

Personalized medicine is the practice of using advanced technology to tailor customized drug therapies based upon an individual's specific disease state. In cancer, tumors display malignant alterations to proteins and genes called mutations. These distinctive mutation signatures make each person's cancer unique. The aim of personalized medicine is to identify these mutations and customize treatment with targeted therapies with the goal of delivering better patient outcomes, fewer adverse side effects and less overall cost to the health care system.

In order to begin to provide personalized medicines, scientists need to have a comprehensive understanding of the mutations present within the tumor cells. This can be done in the traditional fashion through tissue biopsy, whereby a small tissue sample is surgically removed from the actual tumor, or through emerging technology called liquid biopsy, where comprehensive genetic sequencing is used on easier-to-obtain samples, typically blood, bone marrow or urine, to determine the presence of cancer and specific mutations. Liquid biopsy presents a less-invasive process with lower costs and fewer complications. We have long considered personalized medicine to be an emerging theme, but with the growth of liquid biopsy we were able to identify a shift in spending and to begin to formalize investments that we expect can benefit from the secular tailwinds. We believe liquid biopsy will be transformative to the practice of oncology.

Personalized Medicine as an Investable Secular Theme

Our interest in liquid biopsy began when one of our portfolio holdings, Bio-Techne Corporation, announced plans to acquire privately held Exosome Diagnostics in 2018. Exosome has a non-invasive urine test for biopsy rule-out testing in patients with an ambiguous prostate-specific antigen (PSA) test result. This acquisition piqued our interest and caused us to do further deep-dive research on other players in the liquid biopsy space. During this deep dive, we grew comfortable that liquid biopsy, as a less-invasive, less-costly method of characterizing a tumor, would garner market share from, and potentially displace the need for, surgical tissue biopsy. We identified liquid biopsy, or the process used to characterize the genomic profile of an individual's tumor through blood or urine, as one of the first beneficiaries of the personalized medicine theme. Through deep fundamental analysis, we found two companies that we view as attractive investments: Guardant Health and Adaptive Biotechnologies.

Guardant Health is the leader in blood-based complete genomic profiling of tumors through its Guardant-360 liquid biopsy test, the first FDA-approved test for pan-cancer tumor genetic profiling in blood. Guardant-360 is used to match cancer patients with the best-available therapy, a practice called therapy designation. Guardant, through its Lunar-1 program, is working on tests to monitor for cancer recurrence in high-risk patients. The company's Lunar-2

program is developing diagnostic tests for early-stage screening of asymptomatic patients for the presence of cancer. Guardant believes the total addressable markets for its products to be in excess of \$50 bn, with ~\$6bn in therapy designation, ~\$15 billion in cancer monitoring and recurrence and ~\$30 billion in early-stage screening of asymptomatic patients.

Adaptive Biotechnologies is harnessing the power of the human immune system for diagnostics, as well as for therapeutic discovery purposes. Adaptive uses machine learning, in partnership with Microsoft, to map the immune response to many different diseases. The company is matching T-cell receptors and B-cell receptors to certain antigens present within diseases. This type of information can be used in diagnostics and treatment decision and, ultimately, to identify drug therapies. Adaptive's first commercial product, clonoSeq, is used to monitor minimal residual disease (MRD) levels in blood cancer patients to assist in therapy decisions. Importantly, clonoSeq is also being used by biopharmaceutical partners as a primary endpoint in investigational clinical trials with the goal of reducing trial time and speeding effective therapies to market. Adaptive's next line of products is a diagnostic suite called immunoSeq Dx, whereby the company will try to use the immune response to identify difficult-to-diagnose conditions, with an initial focus on Lyme disease, celiac disease and certain cancers. Adaptive has also partnered with Genetech, a division of Roche Pharmaceuticals, to deliver targeted drug candidates for clinical evaluation. We are encouraged by the multiple pathways present for success at Adaptive.

Future of Personalized Medicine

As personalized medicine matures as a secular theme, we believe it will expand beyond liquid biopsy and provide opportunities to identify biopharmaceutical companies investigating targeted therapies. Targeted therapy research should increase the odds of successful clinical trials, thus potentially reducing a portion of the binary risk usually associated with development programs. Diagnostics companies can be in a position to develop companion diagnostics to identify the proper patients for their personalized therapies.

We also believe that technology will assist in personalized medicine as companies develop sensors, activity-tracking devices and vital statistics tracking devices to monitor and aid in the treatment of specific conditions. One example of a portfolio investment tied to this theory is Dexcom, a company that makes continuous glucose monitoring (CGM) systems to aid in the management and treatment of patients with diabetes. Even Apple watches can be used to identify heart problems like atrial fibrillation through their heart rate monitor functionality.

Conclusion

One can envision a day when rather than getting an off-the-shelf therapy, patients will be prescribed a more customized solution specific to the uniqueness of their condition. We believe personalized medicine will lead to better patient outcomes with fewer side effects and reduce the overall cost to the system by reducing the use of ineffective, expensive therapies. Additionally, the technology used for personalized medicines should help to increase the odds of success on targeted clinical trials leading to better therapy options for patients.

We believe we are in the early stages of personalized medicine and are excited about the current and future investment opportunities we can identify through early research on this secular theme.

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The companies identified in this report are examples of holdings and are subject to change without notice. The companies have been selected to help illustrate the investment process described herein. A complete list of holdings is available upon request. The investment examples were selected based on the following criteria – represent Aristotle Atlantic holdings identified under personalized medicine as an investable secular theme as of 6.30.2020.

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