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A conversation with Dr. David Song

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ON COVID-19 RELATED ISSUES

The world is gradually emerging from various forms of lockdowns that have managed to flatten the curve in most countries. However, we are still far from eradicating the disease and the risk remains that the outbreak could flare up again. Representing over 13% of the global equity investible universe, the healthcare industry has taken on a new level of importance as its various constituents are addressing the burden of COVID-19 infections while also racing to develop solutions in diagnostic, therapeutics, and vaccines. The degree of success in these efforts will affect our ability to manage through the global health crisis, and ultimately dictate the pace of economic recovery and the return to normalcy. Indeed, in the face of sharp economic contractions across much of the globe, most industries are dealing with weaker demand and an uncertain outlook. However, the healthcare industry stands out as one of the few with potentially stronger secular demand.

Extensive media coverage of the pandemic, from the White House Coronavirus Task Force briefings to interviews with various experts and survivors, has made us all authorities on COVID-19. We are pleased, however, to have a real expert on our investment team. Dr. David Song has been an integral part of Rockefeller Asset Management's investment team since 2008. Having earned two degrees – Doctor of Medicine and PhD in Healthcare Management and Economics, Dr. Song is steeped in both the scientific and policy aspects of healthcare issues. What follows is an interview with Dr. Song to address some of the key COVID-19 issues on the minds of investors as well as potential investment opportunities.

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ANTIBODY TESTING

Jimmy: Dr. Song, there are three things that we are monitoring closely to determine how life can gradually return to normal: testing, therapeutics, and vaccines. Let's first focus on testing for the Coronavirus antibody, which is believed to be a key component for lifting lockdowns. How is such a test conducted, and how accurate are the results?

Dr. Song: Generally, in a viral infection like COVID-19, a person develops antibodies to the virus that are detectable about one to two weeks after onset of symptoms. A serology test can measure levels of antibodies present in the blood not for active infection, but for prior exposure to COVID-19. Antibodies are a surrogate measure of a patient's immune response to the virus. Typically, an antibody test is conducted through a blood draw at either a physician's office or testing centers from reference laboratories, like Labcorp and Quest Diagnostics. A reference lab can then deliver a result. There are tests where results are given at the physician's office – so-called point-of-care tests, as well. There is some variability in test results depending upon manufacturer. As an example, the serology tests done in a traditional reference lab, utilizing BioMedomics' assay, which is distributed by Becton Dickinson, yield sensitivity and specificity of 89% and 91%, respectively. Sensitivity measures the ability of a test to identify patients with disease, while specificity measures the ability of a test to identify patients without disease. We would also want to distinguish antibody-based tests from other tests that are deployed to measure active COVID-19 infection, by determining the presence of viral nucleic acid (i.e., genetics) in a nasal swab.

Jimmy: It is reported that results from a random testing of 3,000 people in New York State showed that 1 in 5 New York City residents tested positive for antibodies to the coronavirus. Is a person with the antibody immune to COVID-19? For how long? Is it possible that the antibody may relate to other Coronavirus infections, like a common cold, so that having the antibody does not necessarily mean one is immune to COVID-19?

Dr. Song: It is believed that following exposure to COVID-19, a person developing antibodies has immunity to the coronavirus. However, it is not entirely known *how long* such immunity persists. People may also have antibodies to other coronaviruses that caused some common colds. There could be cross-reactivity in COVID-19 antibody testing to some of these other coronaviruses, thus rendering some false positives in a test. Therefore, it is possible that this serology-based calculation in NYC overestimates the true prevalence in this community, especially if the true prevalence is low.

IN SEARCH OF A CURE

Jimmy: Can you comment on some of the promising developments on the therapeutic side, and what are the odds that we will have an effective drug to treat COVID-19 before year end 2020?

Dr. Song: By year-end, we expect to see multiple effective therapeutic approaches to deal with the potential for a second wave of infections.

One widely discussed drug is Gilead Sciences' Remdesivir, which is an antiviral originally developed for the Ebola virus. This drug, which is delivered intravenously in a healthcare facility, recently became available under the FDA's emergency use authorization (EUA). This designation was based primarily on positive data from a randomized controlled trial of Remdesivir vs. placebo in hospitalized COVID-19 patients. This trial, which was sponsored by NIAID (National Institute of Allergy and Infectious Diseases), demonstrated a 31% faster time to recovery (11 days for patients on Remdesivir vs. 15 days on placebo). While not statistically significant, a favorable trend toward mortality was observed (8.0% for Remdesivir vs. 11.6% for placebo). Though not a silver bullet, this drug shows promise and will be deployed initially in hospitalized patients. There is potential for the drug to be combined with other treatments under development.

Jimmy: How about hydroxychloroquine and other drugs?

Dr. Song: I am somewhat skeptical of a benefit for hydroxychloroquine, another widely discussed drug, given potential for adverse cardiac safety issues. That

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said, more rigorous randomized studies will also be available and at least provide a more definitive conclusion on the drug.

Beyond Remdesivir and hydroxychloroquine, a number of companies are working on *antibody-based therapies* that target COVID-19, in order to improve the outcome of infected patients or even provide short-term passive immunity to the virus. Initial trials are set to begin as early as June. Given this approach has worked on other viruses in the past, I view successful development more likely than not. Under the FDA's EUA, antibody-based therapies could be available later this Fall.

One of the biotechnology companies working on this promising antibody-based approach is Regeneron Pharmaceutical. Led by co-founders Dr. Leonard Schleifer and Dr. George Yancopoulos, this Tarrytown, NY-based company has accumulated decades of medical and scientific experience, culminating in expertise in human monoclonal antibody manufacturing technology. Regeneron scientists were able to create an antibody cocktail to treat Ebola virus successfully. We remain optimistic about Regeneron's clinical development in COVID-19, given the depth and experience within the organization coupled with past validations of the antibody approach in multiple viral infections. The company is in the process of enrolling patients early this summer to test its antibody therapeutics on COVID-19 infection. We believe if successful, Regeneron could be positioned to deliver a COVID-19 targeted therapy by this Fall through FDA's EUA.

A number of companies are working on another promising approach, called *convalescent plasma*, which derives antibodies from the donated blood of COVID-19 survivors. Similarly, the plasma-derived antibodies may block viral replication; hopefully more rigorous clinical data will demonstrate significant clinical improvement in COVID-19 patients.

There are also clinical studies that are determining whether drugs that tamper down the immune response in critically ill patients can improve outcomes. It is believed that the body may inadvertently have an immune response "in overdrive," leading to potentially fatal consequences, like multi-organ failure.

In addition, there are growing reports of hospitalized patients experiencing a higher incidence of life-threatening clots. At the end of the day, we believe more knowledge of the sequelae of COVID-19 could lead to significant advances in supportive ICU care, as caregivers gain more experience with COVID-19 patient care.

Jimmy: Reports from South Korea and China indicate that some people who had supposedly recovered from COVID-19 were tested positive again, and some do not show the presence of antibody. The U.S. military is reportedly considering making a past COVID-19 diagnosis as a permanent disqualification for enlistment. Does this mean that there is a serious risk of relapse?

Dr. Song: There's a lot that is being learned about the virus at the time of this publication, given how recent the initial cases have occurred. There may be differences in immune response depending upon many factors, or perhaps the persons purportedly reinfected were actually infected to begin with due to imperfections in diagnostic tools. Despite many unknowns, it is believed that most individuals who have recovered have some degree of immunity.

VACCINES – THE HOLY GRAIL

Jimmy: Ultimately, a vaccine is needed to return life to normal. First of all, do you think it is possible to develop an effective vaccine against the SARS-CoV-2 virus (the COVID-19 virus) given that we may have a moving target with its mutation?

Dr. Song: Clearly, there are outstanding questions on SARS-CoV-2, including natural history and immune response. The evolving genomic profile of the virus has been tracked by analyzing samples from all over the world in real-time. While we do expect the virus to mutate, I do not think that based on these analyses, the genomic profile will be dramatically altered to affect the efficacy of a vaccine currently in development when one becomes available for mass vaccination. In addition, while not peer reviewed, there have been some reports of promising preclinical data of COVID-19 vaccine

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candidates that establish proof of principle. To illustrate, one publication demonstrates efficacy of a COVID-19 vaccine in non-human primates: https://www.biorxiv.org/content/10.1101/2020.04.17.046375v1.full.pdf

Jimmy: What is the progress on various human trials? What do you think is a realistic timeframe for most Americans to get vaccinated? How about extending the vaccination to the entire world?

Dr. Song: Several companies are working on vaccines for COVID-19. Three of the leading companies include Moderna, Johnson & Johnson (J&J), and Astrazeneca. Moderna, which has a novel approach that uses messenger RNA, initiated clinical trials recently. J&J, which utilizes established vaccine technology with ability to scale manufacturing to hundreds of millions of doses, has identified a vaccine candidate in preclinical development and plans to initiate trials no later than September 2020. J&J states it may have a vaccine available by early 2021. Recently, Astrazeneca has teamed up with the Oxford Vaccine Group (from University of Oxford) to develop and manufacture a vaccine based on a weakened version of the common cold (adenovirus) that contains genetic material of the virus' spike protein. Initial clinical data could be available in June.

We do believe that regulation will help accelerate timelines. EUA, which requires a lower hurdle for efficacy and safety than traditional FDA approval, can help accelerate market entry. In addition, we expect surrogate measures of a vaccine's efficacy could also be used to accelerate timelines. Nonetheless, rigorous demonstration of safety should be established to avoid untoward harm on a large population that could be vaccinated. Mass vaccination efforts also require scaling up manufacturing, which may be a hurdle for some vaccine developers. Nonetheless, the US and other well-resourced countries may fund clinical trial efforts and mass production simultaneously, even before safety and efficacy have been established.

Given these accelerated timelines, we believe it is plausible, though somewhat optimistic, to see at least one successful vaccine available for wide population use in the US and some other developed countries *by the middle of 2021*. This is somewhat consistent with the 12 to 18-month timeframe commonly cited by some. That said, given residual technical uncertainties, vaccine development is not a sure thing despite the unprecedented number of vaccines in development. Hence a delay toward the end of 2021 is plausible as well. In addition, public health experts believe given the highly infectious nature of the virus, 60% or more individuals in the population need to be immunized or have exposure to COVID-19 before herd immunity can be achieved. Barriers to mass vaccination, which include lingering hesitation from individuals on known safety or efficacy and potential issues in manufacturing, could delay achievement of herd immunity in the US and other developed countries beyond 2021. We also generally believe mass vaccination in developing countries could take longer as well.

Jimmy: Most policymakers and investors are operating on the assumption that there will be effective therapeutics and vaccines. But what if scientists struggle to come up with these therapeutics in the near-term and vaccines in the long run. In the meantime, could you envision a world where we get back to work, some semblance of normal social life, use public transportation, fly for business and pleasure with everyone wearing a protective mask as the primary defense? Is using masks, social distancing, contact tracing a viable half-measure?

Dr. Song: It is still possible that therapeutic efforts are at best incremental, and that vaccine development could take longer. In that case, it will certainly take longer for normalcy to return. Things like use of protective masks, aggressive diagnostic testing, and contact tracing will linger in public. Since a significant number of people can be asymptomatic or pre-symptomatic, with the potential to spread the virus unknowingly, a mask will help them from infecting others. Public transportation and flying will resume, but with added safety measures regardless of the availability of successful therapeutics and vaccines. In addition to behavioral or cultural adaptation, technology and diagnostics will likely pick up some of the slack; measures to track the infection will go a long way to help workers stay healthy and allow businesses and other institutions to function. Although it would be unfortunate if the

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biopharmaceutical industry struggles to come up with material therapeutic and vaccine solutions, more investment into vaccine and therapeutics will be made to help ensure the protection of front-line workers and the advancement of science to better prepare for the threat of another pandemic.

ESG & POLICY IMPLICATIONS

Jimmy: What are the lessons that we can learn from this pandemic and how do you think healthcare policies will evolve from here?

Dr. Song: The global pandemic will have long-lasting implications on pandemic preparedness and healthcare policies in general. Previous outbreaks of infectious diseases, such as SARS and Ebola, while significant, were confined generally to specific regions. As such, public health efforts, such as pandemic surveillance, vaccine technologies, and build-up of "essential" medical products, lost some traction when those outbreaks abated. COVID-19 has had such a widespread impact, contributing to morbidity and mortality, as well as trillions of dollars of lost or diminished global economic output. Consequently, significant efforts on pandemic preparedness will likely be sustained for the foreseeable future. With respect to the US, focus will be on stockpiling essential products and investing in the US healthcare supply chain. As such, the recent rounds of stimulus will jumpstart efforts in surveillance, vaccine research, and data infrastructure. For instance, scientists will have greater ability to use next-gen nucleic acid sequencing to track dynamically the genomics of COVID-19 and other future viral threats, in order to accelerate therapeutic and diagnostic solutions.

With regard to other aspects of healthcare policy, the acute impacts have led to a rapid rise in unemployment. Greater enrollment in Medicaid will help, but a rise, hopefully transient, in non-poor uninsured will reignite efforts in expanding insurance coverage. Depending on the outcome of the 2020 elections, reforms of the social safety net could be implemented through either an expansion or revision of the Affordable Care Act. While the issue of drug pricing will not go away, the biopharma industry is working toward effective therapeutics and vaccines for COVID-19. Success and substantial efforts are necessary to improve public perception of this industry. The return on investment of effective solutions from this industry is quite high, given significant human suffering, as well as trillions of dollars of economic activity at stake. Hence, the value of the drug industry is readily apparent in the pandemic context. Successful therapeutics will bring leverage or goodwill, which could mitigate some of the risk of onerous regulation on the biopharma industry.

Healthcare policy outside the US will evolve as well. Efforts on vaccine research and surveillance will accelerate similarly. Like the US, other countries with significant resources will view healthcare supply chain as more strategic; the result will likely be more stockpiling of medical goods and greater investment in the healthcare supply chain. Additionally, lessons from the stress on various healthcare systems will also lead to more prioritization on data infrastructure that could help identify best medical practices in real time. Similarly, if the healthcare sector, which is viewed as part of the solution, can demonstrate value through innovation, many companies could thrive. There are negatives as well, as the consequences of higher debt in Europe to deal with the economic impact will lead potentially to austerity measures on healthcare, which could offset investment into life-saving drugs.

Jimmy: You, together with our ESG team, have been engaging with portfolio companies on various issues such as drug pricing policies and supply chain resiliency. In the post-COVID-19 world, what are some of the key ESG issues – healthcare and workplace safety related, for example – that we plan to focus on?

Dr. Song: Our engagement approach focuses on material ESG issues specific to each company, and as a result we are of course factoring company responses to COVID-19 into our shareholder engagements across all sectors.

For healthcare companies, while COVID-19 is acute, both its risks and opportunities are temporary and relatively short term. In contrast, issues upon which we're currently engaging such as value-based drug pricing, regulatory and policy risks, and the health effects of climate change, are chronic and likely more

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permanent long-term risks. So the way in which Rockefeller Asset Management feels we can do our part is by dealing with the short term dislocations while not losing focus on long term issues.

In continuing with scheduled engagements, we have been starting with a discussion on how a company is protecting the health of its global workforce, including its supply chain. In our engagement calls we are seeing that companies with strong ESG management for their material issues have generally been more successful in implementing measures such as getting PPE to their staff and maintaining a high level of technical safety across their supply chains.

INVESTMENT OPPORTUNITIES

Jimmy: Where do you find attractive investment opportunities in healthcare these days?

Dr. Song: We believe there are several attractive investment opportunities in the healthcare sector, which represents a diverse group of businesses – a ripe area for potential alpha generation. The industry has significant long-term innovation tailwinds, from advances in biology to influences from information technology, such as artificial intelligence. Aging, chronic disease, and emerging markets remain significant demand drivers. We think there are a number of biotechnology companies globally with strong genetic and immunology technology foundations that can be deployed productively to come up with therapeutics for areas of unmet medical need.

While the global economy will hopefully return to some level of normalcy soon, some things will never be the same. Diagnostics has proven to be an essential driver of economic and clinical value during the pandemic; hence we see opportunities in non-invasive diagnostics and point-of-care solutions provided by companies in the US and abroad. So-called liquid biopsy, in which blood can be analyzed to screen for cancer in otherwise healthy individuals at risk, could improve mortality in cancer and lower overall costs of cancer care. Point-of-care diagnostics and at-home tests could empower those individuals who may be reluctant to visit a hospital or other medical care in the future due to lingering perceptions of acquiring COVID-19 infections or those deterred by the high cost of healthcare to better manage personal health. In addition, life sciences tools companies are also beneficiaries of stimulus from greater academic funding and pandemic readiness. With virtual medical visits (so-called "telemedicine") here to stay, we believe digital health companies that disrupt healthcare payment and delivery could provide potential opportunities. New models of healthcare delivery can help address the supply-demand problem in healthcare services – in order to lower overall medical costs and improve health.

Jimmy: Thank you, Dr. Song, for sharing your insight. I have long viewed healthcare through an alpha generation lens for our investment strategies. But with this crisis, healthcare has emerged as the most important industry in getting the world back to normalcy. We are glad to have your deep scientific and industry knowledge to help navigate the road to normalcy and beyond.

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