duplex sequencing reduces errors to below one artifactual mutation per ten-million nucleotides making the rarest variants detectable. [TwinStrand]

Once tagged, the complexes are amplified and sequenced. For each molecule, the sequence reads of the polymerase chain reaction (PCR) copies are grouped by

unique tag and strand. Errors are recognized and removed by comparing the sequences of PCR duplicates within each strand group and then between partner strands to find and discount mismatches, increasing the confidence in the authenticity of any mutations that remain.

Everything but the kitchen sink

The limit of detection that duplex sequencing offers—below one in 10 million—is not always necessary. But, for those applications where finding low frequency mutations is critically important, it may be a game changer. Applications where this type of sensitivity could be applied are forensics, microbiome, environmental monitoring, antimicrobial drug selection and drug resistance, tumor evolution, liquid biopsies, prenatal diagnosis, fetal genetic health, immunological health, and unintended off target mutations made through gene editing.

Like his legendary grandfather who invented the polio vaccine, Jesse Salk, MD, PhD and CEO/CSO of TwinStrand, has a technology that may disrupt medical practice. The first space where Salk sees a practical application is in oncology. “The earlier you detect cancer, the more treatable it is” Salk asserts. For the detection of ovarian cancer, the team at TwinStrand has developed a test using a catheter device that can be used during a Pap smear to collect cells to sequence for low frequency variants of the gene TP53— a marker of early cancer.

Another application is in the identification of residual disease in cancers such as acute myeloid leukemia. After a round of multi-drug chemotherapy, if leukemia cells can be identified in the bone marrow, a new drug may be tried. If not, perhaps future, unnecessary treatments can be spared.

The field of genetic toxicology defines whether certain drugs or chemicals are carcinogenic. From the Ames test to laborious and inconclusive rat experiments that take years to perform, this area is not only full of murky science, it is incredibly controversial. TwinStrand’s approach could potentially put to bed the seemingly never-ending controversies that surround everything from weed

killers to hair dye.

An inflection point

TwinStrand is young, with 25 employees. Although their website is sparse, their publication history is extensive. The duplex sequencing technology was first published in a 2012 *Proceedings of the National Academy of Sciences* paper entitled, “**Detection of ultra-rare mutations by next-generation sequencing.**” Since then, Salk and his team have published roughly a dozen other papers related to the technology.

This week, TwinStrand announced the close of \$16 million in Series A funding, including \$12 million in new capital. Madrona Venture Group led the investment with participation from Alexandria Venture Investments, Ridgeback Capital, and Sahsen Ventures. TwinStrand previously raised \$5.5 million in Seed funding, in addition to \$6.4 million in SBIR grants. Salk tells *GEN* that they will use the money to shift from a predominantly R&D operation to a commercial operation with hopes to “double our lab space in the next six months and head count within the next year.”



Credit: Twinstrand

The energy surrounding TwinStrand is picking up, Salk notes with enthusiasm, and the company seems to be at an inflection point at the moment. He explains that the company is moving from “a few people sitting around with a good idea” to receiving positive feedback and obtaining energetic partners. Indeed, TwinStrand is a bronze sponsor of this year’s AGBT general meeting in Marco

Island, FL, with plans to announce a Q1 initial product launch at the meeting in February.

Staying relevant



Jesse Salk, MD, PhD

It is not an uncommon occurrence for Salk to be pulled away from an investor conference to fill out a patient's paperwork or answer a quick question about a prescription. Not your average CEO, Salk maintains a part-time position as a faculty member at the University of Washington where he works as an oncologist at the affiliated VA hospital.

Salk is equally as likely to discuss cancer drug pricing or the issues that surround the medical profession as the cutting-edge technology that is at the center of his company. Even if TwinStrand continues to grow, Salk expects to maintain his position at the hospital, asserting that his clinical work "keeps his skills up." He adds that continuing to see the patients that he has built relationships with keeps him grounded in reality. Also, he reflects that his medical training helps him understand the problems that oncologists face and communicates them to the partners that he needs to keep his business relevant.

For now, in addition to his work as a practicing oncologist, Salk is focused on moving duplex sequencing out of an academic environment into a robust

commercial workflow that is set up for success. Salk adds that “even the most powerful technology in the world won’t be used if it can’t be practically implemented.”



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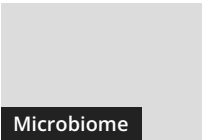
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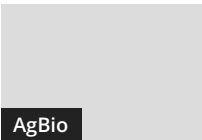
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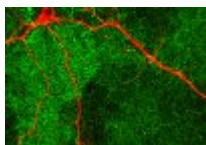


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